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Pleural Manometry for the Characterization of Spontaneous and Tension Pneumothorax

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JHM IRB - eForm A – Protocol

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1. Abstract

A pneumothorax is defined as the presence of air within the pleural space. Patients can be asymptomatic, have mild dyspnea, or significant chest pain and dyspnea, and even hemodynamic instability in the case of a tension pneumothorax (TP).[1] The historical teaching for the cause of hemodynamic instability has been increased pressures within the pleural space causing a shift of the mediastinum, "kinking" of the inferior vena cava and a reduction in cardiac output. Expert guidelines define TP as when the intrapleural pressure (Ppl) is greater than atmospheric pressure for much of the respiratory cycle.[2] Therefore, it follows that Ppl in patients without tension remains below atmospheric pressure for much of the respiratory cycle. However, these manometric definitions remain controversial as Ppl in TP has never been measured and data on Ppl on hemodynamically stable patients is limited. There remains a gap in our current understanding of the pathophysiology of these disease processes. Exploring this unknown can be of clinical significance as pleural manometry is being employed in patients with pleural effusions to guide management. By using recently demonstrated pleural manometric techniques, this study aims to characterize the intrapleural pressures in patients with pneumothorax.

2. Objectives

Primary objectives:

1. Describe the intrapleural pressure throughout the respirator cycle in patients with pneumothorax.

Secondary objectives:

1. Demonstrate a relationship between initial intrapleural pressure and presence of persistent air leaks, need for prolonged chest tube drainages, pleurodesis, intrabronchial valve (IBV) placement, and/or video-assisted thorascopic surgery (VATS).

3. Background

The rate of hospitalization for spontaneous pneumothorax among people age 14 or older is approximately 227 per million.[3] Spontaneous pneumothorax in the absence of trauma can be further classified as primary spontaneous pneumothorax (PSP) or secondary spontaneous pneumothorax (SSP) based on the absence or presence of underlying structural lung disease, respectively. Though recent studies suggest that in some cases conservative management with close observation is an acceptable treatment, definitive evacuation remains a cornerstone of management for patients who are symptomatic or who have a large pneumothorax.[4] Intrapleural

air can be removed by either needle aspiration or introduction of a watersealed catheter into the pleural space. In the event of TP, emergent chest thoracostomy is preferred. In all cases, the goal of treatment remains to re-expand the affected lung, after which the catheter may be removed. If the visceral pleural defect is not healed after 5 days, it is deemed a persistent air leak. In these cases, the chest tube is maintained and more aggressive measures such as pleurodesis, placement of an IBV, or VATS are performed. Unfortunately, there is currently no method to predict which patients will require these more invasive procedures.

The lack of prognostic indicators is not the case in pleural effusions, however. Pleural manometry has been shown to be a useful tool in the management of patients with effusions. Doelken et al. described using an overdamped water manometer or an electronic transducer connected to a thoracentesis catheter for the direct measurement of Ppl with similar accuracy.[5] Traditionally, thoracenteses are aborted after onset of dyspnea or cough, all fluid is drained, or 1L of fluid has been removed. This 1L limit exists to avoid the feared complicated of reexpansion pulmonary edema. However, monitoring of Ppl during drainage and aborting the procedure once Ppl drops below -20 cmH_2O allows for safe drainage of often larger volumes.[6-7] Furthermore, Lan et al. demonstrated that Ppl could diagnose non-expandable lung and predict pleurodesis failure in patients with malignant effusion.[8] Lee et al, recently reported the use of a simple, in-line, digital manometer to measure Ppl in patients with pleural effusion.[9]

Routine use of pleural manometry in the evaluation and management of pneumothorax has not yet been adopted, likely due to the historical difficulty in obtaining measurements and the uncertain clinical benefit they provided. Harrejón et al. found that Ppl in spontaneous pneumothorax was greater in patients that required prolonged drainage.[10] These results were later supported by Kaneda et al who also demonstrated the practicality of measuring Ppl in pneumothorax. Their measurements required only up to 30 seconds by using an electronic manometer connected to an intrapleural catheter.[11] Still to date, Ppl in TP have yet to be reported.

4. Study Procedures

a. Patients admitted with spontaneous, iatrogenic, or tension pneumothorax referred to the section of Interventional Pulmonology will be recruited. Using standard sterile technique, a 14fr catheter will be inserted into the pleural space. An electronic manometer (Compass, Medline Industries, Inc.) will be connected in-line to the introducer needle and Ppl will be recorded for 3-5 respiratory cycles. The catheter will then remain in place per routine standards of practice. Outcome data of patients will be collected including indication for chest tube placement, duration of chest tube placement, need for pleurodesis, IBV, and referral for VATS. Patient data will be de-identified and stored on the SAFE (or equivalently password-protected/secure) desktop at each local institution

b. Johns Hopkins' Interventional Pulmonology (IP) research team will act as the lead coordinating site and Dr. Jeffrey Thiboutot will act as the overall study Principal Investigator. This group already has the contact information for planned non-JHU sites (names & emails/phone numbers for PI & study coordinators at each site). The IP research team will be responsible for ensuring each participating institution has IRB approval and up-to-date human subjects' compliance training.. The JHU IP research team will track IRB approval dates and store copies of each non-Hopkins affiliated site's documents (e.g. IRB approval letters, protocols, consent form templates) on a JHU-password-protected shared drive. Dates and protocol versions of materials sent to each site will also be recorded on a spreadsheet to ensure all sites are using the most current materials. If any local IRB requested edits (besides changing PI & institution

names/contact) are needed, those will be reviewed & approved by JHU's IP research team prior to submission.

c. De-identified data from all sites will be recorded into a JHU-hosted REDCap database. This database includes logging and data lock features to ensure accuracy and compliance. In addition, we will setup "data access groups" which will not only restrict sites to seeing only their own data, but also ensure data is organized sufficiently by site. Any relevant paper source documents will be kept in a locked cabinet at each institution's site. Scanned or electronic copies of source documents will be kept on a secured, password-protected institution-hosted drive (e.g. SAFE desktop for JHU).
d. Adverse Event and Protocol Deviation form will be included in the REDCap data entry forms for this study so that sites can easily report an events/deviations (these forms can be setup with email alerts to the JHU PI & research team for immediate notification). JHU's IP research team will determine if immediate local IRB notification is required or if events/deviations can be sent with annual progress reports.
e. No biospecimens will be collected.
f. Patients will be enrolled over the course of 1 year. The study will not impact length of hospitalization.
g. This is a nonblinded study.
h. Patients will continue to receive standard of care treatments. This study may delay catheter placement by mere seconds to accommodate for Ppl measurements, this delay is negligible and will not impact clinical outcomes as even in the case of tension the pleural air will be evacuated via the introducer needle.
i. This study does not include a placebo group.
j. Participant removal criteria include pneumothorax in which Ppl cannot be reliably measured within 30 seconds.
k. Participants removed from the study will continue to receive standard-of-care treatment.

l. JHU will conduct periodic monitoring of study data (e.g. comparing paper documents to REDCap entries and ensuring source documents like EPR reflect the same information recorded). If necessary, due to continued covid-19 restrictions, these monitoring visits may be performed via Zoom or MS Teams provided sites are able to share EPR screens and scanned paper documents for comparison.

5. Inclusion/Exclusion Criteria

Criteria for recruitment into this study include patients aged 18 or older admitted with clinical or radiographic evidence of new pneumothorax who are referred to Interventional Pulmonology for needle aspiration or tube thoracostomy. TP will be defined as a pneumothorax that results in mean arterial pressure <65 or systolic BP < 90.
Exclusion criteria include bilateral pneumothorax and pregnancy.

6. Drugs/ Substances/ Devices

No medical drugs, substances, or devices are being studied.

7. Study Statistics

a. Primary outcome variables: Inspiratory Ppl, Expiratory Ppl, and Mean Ppl.
b. Secondary outcome variables: Duration of chest tube placement, referral for pleurodesis, IBV placement, and/or referral for VATS.

c. Statistical plan: A student's t-test will be used to determine statistical significance in differences of Ppl between SP and TP. A student's t-test will be used to determine statistical significance in differences of Ppl in the secondary outcomes listed above. A sample size of 100 SP and 25 TP will be used based on expected incidence of disease in recruitment period. Enrollment will be competitive across all sites and the Coordinating Center (JHU's IP research team) will immediately alert PIs and Study Coordinators at the other sites if enrollment is paused or completed.
d. Early stopping rules: Consistent inability to measure Ppl in TP. If study is stopped early, all sites will immediately be notified by JHU's IP research team to terminate enrollment.

8. Risks

a. Enrolled patients will be only those already planned to receive chest tubes or needle aspiration; therefore, this study poses the same risks as these standard procedures. These risks include bleeding, infection, and local tissue damage. The study may delay evacuation of pneumothorax up to 30 seconds while Ppl are being recorded. These risks are independent of participation or non-participation in our study. No provisions are made for a research study-specific injury to the subject.
b. Risks will be mitigated by using the same standard of care for chest tube or needle aspiration. Overall, the delay in chest tube placements will be minimized and negligible by limiting measurement time to 30 seconds.
c. Any unanticipated problems will be reported to the local principal investigator and relayed to their local IRB. In addition, any adverse events or protocol deviations will be relayed to the study Principal Investigator and JHU research team (as lead coordinating site). The Principal Investigator, Co-Investigators, and Study Coordinators will meet as needed to review adverse effects and share information with all sites for reporting (if required by their local IRBs).
d. As participant health data will be collected, there is a risk to confidentiality breach. However, this is mitigated by de-identifying patient data and storing information on SAFE desktops and a JHU-hosted REDCap database.
e. The study does not pose financial risks to participants.

9. Benefits

There are no additional benefits to study participants, as those who do not wish to be involved in the study will still undergo standard of care pneumothorax evacuation. However, society will benefit from the increased pathophysiologic understanding of pneumothorax as results may guide future management.

10. Payment and Remuneration

This study offers no payment or renumeration to participants.

11. Costs

This study incurs no increased costs to the participants.

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