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Clinical Utility of Routine Pleural Manometry During Therapeutic Thoracentesis: a Randomized Trial

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SUMMARY

Background: In patients with non-expandable lung, pleural fluid removal can result in excessively negative pleural pressure, associated with chest discomfort, pneumothorax, and reexpansion pulmonary edema. Monitoring pleural pressure during thoracentesis may reduce discomfort and protect against complications.

Methods: In this prospective randomized single-blind trial, subjects with large pleural effusions at two academic medical centers were randomly assigned (1:1 ratio) to symptom-guided ("control") versus symptom-plus-manometry-guided ("manometry") thoracentesis. All had free-flowing effusions meeting pre-specified criteria suggesting volume of at least 500 milliliters. Subjects, who were blinded to assignment, rated chest discomfort on visual analog scales before, during, and after drainage. Pleural pressure was measured at regular intervals in the manometry group. Drainage was discontinued before complete evacuation for persistent chest discomfort, incessant cough, complication, rapidly falling pleural pressure, or end-expiratory pleural pressure lower than -20 cm H₂O (latter two only in the manometry group). We performed a modified intention-to-treat analysis. The primary outcome was overall procedural chest discomfort through 5 minutes post-procedure. This trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02677883), NCT02677883.

Findings: Between March 4, 2016 and September 8, 2017, 191 patients were screened. One hundred twenty-eight eligible subjects were randomized with four excluded from the final analysis of 62 subjects per group due to manometer malfunction (n=2), inability to access effusion due to pleural tumor burden (n=1), and inability to remain seated (n=1). There was no difference in the primary outcome of overall procedural chest discomfort between groups (mean difference 2.4, 95% CI -5.7-10.5; p = 0.78). Six

asymptomatic pneumothoraces ex-vacuo occurred in the control group; no serious complications occurred in either group.

Interpretation: Measurement of pleural pressure during large-volume thoracentesis does not alter procedure-related chest discomfort. This is the first study to directly assess the impact of pleural manometry on important patient-centered clinical outcomes during thoracentesis, and does not support its routine use.

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PANEL: RESEARCH IN CONTEXT

Evidence before this study

Chest discomfort, reexpansion pulmonary edema, and pneumothorax ex-vacuo complicating thoracentesis have been associated with development of excessively negative pleural pressure in the setting of nonexpandable lung. Routine pleural manometry during aspiration has been advocated as potentially protective against these complications, but prospective comparative studies are lacking.

Added value of this study

This is the first prospective, randomized trial of routine pleural manometry during therapeutic thoracentesis for important clinical and patient-centered outcomes. Manometry did not reduce chest discomfort and there were no serious complications in either group.

Implications of all the available evidence

This randomized trial provides the most methodologically-rigorous evidence to date that routine manometry does not provide clinical or patient-centered benefit during therapeutic thoracentesis, supporting prior prospective case series and retrospective studies which have concluded the same.

INTRODUCTION

Over 1.5 million pleural effusions are diagnosed annually in the United States, making thoracentesis for diagnostic sampling and therapeutic aspiration one of the most commonly performed medical procedures¹⁻³. While generally perceived of as a safe procedure, in the largest series to date (including more than 9,300 thoracenteses performed by expert operators) the complication rate exceeded 3% when large volumes were aspirated, including 2.2% pneumothorax and 0.75% re-expansion pulmonary edema⁴. Complications of therapeutic thoracentesis, including pneumothorax ex-vacuo, chest discomfort, and reexpansion pulmonary edema (REPE), have been associated with increasingly negative pleural pressure resulting from pleural fluid aspiration in the setting of non-expandable lung⁵⁻¹⁰. Pleural pressures lower than -20 cm H₂O are considered excessively negative^{3,7,11}, a threshold based on early animal models in which the risk of complications was minimal at pressures above -20 mmHg (-27 cm H₂O)^{8,9}. Accordingly, there has been intense interest in the pulmonary community in using pleural manometry routinely during therapeutic pleural fluid aspiration to mitigate these pressure-related procedural risks, as evidenced by a growing body of literature and ongoing clinical trials^{1,3,5-7,10,12-17}.

Many pleural disease experts advocate for limiting pleural fluid aspiration based on pleural manometry stop criteria, and a web-based clinical decision support resource widely used in the United States recommends routine pleural manometry during large volume thoracentesis with procedure termination if pleural pressure drops below -20 cm H₂O or pleural elastance exceed 14.5 cm H₂O/L^{1,6,12,15,18}. The British Thoracic Society guidelines recommend limiting drainage to 1.5L to avoid unknowingly precipitating excessively negative pleural pressure¹¹, though larger aspirations are reported to be safe provided manometry is performed, among several findings commonly cited in support of routine pleural manometry⁵⁻⁷. Societal guidelines, however, have not issued recommendations for or

against the use of pleural manometry, citing the lack of comparative studies demonstrating benefit in important patient-centered clinical outcomes during therapeutic thoracentesis¹⁹.

METHODS

Study design and participants

This randomized single-blind trial recruited inpatient and outpatient subjects at two academic medical centers (Vanderbilt University Medical Center, Nashville, TN, USA and Johns Hopkins Hospital, Baltimore, MD, USA). Institutional Review Boards of both institutions approved this trial (VUMC IRB number 151492; JHU IRB number 00119664).

Patients referred to the interventional pulmonary service for therapeutic thoracentesis were screened for eligibility. Adult patients with symptomatic pleural effusions of 500 mL or greater estimated volume were eligible for inclusion. The estimated volume criterion could be satisfied by computed tomography scan of the chest, chest radiograph, or thoracic ultrasound; specific criteria were adapted from prior work regarding volume prediction using these modalities^{20–22}. Exclusion criteria included non-free flowing effusions, inability to maintain a seated position for the procedure, manometry felt to be clinically indicated (at the proceduralist's discretion), and inability to provide informed consent. Table 1 lists complete inclusion and exclusion criteria. All subjects provided written informed consent.

Randomization and masking

We randomly assigned subjects in a 1:1 ratio to symptom-guided (“control”) or symptom-plus-manometry-guided (“manometry”) therapeutic thoracentesis. The sequence of group assignments was generated by computer using permuted blocks of 4 and 6 and was stratified by participating institution. Subjects were assigned by opening a sealed opaque envelope containing group allocation prepared by a research assistant who assisted with data management but not enrollment decisions. Investigators displayed a manometer to all subjects prior to randomization who were informed that brief pauses in drainage would be performed at regular intervals regardless of whether the manometer was being used or not. Thoracentesis catheters were introduced in the posterior hemithorax of seated subjects such

that subjects were unable to see if the manometer was being used and pleural pressure measurements were not verbalized to maintain subject blinding.

Procedures

All thoracenteses were performed using standard sterile technique after pre-procedure thoracic ultrasound to identify optimal catheter placement and adequate local infiltration of plain 1% lidocaine using 5F, 6F, or 8F over-needle-style catheters (Safe-T-Centesis™, BD, Franklin Lakes, NJ, USA or Arrow-Clarke™, Teleflex, Morrisville, NC, USA). Complete evacuation of pleural fluid via manual aspiration using a 60 mL syringe was attempted in all procedures. In all procedures, drainage was paused for 5 to 10 seconds at drainage increments of every 200 mL for the first liter drained then every 100 mL thereafter. Subjects were asked to indicate their current degree of chest discomfort on 100 mm visual analog scales (VAS) during these pauses.

In the control arm, drainage was terminated before complete effusion evacuation for 1) persistent chest discomfort consistent with excessively negative pleural pressure (felt in anterior chest and/or neck, not improved after catheter retraction to exclude diaphragm irritation), 2) intractable cough, or 3) procedural complication.

In the manometry arm, pleural pressure was measured at end-expiration during normal tidal breathing using single-use digital manometers positioned in-line between catheter and drainage tubing (Compass®, Centurion Medical Products, Williamston, MI, USA). During each drainage pause, several tidal respiratory cycles were observed before the end-expiratory pressure was manually recorded. This manometer has previously been shown to provide accurate pleural pressures during thoracentesis¹³. Pleural pressure was measured immediately after intrapleural catheter placement (“opening pressure”), during drainage pauses, and just prior to catheter removal (“closing pressure”). Drainage was terminated before complete effusion evacuation for the same three clinical criteria used in the control group (described above). In addition, drainage was halted if either of the following manometry criteria

were met: 1) pleural pressure lower than -20 cm H₂O, or 2) pleural pressure decline by more than 10 cm H₂O between two measurements to a value less than or equal to -10 cm H₂O. The pressure limit of -20 cm H₂O was chosen based on the historical definition of excessively negative pleural pressure and current practice guidelines^{7,11}; the stop criterion for pleural pressure rapidly falling was included as indicative of abnormal pleural elastance, suggesting trapped or entrapped lung and impending excessively negative pleural pressure.

Subjects indicated their degree of chest discomfort by making vertical marks on visual analog scales presented as 100 mm horizontal lines with labels “No discomfort at all” and “Worst possible discomfort” printed to the left and right of the line, respectively, such that a score of 0 mm represented the former and 100 mm represented the latter. This scoring technique is well-validated for subject-reported pain measurements^{23,24}. Two investigators measured all scales independently; a third investigator arbitrated scoring disagreements. These scales were completed before procedure, just after catheter placement (“open”), at the drainage pause increments detailed above, and after drainage was stopped just prior to catheter removal (“close”). Five minutes after catheter removal, subjects were asked to mark an identical VAS indicating overall chest discomfort incurred from procedure start to five minutes post-procedure. Additional VAS indicating overall procedural discomfort through 15 minutes post-procedure and a similar VAS assessing breathlessness before and after procedure were also completed.

All procedures were timed from catheter insertion to removal. Bedside ultrasound was performed post-procedure to assess for degree of residual effusion and post-procedure chest radiographs were ordered to be completed within one hour of procedure termination on all subjects.

Outcomes

The primary outcome was subject-estimated overall procedural chest discomfort from procedure start through five minutes post-procedure, as measured by VAS at five minutes post-

procedure. A discomfort-based primary outcome was chosen for three reasons: 1) procedural discomfort is a clinically relevant and patient-centered outcome; 2) prospective data already exist suggesting manometry does not prevent REPE or pneumothorax^{5,14,25} while its impact on chest discomfort has not been prospectively investigated; and 3) REPE and pneumothorax complicate therapeutic thoracentesis with far less frequency than chest discomfort.

Secondary outcomes included overall procedure-related discomfort through fifteen minutes post-procedure, change in discomfort scores from open to close, intra-procedure trend in discomfort scores by volume drained, change in breathlessness pre- to post-procedure (all the aforementioned assessed by validated 100 mm VAS^{26,27}), procedure duration, effusion volume drained, rate of complete lung reexpansion (assessed by post-procedure chest film demonstrating pleural apposition and post-procedure ultrasound without more than scant remaining pleural fluid). Post-procedure radiographs were assessed for pneumothorax and re-expansion pulmonary edema by chest radiologist blinded to study allocation.

Statistical analysis

Based on baseline VAS chest pain scores reported in the TIME II trial²⁶ and previously published VAS pain score minimum clinically important difference of 13 mm²³, a two-sample t-test determined a sample size of 128 subjects would have 80% power to detect a decrease in discomfort score of 15 mm (standard deviation, 30 mm) with type I error of 0.05.

Statistical analysis proceeded according to pre-specified analysis plan. Descriptive statistics included means and standard deviations for continuous parameters, percentages and frequencies for categorical parameters, and an investigation for outliers. Assumptions for statistical analysis (e.g. normality and homoscedasticity) were made. Comparisons between groups were made using t-test for continuous variables and Chi-square test for categorical variables. Linear regression was employed to assess the discomfort and breathlessness score differences between two arms. The mean differences

and 95% confidence interval were reported. In order to account for the dependence of repeated measurements, we applied linear model using generalized least square (mixed model with random intercept utilizing AR1 correlation structure) to assess the trend of intra-procedure discomfort scores. Analyses were performed using R 3.3.1.

Finally, two pre-specified sub-analyses were performed: 1) subgroup analysis of the primary outcome in effusions determined to be exudative by Light's criteria²⁸ and 2) trend in VAS discomfort scores up to 1.5L effusion drained. The first was specified because exudates are more likely than transudates to alter pleural elastance and place the subject at risk for excessively negative pleural pressures; as such, this group is hypothesized to potentially benefit most from routine manometry. The second was specified in reference to recommendations that no more than 1.5L be aspirated at one time to reduce the risk of negative-pressure-related complications¹¹, while prior study has demonstrated greater volumes can be aspirated safely when manometry is used^{3,5}. Assuming both are true, a significant reduction in discomfort in the manometry arm could conceivably be driven by only subjects in whom very large volumes were aspirated. This subgroup analyzing only up to the recommended 1.5 L of fluid drained addresses potential confounding attributable to very large effusion aspirations.

A data monitoring committee did not oversee this study as both methods of performing therapeutic thoracentesis are considered standard-of-care, representing minimal study-related risk to subjects. The trial was registered at clinicaltrials.gov, NCT02677883.

Role of the funding source

This study was supported by an unrestricted educational grant from Centurion Medical Products (Williamston, MI, USA). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between March 4, 2016 and September 8, 2017, 191 patients referred for therapeutic thoracentesis were screened. As depicted in Figure 1, 128 eligible patients were randomized, with four subsequently removed from the study at the time of their attempted procedures prior to any procedure or outcome data collection due to manometer malfunction (n=2), inability to access effusion due to pleural tumor burden (n=1), and inability to remain seated (n=1). The final analysis therefore contained 62 subjects in each group; complete primary and secondary outcome data was present for 100% of analyzed subjects.

Subjects were well-matched on baseline characteristics (Table 2). The most common comorbidity was malignancy (78 subjects, 63%) and 70 effusions (56%) were known to be malignant before study procedure. Average pre-procedure chest discomfort and breathlessness noted on the day of thoracentesis were similar between groups (mean discomfort VAS 26.2 ± 27.9 vs. 28.6 ± 30.9 and mean breathlessness VAS 37.6 ± 25.7 vs. 43.3 ± 27.4 , control vs. manometry, respectively).

The primary outcome of overall procedural chest discomfort rated at five minutes post-procedure did not significantly differ between control and manometry groups (mean VAS difference 2.4, 95% CI -5.7 - 10.5; $p = 0.78$; Figure 2). Adjustment for institution, which was a randomization stratification factor, yielded a similar result (mean VAS difference 2.5, 95% CI -5.4 – 10.5; $p=0.53$). On the pre-specified subgroup analysis of the primary outcome, there was no difference in overall procedural discomfort between groups when considering only effusions determined to be exudative (mean VAS difference -5.1, 95% CI -14.2 – 3.9, $p = 0.262$). Likewise, there were no significant differences noted between control and manometry groups on any secondary outcome measures (Table 3, Figure 2), including overall procedural chest discomfort through 15 minutes post-procedure, discomfort at close, intra-procedure trend in discomfort scores according to volume drained (Figure 3; time trend difference

interaction $p = 0.18$), change in breathlessness from pre-procedure average through 15 minutes post-procedure. There also remained no difference between groups on the additional other pre-specific subanalysis of the secondary outcome of intra-procedure trend in VAS discomfort scores when VAS scores corresponding to volumes removed in excess of 1.5L were excluded (time trend difference interaction $p = 0.095$). Finally, a post-hoc comparison for the primary outcome considering only those with prior painful thoracenteses revealed no difference between groups (mean VAS 27.3 ± 23.1 control vs. 24.6 ± 21.1 manometry, $p=0.73$).

Effusion drainage was halted after meeting a pleural pressure stop criterion in 13 manometry cases (21%). Drainage was discontinued for chest discomfort at similar rates in both groups, and procedure duration, volume drained, and rate of complete lung reexpansion did not differ significantly between groups (Table 4, Figure 4). Effusion etiology was established in 107 cases (86%); see Table 5.

Six complications were evident on post-procedure chest radiograph, all pneumothoraces ex-vacuo and all in the control group (9.7%), which represented a significant difference between groups ($p=0.012$). All were asymptomatic and none required intervention. Sixteen ambulatory subjects (13%) failed to report for post-procedure chest radiograph, including seven in the control group and nine in the manometry group.

DISCUSSION

This multicenter single-blind study represents the first randomized trial investigating the impact of routine pleural manometry for important patient-centered clinical outcomes during therapeutic thoracentesis. Routine pleural manometry failed to reduce procedural chest discomfort during therapeutic thoracentesis of large pleural effusions, as assessed by the primary outcome of overall chest discomfort through five minutes post-procedure as well as multiple secondary analyses of discomfort and breathlessness. These data suggest there is no indication for routine manometry during this procedure in terms of patient comfort and – noting no serious complications in either group in this trial and prior prospective studies suggesting manometry does not prevent REPE or pneumothorax – these data question the utility of routine pleural manometry in patients undergoing therapeutic thoracentesis.

Prior work established a relationship between excessively negative pleural pressure and complications, namely REPE, pneumothorax ex-vacuo, and chest discomfort^{3,5-9}. However, not all patients with excessively negative pleural pressure during therapeutic thoracentesis exhibit chest discomfort⁶. This finding, along with the rarity of serious complications if very large aspirated volumes are avoided, support guidelines that recommend no more than 1.5 liters be drained in a single procedure^{6,11,29}. Advocates of routine pleural manometry during large volume thoracentesis highlight the fact that asymptomatic excessively negative pleural pressure can be detected and aspirations exceeding societal recommendations are safely achievable while pressure is being monitored^{5-7,12}. Pleural manometry has been the subject of significant interest in the pulmonary community, as attested by the publication of many related studies in the past decade, the presence of manometry education sessions at most international pulmonary conferences and pleural courses, and several active clinical trials addressing the use of manometry to predict clinically meaningful endpoints (NCT03319186, NCT02805062 and NCT02192138, clinicaltrials.gov)

Manometry has not, however, been shown to protect against REPE, pneumothorax ex-vacuo, or chest discomfort^{5,10,14,25}. REPE is a rare complication found to be independent of pleural pressure, pleural elastance, and volume aspirated in a large prospective series⁵. Two prior series, one retrospective and one prospective, saw development of pneumothorax in 4% and 16% of procedures despite manometry with stop criterion for pleural pressure in negative excess of -25 cm H₂O or -20 cm H₂O, respectively, with most occurring in the setting of nonexpandable lung not suspected pre-procedure^{14,25}. A large retrospective series also failed to note a decrease in procedural chest discomfort when pleural manometry was performed compared to procedures without manometry¹⁰.

Our findings support the aforementioned literature suggesting manometry does not protect against important pressure-related complications during therapeutic pleural aspiration. The failure of manometry to protect against chest discomfort may have several explanations. First, chest discomfort appears inconsistently associated with excessively negative pleural pressure; Feller-Kopman *et al.* found in a large prospective series that only 22% of subjects who developed chest discomfort indicative of excessively negative pleural pressure actually had pleural pressures in negative excess of -20 cm H₂O, and 9% of subjects who did never developed chest discomfort⁶. This observation suggests that pleural pressure discomfort thresholds may vary between individuals. In addition, Heidecker *et al.*, in reporting a series in which manometry did not mitigate the risk of pneumothorax ex-vacuo¹⁴, hypothesized there may be non-uniform stress exerted on visceral pleura in the setting of regional variability in pleural elastance; this may also explain the poor correlation between pain and excessively negative pressure. Second, pleural pressure measurements are obtained during brief intermittent periods of drainage interruptions, leading to substantial periods of “blind time” during which acute changes on pleural pressure may go unnoticed. Third, it is possible that the use of a manometer emboldened the operators in this study to continue drainage in spite of patient symptoms when pleural pressure was otherwise reassuring; blinding the operators to the intervention was impractical. Though not statistically

significant, we do note that scores of overall procedural discomfort are higher in the manometry group, and after 1500 mL drained the trend in discomfort scores in the manometry group increase at a greater rate than in the control group, though the small number of subjects in whom very large volumes were aspirated limits the ability to draw any firm conclusions.

Of principal importance in interpreting the negative results of this trial is whether it represents a true non-difference between symptom-guided and symptom-plus-manometry-guided techniques or a type II error. This study was powered to detect a clinically meaningful difference in discomfort based on prior pertinent investigations (superiority design), met recruitment targets, had no baseline differences between groups, had very few post-randomization drop-outs (all four due to technical issues), and had complete outcome data on 100% of subjects. Primary outcome variability did not exceed the assumed variability used in the power calculation (overall actual standard deviation 22.5, assumed 30). Multiple analyses of chest discomfort data beyond the primary outcome of overall patient-reported procedural discomfort, including pre/post change in discomfort, intraprocedure trend in discomfort, and separate analysis of the exudative effusion subgroup most at risk for excessively negative pleural pressure also failed to demonstrate a difference between groups. We also had relatively few prospective subjects excluded pre-randomization, enhancing the external applicability of these findings. We acknowledge that two secondary outcomes, the open-to-close difference in VAS pain score and change in breathlessness from pre-procedure average through 15 minutes post-procedure, involve post-randomization “baseline” scores theoretically at risk for bias resulting from allocation. This seems unlikely as subjects were blinded to their allocation. The primary outcome and majority of the secondary outcomes and pre-specified sub-analyses are unaffected.

There was a significant difference between groups in the rate of pneumothorax ex-vacuo. Pneumothorax ex-vacuo is felt to represent a consequence of excessively negative pressure with pressure equilibration from air entry into the pleural space, either from a small visceral pleural tears or

irruption of air via the catheter tract. Pneumothorax ex-vacuo is typically asymptomatic (in fact, intentionally allowing entrainment of air via the catheter often improves chest discomfort due to excessively negative pleural pressure) and not felt to represent a complication of thoracentesis per se, but rather a demonstration of the underlying abnormal pleural physiology. By definition, pneumothoraces ex-vacuo do not require therapeutic intervention. Furthermore, as a significant percentage of ambulatory study participants failed to report for post-procedure chest radiograph, the validity of this finding is cannot be guaranteed. Therefore, while it is possible that manometry prevented some pneumothoraces ex-vacuo in our subjects, diagnosing these subjects with abnormal pleural elastance via manometry rather than post-procedure chest radiograph seems clinical advantageous only in those who intend to fly shortly after their procedure.

It is important to clarify that while pleural manometry failed to demonstrate benefit to patients in this trial when performed routinely, it has clear utility in specific clinical circumstances. Pleural manometry elucidates pleural elastance curves, facilitating the diagnosis of trapped or entrapped physiology and may predict the success of chemical pleurodesis, the likelihood of spontaneous indwelling pleural catheter-associated pleurodesis, or the choice of pleurodesis versus indwelling pleural catheter for the palliative management of a recurrent symptomatic effusion^{30,31}. In a patient in which pre-procedure suspicion of trapped or entrapped lung physiology is particularly high or pleurodesis is being considered, pleural manometry may provide crucial insight into the underlying pleural physiology with clinical implications.

In summary, existing data in favor of routine pleural manometry during therapeutic thoracentesis consists of the observation that some patients who develop excessively negative pleural pressure are asymptomatic and case series evidence suggesting volumes in excess of the recommended 1.5L can be safely aspirated if pleural pressure is monitored^{3,6,7}. However, there exist no high-quality comparative studies demonstrating benefit, and prior prospective and retrospective series have

concluded that pleural manometry does not prevent re-expansion pulmonary edema, pneumothorax, or chest discomfort^{5,10,14,25}. Yet, pleural manometry continues to be routinely used despite this poor evidence base. This randomized multicenter trial evaluating the routine use of pleural manometry during aspiration of large-volume pleural effusions suggests that manometry does not reduce pain or improve post-intervention breathlessness, safety, volume drained, or speed of procedure; these data do not support the routine use of pleural manometry during large volume therapeutic thoracentesis.

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Author contributions:

Study concept and design: RJL, JKP, CMM, OBR, NMR, FM

Acquisition of data: RJL, ADL, JKP, CMM, LR, CW, SV, TG, OBR, LY, FM

Analysis and interpretation of data: RJL, ADL, HC, JTH, OBR, LY, IP, NMR, RWL, FM

Drafting of the manuscript: RJL, OBR, NMR, FM

All authors participated in critical revision of the manuscript for important intellectual content and provided final approval to submit this version of the manuscript and have agreed to be accountable for all aspects of the work.

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Table 1. Inclusion and Exclusion Criteria.

Inclusion Criteria
1. Referral for large-volume thoracentesis
2. Symptomatic free-flowing pleural effusion with estimated volume ≥ 500 mL
a. Chest radiograph: effusion filling $\geq 1/3$ the hemithorax ²⁰ , OR
b. CT-scan: maximum AP depth of the effusion $\geq 1/3$ of the AP dimension on the axial image superior to the hemidiaphragm, including atelectatic lung completely surrounded by effusion ²¹ , OR
c. Ultrasound: effusion spanning at least three interspaces, with depth of 3 cm or greater in at least one interspace, while the patient sits upright ^{22*} .
3. Age ≥ 18

Exclusion Criteria
1. Known re-expandable lung on the basis of:
a. Recurrent transudative (by Light's criteria) pleural effusions of known etiology, AND
b. Multiple prior thoracenteses without significant chest discomfort, AND
c. No clinical suspicion that the current effusion is due to other than the known underlying etiology.
2. Inability to provide informed consent
3. Study subject has any disease or condition that interferes with safe completion of the study, e.g. coagulopathy or hemodynamic instability, at proceduralist discretion
4. Pleural effusion is smaller than expected on bedside pre-procedure ultrasound
5. Manometry felt to be clinically indicated, at proceduralist discretion
6. Inability to assume or maintain a seated position for the procedure
7. Presence of multiple loculations on bedside pre-procedure ultrasound

*This criterion represents a simplification of Goeke and Schwerk's volume estimation formula in an upright patient, in which the estimated volume equals the craniocaudal extent of the effusion (cm) multiplied by 90. Therefore, effusions spanning at least 5.5 cm, or approximately three interspaces, are expected to exceed 500 mL.

Table 2. Baseline Subject Characteristics

	Control (n=62)	Manometry (n=62)
Age (years)	64.7 (12.3)	66.8 (11.8)
Male gender	31 (50%)	33 (53%)
Procedure setting		
Outpatient	33 (53%)	39 (63%)
Emergency Department	1 (2%)	1 (2%)
Inpatient, regular ward	24 (39%)	21 (34%)
Inpatient, intensive care unit	4 (6%)	1 (2%)
Smoking status		
Current	0	1 (2%)
Former	37 (60%)	35 (56%)
Never	25 (40%)	26 (42%)
Prior thoracentesis	35 (56%)	24 (39%)
With significant chest discomfort	9 (15%)	17 (28%)
Regular opiate use	16 (26%)	19 (31%)
Known effusion etiology		
Malignant	13 (21%)	18 (29%)
Chylous	1 (2%)	1 (2%)
Hepatic hydrothorax	1 (2%)	0
Other *	1 (2%)	2 (3%)
Comorbidities		
Malignancy	39 (63%)	39 (63%)
Heart failure	4 (6%)	4 (6%)
Chronic kidney disease	5 (8%)	3 (5%)
Cirrhosis	1 (2%)	0

Data are n (%) or mean (SD).

* Other known effusion etiologies pre-procedure: fibrosing mediastinitis (1), post-transplant fibrinopleuritis with entrapment physiology (1), nonspecific pleuritis (1).

Table 3. Pre-, intra-, and post-procedure discomfort and breathlessness scores.

	Control (n=62)	Manometry (n=62)	Mean Difference ^a	95% CI	P value
Average pre-procedure chest discomfort, day of procedure	26.2 (27.9)	28.6 (30.9)	2.5	-8.0 - 12.9	0.641
Average pre-procedure breathlessness, day of procedure	37.6 (25.7)	43.3 (27.4)	5.7	-3.8 - 15.1	0.236
Chest discomfort, open	18.1 (20.3)	18.2 (20.6)	0.1	-7.2 - 7.4	0.979
Chest discomfort, close	30.1 (24.3)	26.4 (23.8)	-3.7	-12.3 - 4.9	0.395
Overall procedural discomfort through 5 minutes post-procedure ^b	23.0 (21.2)	25.4 (24.0)	2.4	-5.7 - 10.5	0.556
Overall procedural discomfort through 15 minutes post-procedure	22.6 (18.5)	22.3 (19.9)	-0.3	-7.2 - 6.5	0.921
Breathlessness, 15 minutes post-procedure	18.1 (18.0)	17.0 (20.1)	-1.1	-7.9 - 5.7	0.751
Change in VAS discomfort, open to close	3.9 (29.7)	-2.3 (36.5)	-6.2	-18.0 - 5.7	0.305
Change in VAS breathlessness, pre- to 15m post	-20.1 (25.8)	-26.2 (31.8)	-6.1	-16.5 - 4.3	0.247

Data are mean VAS scores (SD). VAS = visual analog scale.

^a Manometry minus control.

^b Primary outcome measure.

Table 4. Procedure data.

	Control (n=62)	Manometry (n=62)	Mean difference ^b	95% CI or χ^2	P value
Volume drained (ml)	1087 (453)	1074 (486)	-13.9	-180.9 - 153.2	0.806
Thoracentesis duration (minutes)	14.9 (5.2)	16.4 (6.3)	1.5	-0.6 - 3.5	0.341
Reason for drainage discontinuation					
Stopped spontaneously	32 (52%)	25 (40%)		0	0.969
Chest discomfort	22 (35%)	21 (34%)		0.66	0.415
Intractable cough	7 (11%)	2 (3%)		1.89	0.169
Ppl lower than -20	n/a	9 (15%)			
Rapidly falling Ppl ^a	n/a	4 (6%)			
Aspiration of air	1 (2%)	0			
Vagal episode	0	1 (2%)			
Complication occurred	6 (10%)	0		6.31	0.012
Pneumothorax ex-vacuo	6 (10%)	0		6.31	0.012
Residual post-procedure effusion	25 (40%)	25 (40%)		0.01	0.939
Post-procedure CXR not done	7 (11%)	9 (15%)		0.29	0.592

Data are n (%) or mean (SD). Ppl = pleural pressure. CXR = chest radiograph.

^a Ppl drop >10 cm H₂O between two measurements to a value less than or equal to -10 cm H₂O

^b Manometry minus control

Table 5. Pleural fluid analysis and final effusion diagnoses

	Control (n=62)	Manometry (n=62)
Exudate *	38 (61%)	48 (77%)
Transudate *	14 (23%)	8 (13%)
Effusion etiology		
Malignant	26 (48%)	35 (66%)
Heart failure	7 (13%)	4 (8%)
Post cardiac surgery	5 (8%)	3 (5%)
Chylothorax	2 (4%)	2 (4%)
Hepatic hydrothorax	3 (5%)	0
Chronic kidney disease	1 (2%)	1 (2%)
Parapneumonic	2 (4%)	0
Connective tissue disease	1 (2%)	0
Other †	7 (11%)	8 (13%)
Could not be determined	8 (13%)	9 (15%)

Data are n (%).

* Pleural fluid analysis was not obtained in 6 manometry and 10 control effusions.

† Other etiologies included (n=1 each): other volume overload, fibrosing mediastinitis, granulomatous foreign body reaction, peritoneal dialysis-related, acute histoplasmosis, paramalignant inflammatory exudate, eosinophilic pleuritic, fibrinothorax, splenic infarct, pleural amyloidosis, lung transplant acute rejection, hemothorax after ICD placement, immunotherapy side effect, nonspecific pleuritis confirmed by pleural biopsy, ventriculopleural shunt malfunction / CSF leak.

FIGURES

Figure 1. Trial profile.

Figure 2. Comparison of overall procedural discomfort and breathlessness between manometry and control.

Figure 3. Intra-procedure trend in VAS discomfort scores per volume aspirated.

Figure 4. Procedure duration and volume drained.