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Association between terminal pleural elastance and radiographic lung re-expansion after therapeutic thoracentesis in patients with symptomatic pleural effusion: a post-hoc analysis of a randomised trial

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ABSTRACT

Objectives Recurrent symptomatic effusions can be durably managed with pleurodesis or placement of indwelling pleural catheters. Recent pleurodesis trials have largely relied on lung re-expansion on post-thoracentesis radiograph as an inclusion criterion rather than pleural elastance as determined by manometry, which is an important predictor of successful pleurodesis. We investigated the association between lung re-expansion on post-pleural drainage chest imaging and pleural physiology, with particular attention to pleural elastance over the final 200 mL aspirated.

Design Post-hoc analysis of a recent randomised trial.

Setting and participants Post-results analysis of 61 subjects at least 18 years old with symptomatic pleural effusions estimated to be at least of 0.5 L in volume allocated to manometry-guided therapeutic thoracentesis in a recent randomised trial conducted at two major university hospitals in the USA.

Primary outcome measures The primary outcome was concordance of radiographic with normal terminal pleural elastance over the final 200 mL aspirated. We label this terminal elastance 'visceral pleural recoil', or the tendency of the maximally expanded lung to withdraw from the chest wall.

Results Post-thoracentesis chest radiograph and thoracic ultrasound indicated successful lung re-expansion in 69% and 56% of cases, respectively. Despite successful radiographic lung re-expansion, visceral pleural recoil was abnormal in 71% of subjects expandable by radiograph and 77% expandable by ultrasound. The sensitivity and positive predictive value of radiographic lung re-expansion for normal visceral pleural recoil were 44% and 24%, respectively.

Conclusion Radiographic lung re-expansion by post-thoracentesis chest radiograph or thoracic ultrasound is a poor surrogate for normal terminal pleural elastance. Clinical management of patients with recurrent symptomatic pleural effusions guided by manometry rather than post-thoracentesis imaging might produce better outcomes, which should be investigated by future clinical trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study included pleural effusions of several different aetiologies, though the majority were malignant.
⇒ Both chest radiograph and thoracic ultrasound were used to assess for lung re-expansion.
⇒ Sixty-one patients analysed as part of the study cohort.
⇒ Intermittent, rather than continuous manometry, was employed during thoracentesis.

INTRODUCTION

Each year, 1.5 million pleural effusions are identified in the USA, with many requiring thoracentesis for diagnostic or therapeutic indications.[1] Many patients, most notably those with malignant pleural effusions, develop recurrent symptomatic effusions leading to a significant chronic symptomatic burden. In the USA, malignant pleural effusions account for 125 000 hospital admissions per year and $5 billion in patient charges per year.[2] There has been a shift towards outpatient management in patients with malignant pleural effusions.[3] More durable relief is often sought via pleurodesis, placement of an indwelling pleural catheter (IPC) allowing regular home drainage, or a combined strategy involving instillation of a chemical sclerosant via the IPC to achieve more rapid pleurodesis. Outpatient talc slurry administration via IPC and a daily IPC drainage strategy have been shown in recent randomised trials

to improve pleurodesis rates, though they remained underwhelmingly less than 50% in both.[4 5]

Successful pleurodesis requires direct apposition of the parietal and visceral pleural surfaces, meaning the lung must adequately re-expand after pleural fluid aspiration and maintain expansion long enough for pleurodesis to occur. Pleural elastance, defined as the change in pleural pressure per change in volume of pleural fluid, characterises the degree to which the lung resists re-expansion and is calculated by measuring pleural pressure using a manometer during pleural fluid aspiration. In a healthy individual, the pleural pressure at end of passive expiration is slightly negative, owing to a tendency for the lung to recoil away from the chest wall. Increased pleural elastance means there is a much greater tendency for visceral pleural recoil from the chest wall, which has been shown to hinder successful pleurodesis in prior studies. Elastance exceeding 14.5 or 19 cm H_2O/L has been used previously to define non-expandable lung and predict pleurodesis failure, including a recent study in which pleural elastance exceeding 14.5 H_2O/L measured after 0.5 L fluid aspiration was 93% sensitive and 100% specific for failed pleurodesis.[6 7]

Most recent pleurodesis trials have been conducted in patients with malignant pleural effusions and use radiographic re-expansion as a surrogate for acceptable pleural elastance rather than directly measuring via manometry. However, a recent report found poor correlation between radiographic re-expansion and normal pleural elastance in malignant pleural effusion,[8] raising the possibility that poor rates of pleurodesis in these recent trials might relate to a higher-than-anticipated incidence of abnormal pleural elastance. It is conceivable that terminal elastance, when the lung is near maximal inflation, will best correlate with pleurodesis success as it defines the tendency of the visceral pleura to recoil away from parietal pleura when the lung is in the state at which pleurodesis would occur. We report an analysis of terminal pleural elastance, which we term 'visceral pleural recoil' (VPR), in a cohort of patients who underwent thoracentesis with manometry as part of a recent randomised trial[9] and examine its relationship with radiographic lung re-expansion.

METHODS

We analysed manometric and radiographic data from 61 thoracenteses performed with manometry at two academic centres as part of a recent randomised trial, with methods fully described previously.[9] Briefly, patients were at least 18 years of age with an estimated pleural effusion volume of at least 500 mL based on radiographic criteria. Patients were excluded if radiographic features suggested the effusion was not free-flowing, were unable to maintain a seated position, had coagulopathy or other patient factors presenting more than minimal risk as determined by the operator, or were unable to consent for the study. Pleural pressure was measured using an inline single-use digital manometer (Compass, Centurion

Medical Products, Williamston, Michigan, USA) just after thoracentesis catheter placement, after manual syringe aspiration of every 100 mL over the first litre drained, then every 200 mL thereafter. Pleural pressure was recorded at end expiration during normal tidal breathing. The procedure was stopped when no further fluid could be aspirated, persistent cough or chest discomfort developed, or pleural pressure became lower than −20 cm H_2O. Bedside thoracic ultrasound examination and chest radiograph were performed after each procedure.

Lungs were considered re-expanded by ultrasound if no more than scant pleural fluid remained (per performing operator and confirmed by second investigator review of saved post-procedure ultrasound images) and by chest radiograph if there was ≥75% pleural apposition (confirmed by two investigators with discussion with a third investigator in the event of disagreement). This definition was chosen to align with inclusion criteria used in recent major trials of pleurodesis.[5] Elastance curves were plotted. VPR, defined as elastance over the final 200 mL aspirated, was calculated for each case. The very last pressure measurement was discarded if no pleural fluid was present on post-procedure thoracic ultrasound examination to avoid interference by local pleural deformation forces accompanying complete evacuation of pleural fluid. VPR >14.5 cm H_2O/L was considered abnormally elevated.[10]

Statistical analysis

The primary outcome was concordance of radiographic re-expansion post-procedure as assessed by chest radiograph and thoracic ultrasound with normal VPR. Descriptive statistics including mean VPR in those with radiographic re-expansion and non-expansion, overall rates of radiographic re-expansion and overall rates of abnormal VPR were calculated. The sensitivity, specificity, positive predictive value and negative predictive value of radiographic re-expansion for normal VPR were also calculated. Between-group comparisons of VPR were calculated using Student's t-tests. All analyses were performed using JASP V.0.15 (University of Amsterdam, The Netherlands).

Patient and public involvement

Patients and the public were not involved in the design or reporting of this post-hoc analysis of clinical trial data.

RESULTS

Manometry data from 61 patients randomised to manometry-guided large volume thoracentesis were analysed. Most were outpatient current or former smokers (see table 1). Most patients (36 of 61) had a comorbid active malignancy, and 35 of 61 (57%) effusions were ultimately determined to be malignant; other aetiologies included were heart failure (8%), post-cardiac surgery (5%), chylothorax (4%), could not be determined (15%) and other (each identified in a single subject, including

Table 1 Baseline subject characteristics

	Manometry (n=61)
Age (years)	66.7 (11.8)
Male gender	32 (52%)
Procedure setting	
Outpatient	38 (62%)
Emergency department	1 (2%)
Inpatient, regular ward	21 (34%)
Inpatient, intensive care unit	1 (2%)
Smoking status	
Current	1 (2%)
Former	34 (56%)
Never	26 (42%)
Prior thoracentesis	24 (39%)
With significant chest discomfort	17 (28%)
Regular opiate use	19 (31%)
Previously known effusion aetiology	
Malignant	18 (29%)
Chylous	1 (2%)
Hepatic hydrothorax	0
Other*	2 (3%)
Comorbidities	
Malignancy	39 (64%)
Heart failure	4 (6%)
Chronic kidney disease	3 (5%)
Cirrhosis	0

Data are n (%) or mean (SD).
*Other known effusion aetiologies pre-procedure: post-transplant fibrinothorax with entrapment physiology (1), non-specific pleuritis (1).

	Normal VPR (≤14.5)	High VPR (>14.5)	D/C Reason
Fully expandable	7 (88%)	14 (54%)	Dry
	1 (12%)	4 (15%)	Pain
	0	0	Cough
	0	0	Vagal
	0	8 (31%)	Ppl criterion
Nonexpandable	1 (10%)	3 (18%)	Dry
	7 (70%)	8 (47%)	Pain
	2 (20%)	0	Cough
	0	1 (6%)	Vagal
	0	5 (29%)	Ppl criterion

*percents are within quadrant

Figure 1 Reasons for thoracentesis discontinuation by VPR. D/C, discontinuation; Ppl, pleural pressure; VPR, visceral pleural recoil.

chronic kidney disease, other volume overload, pleural amyloidosis, acute lung transplant rejection, non-specific pleuritis confirmed by pleural biopsy, splenic infarct). Ten outpatients failed to report for post-procedure chest radiograph. Post-procedure thoracic ultrasound data were available for all cases. Reasons for thoracentesis discontinuation are detailed in figure 1.

Lung re-expansion was noted in 55.7% (34 of 61) of patients by ultrasound and 68.6% (35 of 51) by chest radiograph. In the 51 patients with adequate data to assess re-expansion by both ultrasound and chest radiograph, concordance was noted in 86% (44 of 51). VPR was abnormally elevated in 70.4% (44 of 61) of cases overall, including 71.4% (25 of 35) of subjects expandable by chest X-ray (CXR) and in 76.5% (26 of 34) expandable by ultrasound, not different than the rate of abnormal VPR in subjects with non-expandable lung by either imaging criteria (68.8%, p=0.85% and 63%, p=0.25, respectively, figure 2). There was no difference in mean VPR between expandable versus non-expandable lungs by CXR (28.6 ± 21.6 cm H_2O/L vs 34.1 ± 34.4, p=0.49). Likewise, there was no significant difference in VPR in expandable versus non-expandable lungs by ultrasound (34.4 ± 29.2 cm H_2O/L vs 33.4 ± 36.9, p=0.91). The sensitivity, specificity and positive predictive value of radiographic lung re-expansion for normal VPR were 44.4%, 39.5% and 23.5%, respectively (figure 3).

DISCUSSION

This analysis of manometry data from a recent multi-centre randomised trial demonstrates poor concordance between radiographic re-expansion and normal terminal elastance. Successful lung re-expansion demonstrated by post-pleural drainage imaging, with positive predictive value for normal VPR of only 24%, is a very poor surrogate for normal pleural physiology. This may have implications for the odds of successful pleurodesis, the choice of IPC versus pleurodesis in recurrent symptomatic pleural effusions and in the design of future pleurodesis trials. We focused on the terminal pleural elastance, or VPR, as this represents the tendency of the visceral pleural to recoil from the parietal pleura at maximal inflation, that is, where pleurodesis would occur.

Our findings confirm and expand on key findings reported by Chopra and colleagues in a retrospective series of 70 thoracenteses for malignant pleural effusions performed with pleural manometry, in which a substantial degree of discordance was found between degree of radiographic re-expansion by post-procedure chest radiograph and expected pleural elastance.[8] This included 28% of patients expandable by chest radiograph but with an elevated pleural elastance and 34% with non-expandable lung by radiograph but with normal pleural elastance. Analogously, our investigation finds 71% of patients expandable by imaging had abnormally elevated VPR and 37% non-expandable by imaging had normal VPR.

There are several important differences between these studies which might account for differences in the degree to which discordance was observed between post-procedure imaging and pleural elastance. Chopra and

Figure 2 Pleural elastance curves of expandable versus non-expandable lungs. VPR, visceral pleural recoil.

colleagues considered both overall pleural elastance and terminal elastance in patients with a biphasic elastance curve. In contrast, our series focused only on terminal elastance. Chopra and colleagues also used a more stringent definition of radiographic re-expansion than the present investigation, requiring 90% pleural apposition on post-thoracentesis chest radiograph compared with 75% in this study. The 75% threshold used in the current work was chosen to align with that used to define eligibility in recent major trials including IPC-PLUS,[5] but might have resulted in some patients being labelled radiographically expandable that would have been labelled non-expandable at the 90% apposition threshold used by Chopra and colleagues, with impact on the rates of observed radiographic–manometric discordance. Our study describes the relationship between expansion by post-procedure thoracic ultrasound and terminal elastance, not included in the prior work, which produced similar findings as chest radiograph data. Our study also included non-malignant effusions; although pleurodesis is most commonly performed in the setting of malignant effusion, it remains an option for select recurrent symptomatic non-malignan effusions and therefore our finding that substantial radiographic–manometric discordance

persists in a cohort including 43% benign effusions is noteworthy. Finally, we calculated the sensitivity, specificity, and positive predictive value of lung re-expansion for normal VPR as 44%, 40%, and 24%, respectively.

Our data suggest the assumption that ≥75% radiographic re-expansion implies normal pleural physiology is invalid. Further, use of post-procedure thoracic ultrasound or a more stringent radiographic definition of expandable, as Chopra and colleagues reported, also appears unable to accurately distinguish normal from abnormal pleural elastance. This, with additional recent and prior research suggesting abnormal elastance predicts poor pleurodesis outcomes,[6 7 11 12] has significant implications for both clinical care and future clinical trials of pleurodesis. Recent IPC and pleurodesis trials have demonstrated disappointingly low rates of pleurodesis success. In the TIME2 trial, there was a 29% pleurodesis failure rate in the talc arm and 49% in the IPC arm.[13] In the ASAP trial, pleurodesis failure occurred in 53% of patients with malignant pleural efuffison undergoing a more aggressive daily drainage strategy.[4] The IPC-PLUS trial reported a pleurodesis success rate of 43% at day 35 in the talc group.[5] These accumulating data suggest use of chemical sclerosants or more aggressive IPC drainage benefits some but not all. We hypothesise that imprecise patient selection by surrogate radiographic re-expansion criteria plays a significant role in high rates of pleurodesis failure in these trials and by extension clinical practice grounded in these trial results. Using manometry and calculating VPR to select patients for pleurodesis may improve patient selection for these procedures and lead to better clinical outcomes. This hypothesis should be tested in a future randomised controlled trial.

It is important to note that several prior studies have failed to demonstrate a significant correlation between routine use of pleural manometry and clinical outcomes such as re-expansion pulmonary oedema or chest discomfort, including the trial from which the data for this study originate.[9 14] Some authors note that other factors,

	Normal VPR (≤14.5)	High VPR (>14.5)	Total
Fully expandable	8 (23.5%)	26 (76.5%)	34
Nonexpandable	10 (37.0%)	17 (63%)	27
Total	18 (29.5%)	43 (70.5%)	61

Figure 3 Relationship of radiographic re-expandability to VPR. VPR, visceral pleural recoil.

including absolute values of pleural pressure and chest discomfort during thoracentesis, might be more accurate clinical guides during pleural fluid aspiration, and some have argued that manometry may lead to incorrect clinical decisions, is time-consuming and requires additional training.[14 15] However, given several trials have demonstrated high pleural elastance predicts pleurodesis failure, using pleural manometry to guide pleurodesis-related interventions may be warranted.[7 11] Indeed, a pilot study of one such protocol for elastance-directed malignant pleural effusion management has recently been published.[12]

Limitations of this study include the modest number of patients analysed (n=61). In addition, 10 of those patients did not return for their post-procedure chest radiograph, resulting in only 51 patients with complete radiographic data for analysis. Additionally, digital manometers were used with standard single-channel thoracentesis catheters which permitted only intermittent pleural pressure measurements. This is common practice, but continuous manometry has been developed and eliminates the 'blind time' between measurements which may allow for higher-fidelity elastance calculations.

CONCLUSION

Terminal pleural elastance, labelled visceral pleural recoil or VPR, correlates poorly with radiographic re-expansion by chest radiograph and thoracic ultrasound. VPR, as a direct measure of pleural pressure, more accurately identifies abnormal pleural physiology and the potential for sufficient durable pleural apposition, and consequently may be a better predictor of pleurodesis outcomes. A randomised controlled clinical trial should be conducted to examine VPR as a means of patient selection for pleurodesis.

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