Non-invasive Positive Expiratory Pressure (nPEP) Device for TBM-associated Cough

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Abstract

We aim to determine if an expiratory resistance device that delivers non-invasive positive expiratory pressure (nPEP) will abort coughing paroxysms, reduce airway resistance and improve quality of life in patients with tracheobronchomalacia (TBM) who are not candidates for tracheal stenting.

Research Summary

Patients at Duke University Hospital referred to General Pulmonary and Interventional Pulmonary services for evaluation of severe, debilitating TBM-related cough and possible tracheal stenting, but who are not candidates for tracheal stenting due to their airway anatomy, will be given the nPEP device.

The nPEP device is assembled using mostly existing components with a history of respiratory applications. Specifically, a standard, adjustable (5-20 cm H_2O) positive end expiratory pressure (PEEP) valve manufactured for attachment to a manual resuscitator (commonly known as bag-valve-mask) device is connected to a flexible respiratory mask. Patients will be instructed by the study team as to how to use the nPEP device. The patients will trial the nPEP device immediately during their clinical encounter and will be given a mask to take home for 2 weeks.

Objectives-primary

The primary objective is to determine if use of the nPEP device can decrease cough severity and improve cough related quality of life (QOL).

Objectives-secondary

The secondary objective is to determine if use of the nPEP device improves airway physiology by decreasing proximal airway resistance as assessed by impulse oscillometry.

Objectives & hypothesis

Background and significance- Tracheobronchomalacia (TBM) is a condition in which the cartilage and/or other connective tissue in the trachea and bronchi are weak, resulting in collapse of those large airways during exhalation, especially forceful exhalation as occurs with coughing [1]. The airway collapse with coughing leads to further, ongoing coughing, possibly because mechanical stimulation of the mucosa during collapse may cause localized mucosal inflammation or stimulation of neural circuits that control cough.

TBM can cause a range of symptoms, including debilitating paroxysms of coughing, dyspnea, wheezing, and recurrent respiratory infections. In severe cases of TBM-related cough, patients experience morbidity including QOL impairment, social isolation, fatigue, loss of ability to work, recurrent hospital and even intensive care unit admissions.

The only curative treatment for TBM is a surgical procedure called tracheobronchoplasty, in which the chest is opened and the posterior membrane of the trachea and/or bronchi are surgically affixed to nearby structures, with or without implantation of surgical mesh [2]. This is an approximately 6 hour procedure performed only at specialized centers with appropriate expertise, and only after patients have undergone and proven to benefit from temporary implantation of a tracheal/bronchial stent in the region of collapse. Many patients are not candidates for tracheobronchoplasty itself due to medical comorbidities, prefer to avoid the

associated risks, or are not candidates for the required tracheal stenting due to trachea size or anatomy. These patients are left without a viable therapeutic option for their severe cough.

Continuous positive airway pressure (CPAP) devices have been reported to stop or prevent cough in TBM, presumably through the pneumatic stenting of large airways to maintain their patency during exhalation [3]. CPAP devices, however, are not labeled for this indication and their functional utility is very limited given size of the device, need for a power source, and multiple steps to don the equipment that are not easily completed while actively and uncontrollably coughing. We hypothesize that use of the nPEP device will result in decreased cough severity and improve cough quality of life by decreasing proximal airway resistance as assessed using impulse oscillometry.

Design

Ten subjects with chronic cough and TBM diagnosed by bronchoscopy or computed tomography (CT) scan will be recruited. Comorbid conditions that can cause chronic cough, such as asthma, COPD, and GERD, must be treated if present, for subjects to qualify. At the pre-baseline visit (V-1), after obtaining written informed consent, each subject will complete validated cough questionnaires to quantify their cough severity and cough-related QOL at baseline. The baseline visit (V1) will occur approximately two weeks later, after a run-in period to minimize observation bias related to the cough questionnaires. At V1, the cough questionnaires will be repeated and subjects' airway resistance and reactance will be measured with impulse oscillometry (IOS). Subjects will then be given the nPEP device by the study team and instructed on its use. Approximately two weeks after device delivery, at the follow-up visit (V2), cough questionnaires and IOS will be repeated and they will be asked for feedback regarding device design and user experience. Subjects may then be entered into a cohort for up to six additional months, during which there will be no study visits or procedures, but subjects may be contacted by investigators for additional narrative feedback on the device and its use.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Age ≥18 years
- Chronic cough for at least 8 weeks
- Visualization of ≥50% collapse of the trachea or mainstem bronchus on CT scan or bronchoscopy
- No upper or lower respiratory infection within 4 weeks
- Negative evaluation or treatment response for cough:
    - Asthma (negative spirometry or treatment with oral corticosteroids or ≥moderate dose of inhaled corticosteroids)
    - GERD (negative pH probe or treatment with proton pump inhibitor)
    - Upper airway disease (nasal or oral corticosteroids, antihistamines)
    - COPD (negative spirometry or treatment with triple-inhaled therapy [≥moderate dose of inhaled corticosteroids, long-acting muscarinic antagonist, and long-acting beta agonist])
- Having capacity to provide legal written informed consent

Exclusion Criteria:

- History of tracheobronchoplasty or chronic tracheal stenting
- Current tracheostomy
- History of external chest trauma
- History of mediastinal goiter

- Current smoking within 6 months
- Current use of ACE inhibitor within 6 weeks
- Primary parenchymal lung disease
- History of:
    - Sarcoidosis
    - Interstitial lung disease
    - Chronic mycobacterial infection
    - Lung cancer
    - Lung transplantation
- Unstable congestive heart failure
- History of spontaneous pneumothorax
- Other medical conditions that interfere with participation in the study

Screening
Potential subjects will be identified through two mechanisms:
1. Potential subjects can be referred to the investigators by their physicians
2. Study staff will identify qualifying subjects within the Duke electronic medical record (EMR) by searching for Duke patients with "tracheobronchomalacia" or its synonyms on their EMR problem list or in the text of a CT scan, discuss potential eligibility with each patient's physician or provider, and, if appropriate, ask the patient's physician to contact the patient regarding the study.

Up to 20 patients will be screened to achieve a total of 10 enrolled participants.

Study Interventions
After informed consent is obtained, study subjects will be given an nPEP device to use for two weeks. During this time participants will be asked to remain on their current medical regimen and not to make any dose changes or add new drugs, unless indicated by their primary care provider. Impulse oscillometry will be measured at V1 and 2 weeks later at V2 to assess effect of the nPEP device on airway physiology.

Description of assessments

a. Medical history: Should include all medically significant events prior to enrollment, including surgical procedures.
b. Physical exam (PE): Examination of the head, neck, chest, lungs, heart, abdomen, and extremities.
c. Impulse oscillometry: A noninvasive and rapid technique in which small pressure oscillations are applied through a mouthpiece to measure pulmonary resistance and reactance, which are graphically displayed.
d. Cough questionnaires: The Cough Specific Quality of Life Questionnaire (CQLQ), Leicester Cough Questionnaire (LCQ), and Cough Visual Analog Scale (Cough-VAS)

Study visits
Pre-baseline visit (V-1, -2 weeks [window -14 to -30 days])

- Review and sign informed consent
- Medical history
- Concomitant medication review
- Physical exam

- Cough questionnaires
    - Cough Specific Quality of Life Questionnaire (CQLQ)
    - Leicester Cough Questionnaire (LCQ)
    - Cough Visual Analog Scale (Cough-VAS)

Baseline visit (V1)

- Update medical history
- Concomitant medication review
- Impulse oscillometry
- Cough questionnaires
    - Cough Specific Quality of Life Questionnaire (CQLQ)
    - Leicester Cough Questionnaire (LCQ)
    - Cough Visual Analog Scale (Cough-VAS)
- Delivery of nPEP device and instruction on its use

Visit 2 (V2, +2 weeks [window +11 to +28 days])

- Update medical history
- Concomitant medication review
- Impulse oscillometry
- Cough questionnaires
    - Cough Specific Quality of Life Questionnaire (CQLQ)
    - Leicester Cough Questionnaire (LCQ)
    - Cough Visual Analog Scale (Cough-VAS)
- Exit interview re: subject experience and preferences regarding device design and use

Cohort for Ongoing Device Feedback

Subjects may be entered into a cohort at the time of study completion, continuing for six months. During this time, no study procedures are planned, but subjects may be contacted and asked to give further opinions regarding any changes in device design and function that may occur after they have completed the study. Each communication or contact that occurs while in this cohort will be voluntary, and subjects may decline or opt out of these communications at any time.

	Pre-baseline Visit -1 (V-1) Week -2 *window -14 to -30 days*	Baseline Visit 1 (V1) Day 0	Follow-up Visit 2 (V2) Week +2 *window +11 to +28 days*	Unscheduled visit
Consent	X			
Medical History	X			
Interval medical history		X	X	X
Concomitant medication review	X	X	X	X
PE	X			X*
IOS		X	X	
Cough/QOL Questionnaires: CQLQ LCQ C-VAS	X	X	X	X
Device demo and instructions		X		
Adverse event review			X	X
Exit interview			X	X*

*At investigator's discretion

Device Description

The nPEP device is intended as a single-patient, adjustable expiratory resistance device that provides positive pressure (5 to 20 cm H_2O) during expiration. The device is assembled using mostly existing components with a history of respiratory applications. Specifically, a standard, adjustable (5-20 cm H_2O) positive end expiratory pressure (PEEP) valve manufactured for attachment to a manual resuscitator (commonly known as bag-valve-mask) device is connected by a connector piece to a flexible respiratory mask. The connector piece contains a one-way valve to allow for inspiration through the mask. The user may adjust the resistance of the device by rotating the top of the PEEP valve, until the desired effect (cessation of coughing episodes) is obtained.

Fig. 1. nPEP device

Potential Benefits
Subjects may experience direct benefit from the device, including reduction in cough symptom severity and increase in cough-related QOL. There is also a potential scientific and societal benefit in that this pilot study will enhance understanding of whether or not an nPEP device could be further studied in order to present a non-invasive alternative to tracheobronchoplasty for patients with TBM-related cough.

Potential Risks
Potential risks related to participation in this pilot study include risk to privacy, risk of skin irritation from device components, and risk of pneumothorax from positive pressure during cough. Privacy risk will be minimized by securing all personal health information in a locked cabinet or office, entering data into an electronic database protected by the Duke University firewall, and using only de-identified data in data exports. Risk of skin irritation from the device is minimal, given that the mask used is an approved, off-the-shelf component used in other medical applications, and contact dermatitis is a mild condition typically relieved by withdrawal of the offending agent; a literature review has indicated that contact dermatitis is very rare following use of medical facemasks. There is a potential theoretical risk of pneumothorax. The expectation is that this would be a rare occurance as the pathophysiology of TBM is such that central airway resistance likely prevents the pressure set at the device from being transmitted to the distal small airways or lung parenchyma. The maximum resistance applied by the device (20 cm H_2O) remains very small in comparison to the intrathoracic pressure generated through coughing itself, which has been shown to be in the range of 136-340 cm H_2O [4]. Regardless, patients with personal history of prior pneumothorax or primary parenchymal lung disease will be excluded.

Costs to subject
There will be no additional costs to subjects of the study. Routine care will be charged to the participant or their insurance.

Subject reimbursement
Subjects will be reimbursed a total of $50 for study completion. This will be issued upon completion of Visit 2.

Data analysis
Statistical analyses include: a) descriptive and summary statistics of demographic and clinical variables, b) pre and post nPEP device treatment comparison of the primary and secondary outcomes (cough quality of life) using paired t-test for normally distributed and transformed data or Wilcoxon's Signed Rank test for non-parametric paired data, and c) pre and post nPEP device assessment of airway physiology as assessed by impulse oscillometry.

Data will be collected on paper forms and stored in each patient's research binder on a secure location. Data will be entered into Redcap for subsequent analysis.

Data and Safety Monitoring
In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research, all AE reports will be reported per the DUHS IRB policies.

Role of external personnel
No external personnel

References

1 Carden KA, Boiselle PM, Waltz DA, Ernst A. Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. Chest. 2005Mar;127(3):984-1005. PubMed PMID: 15764786.

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