Routine monitoring with pleural manometry during therapeutic large-volume thoracentesis to prevent pleural-pressure-related complications: a multicentre, single-blind randomised controlled trial

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Summary

Background In patients with non-expandable lung, removal of pleural fluid can result in excessively negative pleural pressure, which is associated with chest discomfort, pneumothorax, and re-expansion pulmonary oedema. Pleural manometry is widely used to safeguard against pressure-related complications during thoracentesis despite little evidence to support the approach. We investigated whether monitoring of pleural pressure with manometry during thoracentesis could protect against complications compared with assessment of symptoms alone.

Methods We did a prospective randomised single-blind trial involving patients with large pleural effusions at two academic medical centres in, Nashville, TN, and Baltimore, MD, USA. Eligible patients were adults with free-flowing effusions estimated to be at least 0·5 L who could remain seated throughout the procedure. Patients were randomly assigned 1:1 to receive thoracentesis guided by symptoms only (control) or by symptoms plus manometry at timepoints based on volume drained. The randomisation schedule was computer generated, used permuted blocks of four and six, and was stratified by participating institution. Patients, who were masked to study-group assignment, were asked to rate chest discomfort on 100 mm visual analogue scales before, during, and after drainage. In both groups drainage was discontinued before complete evacuation of pleural fluid if patients developed persistent chest discomfort, intractable cough, or other complications. In the manometry group, an additional criterion for stopping was if end-expiratory pleural pressure was lower than –20 cm H_2O or declined by more than 10 cm H_2O between two measurements to a value less than or equal to –10 cm H_2O. The primary outcome was overall chest discomfort from before the start to after the procedure measured by patients 5 min after the end of drainage. Analysis was by modified intention to treat (ie, included all patients with any procedure or outcome data). This trial is registered with ClinicalTrials.gov, number NCT02677883.

Findings Between March 4, 2016, and Sept 8, 2017, 191 patients were screened, of whom 128 were randomly assigned treatment and 124 were included in the final analysis (62 in each group). Four patients were excluded because of manometer malfunction (n=2), inability to access effusion due to pleural tumour burden (n=1), and inability to remain seated (n=1). Groups did not differ for the primary outcome (mean difference in chest discomfort score 2·4 mm, 95% CI –5·7 to 10·5, p=0·56). Six (10%) of 62 patients in the control group had asymptomatic pneumothorax ex vacuo compared with none in the manometry group (p=0·01). No serious complications occurred in either group.

Interpretation Measurement of pleural pressure by manometry during large-volume thoracentesis does not alter procedure-related chest discomfort. Our findings do not support the routine use of this approach.

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Introduction

More than 1·5 million pleural effusions are diagnosed annually in the USA, making thoracentesis for diagnostic sampling and therapeutic aspiration one of the most commonly performed medical procedures.[1–3] Although generally perceived as being a safe procedure, in a series of more than 9300 thoracenteses performed by expert operators, the complication rate exceeded 3% when large volumes (>1·5 L) were aspirated, including incidence of 2·2% for pneumothorax and 0·75% for re-expansion pulmonary oedema.[4] Complications of therapeutic thoracentesis, including pneumothorax ex vacuo, chest discomfort, and re-expansion pulmonary oedema, have been associated with increasingly negative pleural pressure resulting from aspiration of pleural fluid in patients with non-expandable lung.[5–10] Pleural pressures lower than –20 cm H_2O are deemed to be excessively negative.[3,7,11] This threshold was based on early animal models in which the lowest risk of complications was seen at pressures greater than –20 mm Hg (–27 cm H_2O).[8,9]

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Research in context

Evidence before this study

Therapeutic thoracentesis is among the most commonly performed procedures in clinical medicine. Aspiration of pleural fluid in patients with non-expandable lung increases negative pressure in the pleural space, associated with procedural complications, including pneumothorax, re-expansion pulmonary oedema, and chest discomfort, in observational human studies, animal models, or both. Monitoring of pleural pressure during therapeutic thoracentesis has, therefore, garnered interest as a potential safeguard against these pressure-related events. We searched PubMed for articles published before July 1, 2018, reporting studies of pleural manometry during thoracentesis, using the search term "((((thoracentesis[Title]) OR pleural[Title]) AND manometry[Title]) OR manometer[Title]) OR pressure[Title])". We found no randomised trials on this topic, but in multiple prospective observational or retrospective series, manometry has precisely defined pleural elastance curves (with potential implications for choice of future palliative pleural interventions) and identified excessively negative pleural pressure in the small number of patients who remain asymptomatic despite potentially harmful pleural pressure. Several studies have suggested that the 1·5 L aspiration limit recommended by the British Thoracic Society can be safely exceeded if manometry is used to monitor pleural pressure during thoracentesis. However, the largest clinical series showed no benefit. Society guidelines have not recommended for or against routine monitoring with pleural manometry, citing insufficient evidence, but it continues to be widely used and advocated.

Added value of this study

In this prospective randomised trial, we used clinical and patient-centred outcomes to assess the use of routine pleural manometry during therapeutic thoracentesis. Manometry did not reduce chest discomfort or improve breathlessness after the procedure, volume drained, or speed of procedure. No patients in either group had serious complications. This trial provides methodologically rigorous evidence that routine manometry does not provide clinical or patient-centred benefits during therapeutic thoracentesis.

Implications of all the available evidence

Although in specific situations pleural manometry might be beneficial, we found that routine pleural manometry does not lessen the risk of serious complications during therapeutic thoracentesis or reduce discomfort or breathlessness. Our findings reinforce those from previous prospective series and retrospective studies.

Pleural manometry monitoring to mitigate these pressure-related procedural risks during thoracentesis has become widely used.[1,3,5–7,10,12–17]

Many pleural disease experts and a web-based resource aimed at supporting clinical decision making that is widely used in the USA advocate limiting aspiration of pleural fluid during large-volume thoracentesis based on pleural manometry criteria. Termination of the procedure is recommended if pleural pressure drops to less than –20 cm H_2O or pleural elastance exceeds 14·5 cm H_2O/L.[1,6,12,15,18] By contrast the British Thoracic Society recommends limiting drainage to 1·5 L fluid to avoid excessively negative pleural pressure.[11] Several reports have indicated that aspiration of larger volumes is safe if manometry is used,[5–7] but no society guidelines yet make this recommendation, citing insufficient comparative evidence.[19] We did a randomised clinical trial to investigate whether monitoring of pleural pressure with manometry during thoracentesis could protect against complications compared with assessment of symptoms during fluid aspiration.

Methods

Study design and participants

We did a randomised single-blind trial at two academic medical centres, Vanderbilt University Medical Center, Nashville, TN, USA, and Johns Hopkins Hospital, Baltimore, MD, USA. Inpatients and outpatients referred to the interventional pulmonary service for therapeutic thoracentesis were screened for eligibility. Adults (age ≥18 years) with symptomatic pleural effusions estimated to be at least of 0·5 L in volume were eligible for inclusion. Effusion volume was estimated to be at least 0·5 L if one or more of the following criteria were met: effusion filling at least a third of the hemithorax on chest x-ray,[20] maximum anteroposterior depth of effusion at least a third of the anteroposterior dimension on the axial CT image superior to the hemidiaphragm (including atelectatic lung completely surrounded by effusion),[21] or effusion spanning at least three interspaces on ultrasonography, with a depth of 3 cm or greater in at least one interspace while the patient was sitting upright.

Exclusion criteria included non-free-flowing effusions, inability to maintain a seated position for the procedure, manometry judged to be clinically indicated by the person doing the procedure, and inability to provide informed consent. We also excluded patients with known re-expandable lung based on recurrent transudative pleural effusions (according to Light's criteria[23]) of known cause, multiple previous thoracenteses without substantial chest discomfort, and no clinical suspicion that the current effusion was due to anything other than the known underlying cause; any disease or disorder that would interfere with the safe completion of the study (eg, coagulopathy or hemodynamic instability) at the discretion of the person doing the procedure; and pleural effusion smaller than expected based on bedside ultrasonography or with multiple loculations on ultrasound scans before the procedure.

The study was approved by the institutional review boards of the two study institutions (Vanderbilt University Medical Center, 151492; Johns Hopkins Hospital, 00119664). All patients provided written informed consent.

Randomisation and masking

We randomly assigned patients 1:1 to receive thoracentesis guided by symptoms alone (control) or symptom plus manometry. The sequence of group assignments was generated by computer, using permuted blocks of four and six and stratified by institution. Treatment assignments were provided in sealed opaque envelopes prepared by a research assistant (LR) who assisted with data management but not enrolment decisions.

Patients were unaware of study group allocation. Investigators showed all patients a manometer and told them that there would be regular brief pauses in drainage regardless of whether or not the manometer was being used. A thoracentesis catheter was introduced in the posterior hemithorax of a seated patient and a manometer attached to the in-line end of the catheter near the patient's skin such that they could not see whether the manometer was being used. To maintain masking of study group during the procedure, measurements of pleural pressure were not reported verbally.

Procedures

All patients underwent thoracic ultrasonography to identify the optimum catheter placement area, where local infiltration of plain 1% lidocaine was administered before a 5, 6, or 8 F over-needle-style catheter (Safe-T-Centesis, BD, Franklin Lakes, NJ, USA or Arrow-Clarke, Teleflex, Morrisville, NC, USA) was placed. The procedure was done with the standard sterile technique. Complete evacuation of pleural fluid via manual aspiration with a 60 mL syringe was attempted in all patients. Drainage was paused for 5–10 s per 200 mL fluid drained for the first 1 L, then per every 100 mL thereafter. During each pause, patients was asked to indicate his or her degree of chest discomfort on a 100 mm visual analogue scale (VAS).[23,24]

In the manometry group, end-expiratory pleural pressure was measured during normal tidal breathing with a validated single-use digital manometer (Compass, Centurion Medical Products, Williamston, MI, USA) positioned in line between the catheter and drainage tubing.[13] Pleural pressure was measured immediately after intrapleural placement of the catheter, during drainage pauses, and just before catheter removal. For each measurement, to account for variation, we observed several tidal respiratory cycles and manually recorded the most frequent end-expiratory pressure.

In both treatment groups, drainage was terminated before complete effusion evacuation if patients experienced persistent chest discomfort consistent with excessively negative pleural pressure (felt in anterior chest, neck, or both and unimproved after catheter retraction to exclude diaphragm irritation), intractable cough, or procedural complications. Additionally, in the manometry group drainage was stopped if pleural pressure dropped to less than –20 cm H_2O or declined by more than 10 cm H_2O between two measurements to a value of –10 cm H_2O or lower. The pressure limit of –20 cm H_2O was chosen based on the historical definition of excessively negative pleural pressure and current practice guidelines.[7,11] The stop criterion for rapidly falling pleural pressure was adapted from the classic pleural elastance curves of Light and colleagues[3] and was included as an indicator trapped or entrapped lung and impending excessively negative pleural pressure.

Chest discomfort was measured on a 100 mm horizontal VAS with the labels "No discomfort at all" at 0 and "Worst possible discomfort" at 100 mm. This scoring technique is well-validated for patient-reported pain measurements[23,24] Two investigators assessed scores independently, and scoring disagreements could be arbitrated by a third investigator (RJL, LR, ADL, and LY). VAS scoring was done before the procedure, just after catheter placement, during all drainage pauses, and after drainage was stopped but before catheter removal. We also collected VAS scores for overall chest discomfort from the start of procedure to 5 min and 15 min after the procedure and for breathlessness before and 15 min after completion of the procedure.[25,26]

Procedures were timed from catheter insertion to removal. Bedside ultrasonography was done immediately after the procedure to assess the degree of residual effusion. Chest x-rays were done within 1 h of procedure completion to check for pleural apposition, and were assessed for pneumothorax and re-expansion pulmonary oedema by a chest radiologist unaware of study group allocation.

Outcomes

The primary outcome was patient-reported overall chest discomfort from the start to after the procedure, measured by patients 5 min after the end of drainage. We chose a discomfort-based primary outcome for three reasons: procedural discomfort is a clinically relevant and patient-centred outcome; prospective data suggest that manometry does not prevent re-expansion pulmonary oedema or pneumothorax[5,14,27] but its effect on chest discomfort has not been prospectively investigated; and re-expansion pulmonary oedema and pneumothorax complicate therapeutic thoracentesis with far less frequency than chest discomfort.

Secondary outcomes were overall chest discomfort from the start to 15 min after completion of the procedure, change in discomfort scores between the start and end of the procedure, trend in discomfort scores by effusion volume drained, change in breathlessness from the start and to 15 min after the end of the procedure, procedure duration, effusion volume drained, and frequency of complete lung re-expansion after the procedure (shown

by scant remaining pleural fluid on ultrasonography and pleural apposition on chest x-ray).

Statistical analysis

Based on baseline VAS chest pain scores reported in the TIME II trial,[25] and the previously reported minimum clinically important difference in VAS pain scores of 13 mm,[23] a two-sample *t* test was used to determine that a sample size of 128 patients (64 in each group) would provide 80% power to detect a 15 mm decrease in VAS score for chest discomfort (SD 30 mm) with probability of a type I error set at $\alpha=0\cdot05$.

All analyses were done with R version 3.3.1. Statistical analysis proceeded according to a prespecified analysis plan. Analyses were done by modified intention to treat (ie, including all patients with any procedure or outcome data). Descriptive statistics included means and SDs for continuous variables, percentages and frequencies for categorical variables, and an investigation for outliers. We assumed normality and homoscedasticity for statistical analyses. For comparisons between groups we used the *t* test for continuous variables and χ^2 test for categorical variables. Linear regression was employed to assess differences in chest discomfort and breathlessness scores between groups, which are reported as mean differences and 95% CIs. To account for the dependence of repeated measurements, we applied a linear model with generalised least squares (a mixed model with random intercept) with the AR1 correlation structure in R to assess the trends of discomfort scores during the procedure.

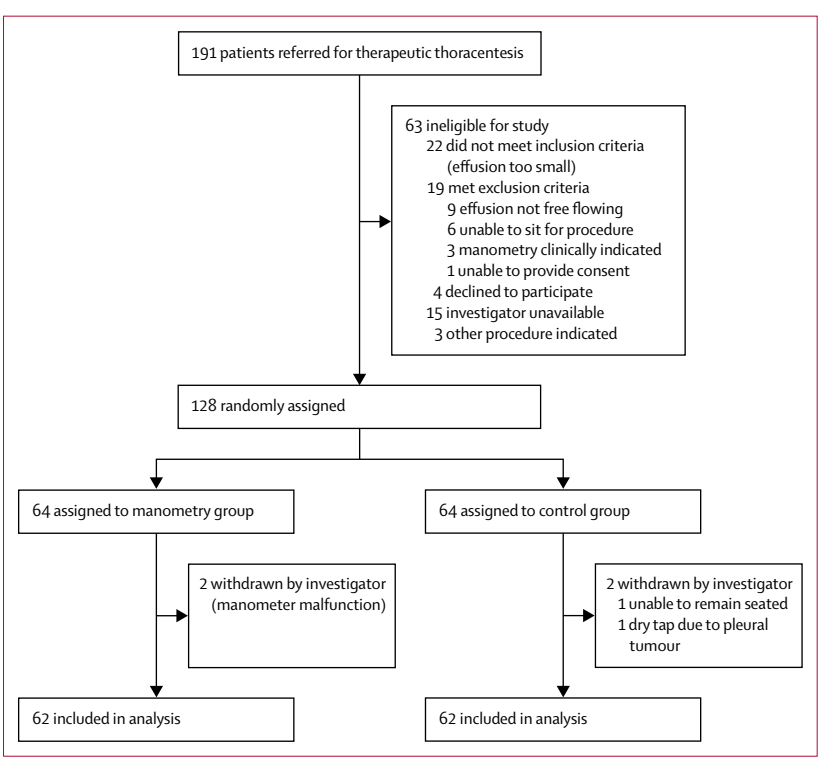

Figure 1: **Trial profile**

We did two prespecified subanalyses: a subgroup analysis of the primary outcome in effusions determined to be exudative by Light's criteria,[28] and trends in VAS chest discomfort scores in patients with less than or equal to 1·5 L fluid drained. The hypothesis for the first subanalysis was that exudates would be more likely than transudates to alter pleural elastance and, therefore, make it impossible to develop excessively negative pleural pressure, meaning that patients with exudates might benefit more from manometry. The second subanalysis was done because the British Thoracic Society guidelines[11] suggest that no more than 1·5 L fluid should be aspirated at one time to keep the risk of negative-pressure-related complications to a minimum, but a study has shown that greater volumes can be aspirated safely when manometry is used.[3,5] Assuming that both are true, a significant reduction in chest discomfort in the manometry group could conceivably be driven by patients in whom very large volumes were aspirated, and this analysis would address this potentially confounding effect.

A data monitoring committee did not oversee this study because both approaches to therapeutic thoracentesis are standard and represent minimum study-related risk to patients. This trial is registered with clinicaltrials.gov, number NCT02677883.

Role of the funding source

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 Sept 8, 2017, 191 patients referred for therapeutic thoracentesis were screened. 128 patients were eligible and randomly assigned treatment (figure 1). Four patients were excluded after being randomly assigned but before undergoing the thoracentesis procedure (figure 1). The final analysis included 62 patients in each group with complete primary and secondary outcome data.

Patients were well matched at baseline (table 1). The most common comorbidity was malignant disease (78 [63%] patients), and 31 (25%) of 124 effusions were known to be due to malignancy before thoracentesis (table 1). Average chest discomfort and breathlessness on the day of thoracentesis before the procedure were similar in the two groups (table 2).

The primary outcome of overall procedural chest discomfort rated at 5 min after the procedure did not significantly differ between the control and manometry groups (mean difference in VAS scores 2·4 mm, 95% CI −5·7 to 10·5, p=0·56; figure 2). After adjustment for institution, the results remained similar (2·5 mm, 95% CI −5·4 to 10·5, p=0·53). Overall procedural discomfort in patients with effusions determined to be

	Control (n=62)	Manometry (n=62)
Age (years)	64·7 (12·3)	66·8 (11·8)
Men	31 (50%)	33 (53%)
Women	31 (50%)	29 (47%)
Procedure setting		
Outpatient	33 (53%)	39 (63%)
Emergency department	1 (2%)	1 (2%)
Inpatient		
Regular ward	24 (39%)	21 (34%)
Intensive-care unit	4 (6%)	1 (2%)
Smoking status		
Current	0	1 (2%)
Former	37 (60%)	35 (56%)
Never	25 (40%)	26 (42%)
Previous thoracentesis	35 (56%)	24 (39%)
Severe chest discomfort	9 (15%)	17 (28%)
Regular opiate use	16 (26%)	19 (31%)
Known cause of effusion		
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 mean (SD) or n (%). *Other causes were fibrosing mediastinitis (n=1), post-transplant fibrinothorax with entrapment physiology (n=1), and non-specific pleuritis (n=1).

Table 1: **Baseline characteristics**

	Mean (SD) VAS score		Mean difference (95% CI)	p value
	Control (n=62)	Manometry (n=62)		
Before procedure*				
Average chest discomfort	26·2 (27·9)	28·6 (30·9)	2·5 (–8·0 to 12·9)	0·64
Average breathlessness	37·6 (25·7)	43·3 (27·4)	5·7 (–3·8 to 15·1)	0·24
During procedure				
Chest discomfort				
Catheter placement	18·1 (20·3)	18·2 (20·6)	0·1 (–7·2 to 7·4)	0·98
Catheter removal	30·1 (24·3)	26·4 (23·8)	–3·7 (–12·3 to 4·9)	0·40
Change in VAS discomfort from open to close	3·9 (29·7)	-2·3 (36·5)	–6·2 (–18·0 to 5·7)	0·31
After procedure				
Overall discomfort				
At 5 min†	23·0 (21·2)	25·4 (24·0)	2·4 (–5·7 to 10·5)	0·56
At 15 min	22·6 (18·5)	22·3 (19·9)	–0·3 (–7·2 to 6·5)	0·92
Breathlessness at 15 min	18·1 (18·0)	17·0 (20·1)	–1·1 (–7·9 to 5·7)	0·75
Change in VAS breathlessness at 15 min compared with before procedure	–20·1 (25·8)	–26·2 (31·8)	–6·1 (–16·5 to 4·3)	0·25

VAS=visual analogue scale. *On the day of the procedure. †Primary outcome measure.

Table 2: **Discomfort and breathlessness**

exudative did not differ between groups (mean difference in VAS scores –5·1 mm, 95% CI –14·2 to 3·9, p=0·26).

We found no significant differences between the control and manometry groups for any of the secondary outcome measures (table 2, figures 2, 3). The trend in VAS chest discomfort scores excluding volumes removed in excess of 1·5 L also did not differ between groups ($p_{interaction}$=0·10). A post-hoc comparison of the primary outcome among patients with previous painful thoracentesis revealed no difference between groups (mean VAS score 27·3 [23·1] mm in the control group *vs* 24·6 [21·1] mm in the manometry group, p=0·73).

Effusion drainage was halted after meeting a pleural pressure stop criterion in 13 (21%) of 62 patients in the manometry group (table 3). Drainage was discontinued for chest discomfort in similar numbers of patients in the two groups, and procedure duration, volume drained, and rate of complete lung re-expansion did not differ significantly (table 3, figure 4). The cause of effusion was established in 107 (86%) patients (table 4).

Six (10%) of 62 patients in the control group had pneumothorax ex vacuo evident on chest x-ray after the procedure. No patients in the manometry group developed pneumothorax, representing a significant difference between groups (p=0·01). No patient with pneumothorax had symptoms or needed intervention. No other complications occurred in either group. 16 (22%) of 72 ambulatory patients did not attend for chest radiography after the procedure (seven in the control group and nine in the manometry group).

Discussion

In this multicentre single-blind randomised controlled trial, we assessed patient-centred clinical outcomes during therapeutic thoracentesis for large pleural effusions. Our data suggest that routine use of manometry during thoracentesis will not reduce procedural chest discomfort or affect breathlessness and, therefore, does not improve patients' comfort. Additionally, we noted no serious complications in the control group. These data, alongside those from previous prospective studies suggesting that manometry does not prevent re-expansion pulmonary oedema or pneumothorax, lead to questions about the usefulness of pleural manometry.

Previous studies have identified associations between excessively negative pleural pressure and re-expansion pulmonary oedema, pneumothorax ex vacuo, and chest discomfort.[3,5–9] However, not all patients with excessively negative pleural pressure during therapeutic thoracentesis have chest discomfort.[6] This finding, along with the rarity of serious complications if aspiration of very large effusion volumes in a single procedure are avoided,

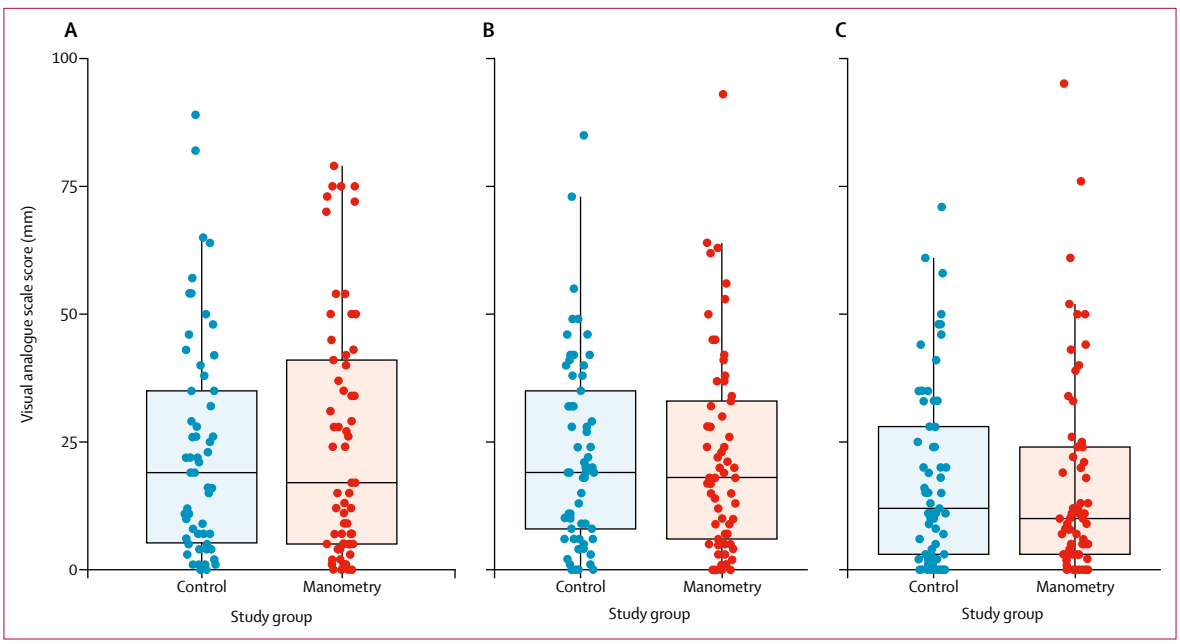

Figure 2: **Comparison of overall procedural discomfort and breathlessness between the control and manometry groups**
(A) Overall chest discomfort from the start to 5 min after completion of thoracentesis. (B) Overall chest discomfort from the start to 15 min after completion of thoracentesis. (C) Breathlessness from before to 15 min after completion of thoracentesis.

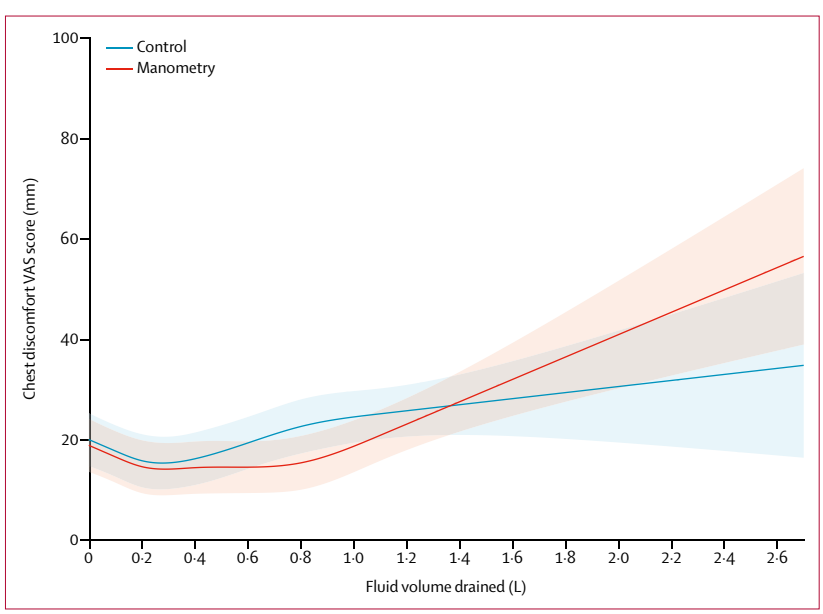

Figure 3: **Trend in chest discomfort VAS scores per volume of fluid aspirated**
Data are mean VAS scores and 95% CIs. VAS=visual analogue scale.

support the recommendation that no more than 1·5 L be drained in one procedure.[6,11,29] Advocates of manometric pleural monitoring during large volume thoracentesis note that asymptomatic excessively negative pleural pressure can be detected, which they suggest allows aspirations exceeding recommendations to be safely achieved.[5–7,12] Uptake of manometry has been widespread; many studies of pleural manometry have been reported in the past decade, manometry education sessions are provided at most international pulmonary conferences and pleural courses, and several ongoing clinical trials are addressing the ability of manometry to predict clinically meaningful endpoints (NCT03319186, NCT02805062, and NCT02192138).

Monitoring with manometry during thoracentesis, however, has not been shown to protect against re-expansion pulmonary oedema, pneumothorax ex vacuo, or chest discomfort.[5,10,14,27] Re-expansion pulmonary oedema is a rare complication that was independent of pleural pressure, pleural elastance, and volume of aspirated effusion in a large prospective series.[5] Two earlier series, one retrospective[14] and one prospective,[27] found pneumothorax after eight (4%) of 192 and nine (16%) of 57 procedures, despite pleural pressure stop criteria of –25 cm H_2O and –20 cm H_2O measured by manometry. In most patients, pneumothorax occurred when non-expandable lung was not suspected before the procedure. A large retrospective series also showed no decrease in chest discomfort after thoracentesis when pleural manometry was used compared with patients who underwent procedures without manometry.[10]

Our trial provides robust evidence that supports previous findings of no protection against important pressure-related complications with the use of manometry during therapeutic pleural aspiration. The lack of protection against chest discomfort with manometry could have several explanations. First, chest discomfort seems to be inconsistently associated with excessively

negative pleural pressure. Feller-Kopman and colleagues[6] found in a large prospective series of 169 patients that only four (22%) of 18 patients who developed chest discomfort indicative of excessively negative pleural pressure and 12 (9%) 140 who had no symptoms had pressures greater than –20 cm H_2O. This observation suggests that pleural pressure thresholds for chest discomfort vary between individuals. Heidecker and colleagues,[14] found that manometry did not mitigate the risk of pneumothorax ex vacuo and hypothesised that stress exerted on visceral pleura could be non-uniform due to regional variability in pleural elastance, which might also explain the poor correlation between pain and excessively negative pressure. Second, measurements of pleural pressure are obtained during brief drainage interruptions, which means that for substantial periods pressure is not measured, during which acute changes on pleural pressure might go unnoticed. Third, the use of a manometer in this study might have emboldened the operators to continue drainage despite the patient's symptoms if pleural pressure was otherwise reassuring; we were unable to mask operators to the study group. Scores for overall procedural discomfort were higher in the manometry group, although not significantly so, and in patients from whom more than 1·5 L effusion was drained, there was a trend towards more rapidly increasing chest discomfort VAS scores than in the control group. Only a small number of patients, however, had very large volumes of effusion aspirated, which limits the ability to draw any firm conclusions.

Of principal importance in interpreting the negative results of this trial is whether they represent a true non-difference between symptom-guided and manometry-guided thoracentesis (type II error). This study was powered to detect a clinically meaningful difference in discomfort based on previous investigations (superiority design), met recruitment targets, had no baseline differences between groups, had very few dropouts after randomisation (and all were due to technical issues), and had complete outcome data on 100% of patients who underwent thoracentesis. Variability of the primary outcome did not exceed the assumed variability used in the power calculation (overall SD 22·6 compared with the assumed SD of 30). Multiple analyses of chest discomfort data beyond the primary outcome, including change in discomfort from before to after thoracentesis, trend in discomfort during the procedure, and outcomes among patients most at risk of excessively negative pleural pressure, also showed no differences between groups. Finally, among 191 screened patients, 41 (21%) were excluded before randomisation (22 who did not meet inclusion criteria and 19 who met exclusion criteria), which is quite low and enhances the external applicability of our findings. We acknowledge that two secondary outcomes—change in VAS chest discomfort score from before to the end of drainage and change in breathlessness from before to 15 min after completion of the procedure—involve baseline scores obtained after random assignment that, theoretically, are at risk of bias resulting from allocation. It seems unlikely, however, that our results were affected by this bias because patients were masked to study group. The primary outcome, the other secondary outcomes, and the prespecified subanalyses were unaffected.

The frequency of pneumothorax ex vacuo was significantly greater in the control group than in the manometry group. Pneumothorax ex vacuo is a consequence of excessively negative pressure resulting in pressure equilibration by air entry into the pleural space, either from a small visceral pleural tear or irruption of air

	Control (n=62)	Manometry (n=62)	Mean difference	p value
Volume drained (mL)	1087 (453)	1074 (486)	–13·9 (95% CI –180·9 to 153·2)	0·81
Thoracentesis duration (min)	14·9 (5·2)	16·4 (6·3)	1·5 (95% CI –0·6 to 3·5)	0·34
Drainage stopped				
Stopped spontaneously	32 (52%)	25 (40%)	χ^2=0	0·97
Chest discomfort	22 (35%)	21 (34%)	χ^2=0·66	0·42
Intractable cough	7 (11%)	2 (3%)	χ^2=1·89	0·17
Pleural pressure fell to less than –20 cm H_2O	NA	9 (15%)	NC	NC
Rapid fall in pleural pressure†	NA	4 (6%)	NC	NC
Aspiration of air	1 (2%)	0	NC	NC
Vagal episode	0	1 (2%)	NC	NC
Complication	6 (10%)	0	χ^2=6·31	0·01
Pneumothorax ex vacuo	6 (10%)	0	χ^2=6·31	0·01
Residual post-procedure effusion	25 (40%)	25 (40%)	χ^2=0·01	0·94
Post-procedure chest x-ray not done	7 (11%)	9 (15%)	χ^2=0·29	0·59

Data are n (%) or mean (SD). NA=not applicable. NC=not calculable. *Drop of >10 cm H2O between two measurements to a value ≤–10 cm H2O.

Table 3: **Procedure data**

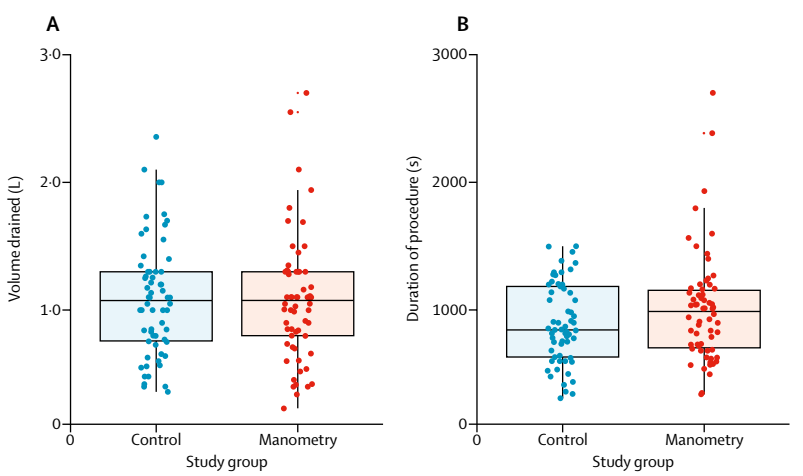

Figure 4: **Comparison of volume drained and procedure duration between the control and manometry groups**
(A) Volume drained. (B) Duration of procedure from placement to removal of catheter.

	Control (n=62)	Manometry (n=62)
Exudate*	38 (61%)	48 (77%)
Transudate*	14 (23%)	8 (13%)
Effusion cause		
Malignant	26 (48%)	35 (66%)
Heart failure	7 (13%)	4 (8%)
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%)

*Analysis not done in effusions from ten control and six manometry patients. †Other causes were other volume overload, fibrosing mediastinitis, granulomatous foreign body reaction, peritoneal dialysis-related, acute histoplasmosis, paramalignant inflammatory exudate, eosinophilic pleuritic effusion, fibrinothorax, splenic infarct, pleural amyloidosis, lung transplant acute rejection, haemothorax after placement of an implantable cardioverter defibrillator, immunotherapy side-effect, non-specific pleuritis confirmed by pleural biopsy, and ventriculopleural shunt malfunction of cerebrospinal fluid leak (all n=1).

Table 4: **Causes of effusion**

via the catheter tract. Pneumothorax ex vacuo is typically asymptomatic (in fact, intentionally allowing air entrainment via the catheter often improves chest discomfort due to excessively negative pleural pressure) and is not thought to represent a complication of thoracentesis, but rather a demonstration of the underlying abnormal pleural physiology for which no therapeutic intervention is needed or indicated. Furthermore, because more than 10% of patients in this study (11% in the control group and 15% in the manometry group) did not attend chest radiography after thoracentesis, the validity of our finding cannot be guaranteed. Therefore, although manometry might have prevented some cases of pneumothorax ex vacuo in our patients, diagnosing abnormal pleural elastance by manometry rather than postprocedure chest radiography seems clinically advantageous only in individuals who intend to travel by air shortly after their procedure.

Although we found no benefit with routine use of pleural manometry, we note that it is clearly useful in specific clinical circumstances. Pleural manometry elucidates pleural elastance curves, facilitating the diagnosis of trapped or entrapped lung, and might predict the success of chemical pleurodesis and the likelihood of spontaneous pleurodesis with an indwelling pleural catheter and, therefore, inform the choice of treatments for the palliative management of a recurrent symptomatic effusion.[30,31] In a patient in whom trapped or entrapped lung is strongly suspected before thoracentesis or in whom pleurodesis is being considered, pleural manometry might provide crucial insight into the underlying pleural physiology with clinical implications.

This study has several limitations. First, it was not powered to detect differences between groups in the frequency of pneumothorax ex vacuo or re-expansion pulmonary oedema, of which the latter is the most clinically serious pressure-related complication of thoracentesis. Re-expansion pulmonary oedema is, however, rare, and instead we chose to power the study to assess differences in chest discomfort, which occurs frequently and is an important patient-centred outcome. Second, pleural pressure could only be accurately measured when fluid aspiration was paused. Continuous pleural manometry during fluid aspiration might allow operators to see abrupt changes in pleural elastance sooner. However, devices that enable continuous pleural manometry are not available for routine clinical use and, therefore, we used the standard approach of using a validated single-use digital manometer. Future comparative studies using continuous manometry might be useful. Third, this was not a study of very-large-volume thoracentesis (>1·5 L), for which manometry might offer more benefit. Nevertheless, among the few patients who had more than 1·5 L effusion drained, there was a trend towards more chest discomfort in the manometry group than in the control, which argues against a benefit of manometry in this subgroup. Finally, the use of baseline VAS scores after allocation could have led to bias, but we believe that masking of study group allocation prevented any effect on the two implicated secondary outcomes.

Data taken to support the use of routine monitoring with pleural manometry during therapeutic thoracentesis indicate that some patients who develop excessively negative pleural pressure are asymptomatic and that volumes of fluid greater 1·5 L might be safely aspirated if pleural pressure is monitored.[3,6,7] Despite widespread routine use, no high-quality comparative studies have shown benefits with the use of manometry, and prospective and retrospective series have concluded that pleural manometry does not prevent re-expansion pulmonary oedema, pneumothorax, or chest discomfort.[5,10,14,25] Our randomised multicentre trial showed no reduction in pain or improvements in postintervention breathlessness, safety, volume drained, or speed of procedure. Our data, therefore, do not support the routine use of pleural manometry during large-volume therapeutic thoracentesis.

Contributors

RJL, JKP, CMM, OBR, NMR, FM conceived and designed the study. RJL, ADL, JKP, CMM, LR, CW, SV, TG, OBR, LY, FM collected data. RJL, ADL, HC, JTH, OBR, LY, IP, NMR, RWL, FM analysed and interpreted the data. RJL, OBR, NMR, FM drafted the Article. All authors participated in critical revisions of the paper 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.

Declaration of competing interests

We declare no competing interests.

Data sharing statement
Deidentified individual participant data will be available from publication for 5 years. A data dictionary and study protocol will be available from publication. Data will be shared with researchers who have methodologically sound proposals to achieve the aims set out. Proposals should be directed to fabien.maldonado@vumc.org. Data will be made available via a third-party Mendeley Data link.

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