Symptom Palliation in Advanced Diffuse Parenchymal Lung Disease
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Case Presentation

- 85 yo man with idiopathic pulmonary fibrosis (IPF) for 4 years presents with increasing dyspnea on exertion and increasing oxygen need progressing over preceding 6 months
  - He is only able to ambulate 20–30 feet before onset of severe dyspnea
  - He requires 6 lpm via nasal cannula to maintain an SaO2 of 92%
  - He experiences a frequent nocturnal cough which responds to oral opioids, though he dislikes the sedative side effect
  - Bronchodilators have been ineffective
  - He cites recent depression and endorses worsening anorexia

Physical Examination

- Slight, thin man with resting dyspnea and subtle anterior scalenus retraction
- Lung exam demonstrates diffuse “velcro” crackles
- Cardiac exam demonstrates resting tachycardia with a HR of 120 bpm
- Extremities are cachectic, with trace ankle edema. Clubbing is absent
- Neurologic exam is unremarkable
- CXR demonstrates chronic interstitial changes without new infiltrates
Clinical Discussion

- After confirming spirometric decline and ruling out reversible causes of worsening respiratory failure the clinician and patient agree symptoms are consistent with expected progression of IPF
- The patient, having expected his decline, opts for palliative care and admission to hospice

Clinical Questions

- What are the categories of restrictive lung diseases?
- What are the mechanics of restrictive lung disease and how do they relate to the symptoms?
- What is the management of dyspnea and cough in these patients?
- Is there a role for noninvasive mechanical ventilation for palliation of symptoms?

Categories of restrictive lung diseases

- Respiratory disease of extrapleural, pleural or parenchymal origin resulting in restriction of lung expansion
  - Parenchymal (Interstitial lung diseases (ILD))
    - Interstitial pneumonias
    - Idiopathic pulmonary fibrosis
    - Collagen vascular disease–associated interstitial lung disease
    - Pneumococcioses
  - Pleural
    - Pleural fibrosis/fibrothorax
    - Malignant pleural disease
- Extrapleural
  - Obesity
  - Neuromuscular disease
  - Thoracic deformity
Pulmonary function as it relates to chest restriction

- **Suggested Restriction**
  - Suggested by low Forced Vital Capacity (FVC)
  - Requires confirmatory measurement of Total Lung Capacity (TLC)
  - Restriction results from decreased pulmonary compliance
    - Intraparenchymal
    - Extrathoracic

Symptoms of Restrictive Lung Disease

- **Dyspnea**
  - Chronic
  - Episodic
  - Exertional
  - Crisis
- **Cough**
  - Dry
  - May be paroxysmal or persistent
  - May be compounded by other causes of chronic cough
    - GERD
    - Post-nasal drip
    - Upper airway cough syndrome
- **Chest pain (uncommon)**
  - Musculoskeletal splinting
  - Central chest pain
- **Wheezing (uncommon)**
  - Suggests concomitant airways disease

Mechanisms of dyspnea in the advanced parenchymal lung disease patient

- Dyspnea is principle symptom for most ILDs
- Mechanisms of dyspnea are poorly understood or studied
- Dyspnea occurs as ventilatory demand increases relative to capacity
- Hypoxemia alone does not account for level of dyspnea

Unitary concepts for dyspnea in parenchymal lung disease

- Central increased efferent motor output
- Mismatch between efferent output and afferent input from peripheral mechanoreceptors

Mechanics of dyspnea in restrictive lung disease

- Decreased inspiratory capacity and inspiratory reserve volume
- Constrained tidal volume/inspiratory capacity with increased respiratory drive
- Increased dead space ventilation
- Conscious awareness of dyspnea driving increased ventilation
- Neuromechanical uncoupling of voluntary and volitional respiratory drive
Assessment of dyspnea

- Triggers
  - Progression of the primary disease
  - Pain
  - Adequacy of oxygen therapy
  - Medications
- Duration
- Intensity
- Biopsychosocial assessment
  - Anxiety or depression
  - Sensation of imminent death
  - Caregiver/environment role

Mularski RA. Ann Am Thorac Soc. Vol. 10 2013: s98-s106

Borg Dyspnea Scale

- Adapted from a scale to rate perceived exertion
- Has a higher reproducibility than visual scales
- Allows prospective quantitation of dyspnea
- May facilitate assessment medication effectiveness
- Not explicitly validated in advanced lung disease


The “Dyspnea Crisis”

- Sustained and severe resting breathing discomfort

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Role of oxygen for dyspnea in advanced parenchymal lung disease

- **Oxygen therapy**
  - Hypoxemia is common to advanced end stage lung disease
  - Dyspnea may be improved in patients with resting hypoxemia by application of supplemental oxygen
  - Exertional dyspnea does improve with use of supplemental oxygen
  - Patients and family may have a psychological tie to supplemental oxygen


Opioids and control of respiration

- **Opioid receptors** are found throughout respiratory control centers
  - Brainstem, thalamus, cingulate cortex
    - Suppression of respiratory rhythm
  - Peripheral airway mechanoreceptors
  - Vagal afferents
  - Carotid body
    - Chemoreceptors
      - Suppression of hypoxic ventilatory response

Pattinson, KTS. British Journal of Anaesthesia 100(6): 747–758

Opioid therapy

- Therapeutic backbone for dyspnea management in these patients
- Opioid therapy should be individualized to patients based upon therapeutic response and co-management of pain
- Respiratory suppression from opioid therapy is likely overstated in this population
  - Of 11 studies, including arterial blood gas data, only 1 study demonstrated adverse effect on oxygenation (without concomitant increased pCO2 >40 mm Hg)
- Nebulized opioids are ineffective and should not be used
- Prevention of opioid–related obstipation is fundamental
Role of benzodiazepines for treatment of dyspnea is unclear

- Cochrane Meta-analysis
  - Few good studies
  - Review of 6 qualifying RCTs (patients receiving and not receiving opioid therapy)
    - No improvement in breathlessness in 5 of 6 studies
      - COPD
      - Cancer
      - IPF and ILDs have not been studied
      - Anxiety was not reduced
    - High rate of side effects
      - Somnolence
      - Dizziness
    - No change in pCO2 noted in qualifying studies

Simon, KT. Cochrane Database Syst Rev. 2010 Jan 20;(1)

Role of bronchodilators in advanced parenchymal lung disease

- Inhaled bronchodilators (BD) (i.e. albuterol, ipratropium) have little role in pure restrictive lung disease

- Adrenergic and anticholinergic side effects may increase dyspnea and cause symptomatic tachycardia

- Patients with concomitant obstructive lung disease (i.e. combined pulmonary fibrosis and emphysema) may benefit from BD therapy

- Treatment with BD should be individualized to the patient’s disease(s)

Adjunct therapies for dyspnea

- Pulmonary rehabilitation
  - Two RCTs demonstrating improved QoL w/ trend towards improvement on dyspnea questionnaires

- Oral corticosteroids
  - Single center and retrospective data suggesting improvement
  - Side effects significant

- Sildenafil
  - Weak to moderate evidence for improvement in exertional dyspnea

Noninvasive mechanical ventilation and palliation of dyspnea

- There is no data for the use of NIV in palliation of dyspnea in patients with ILD
- NIV may assist in overcoming high elastance/low compliance of restrictive lung diseases
- May have a role in management of acute exacerbation of ILD/IPF
  - Avoidance of intubation
  - Treatment of refractory hypoxemia
  

Action plan for crisis dyspnea

- Easy to implement care plan for dyspnea crisis
- Adaptable, individualized approach to symptom management
- Use a feedback analysis to augment the care plan for future crises

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Cough is common in parenchymal lung disease

- 73–86% of patients experience cough
- Cough frequency is increased during daytime
- Surveyed QOL is reduced in patients citing increased cough frequency

Mechanisms of cough in advanced interstitial lung disease

- Upregulation of sensory neurons within the lung
  - Increased sensitivity to inhaled irritants
- Small airways inflammatory change
- Concomitant causes of cough
  - Tobacco use
  - GERD
  - Allergic rhinitis/Post-nasal drip
  - Airway hyperresponsiveness


Goals of therapy for cough

- Minimize (if not eliminate) cough
- Minimize therapeutic side effects
- Identify and mitigate cough triggers
  - Dysphagia
  - Environment
- Identify and treat secondary causes of cough
  - Medication side effects
    - Bronchodilators
    - ACE inhibitors
    - GERD
  - Post-nasal drip
  - Airways diseases
  - Tobacco use
**Opioids for chronic cough**

- Meta-analysis of 11 studies of opioids vs. placebo demonstrated decreased cough and improved QoL by questionnaire
- Codeine is the most commonly studied opioid
- Effectiveness of codeine is extrapolated to other agents
  - Morphine
    - Low dose 5–10 mg q12h
  - Hydrocodone
  - Oxycodone
- Low dosage ceiling for effectiveness in cough


**Corticosteroids for cough in ILD**

- Cough may respond to corticosteroid therapy in steroid-responsive ILDs
  - Sarcoidosis
  - Hypersensitivity pneumonitis
  - Collagen-vascular disease associated ILD
- Corticosteroid therapy reduces sensitivity to substance P and capsaicin in IPF patients
  - Reduced cough in 6 patients
  - Prednisone therapy w/ azathioprine is linked to increased risk of death and adverse outcome in IPF patients
- Significant side effect burden


**Gabapentin**

- Ryan NM et al. Lancet 2012; 380:1583–89
  - Single center RCT
  - N=62
  - Gabapentin (titrated to 1800 mg/d) vs placebo X10 weeks
  - Statistically improved cough-specific QoL by Leicester Cough Questionnaire
  - Improvement of cough was not sustained after drug withdrawal
Thalidomide

  - Single center RCT (N=25)
  - Thalidomide 50–100 mg qHS X 12 wk vs placebo
  - Significant improvement in Cough QoL questionnaire and Visual analogue scale of cough
  - 3 fold increase in adverse events in treatment group
    - Constipation (36%)
    - Dizziness (27%)

Other Non-opioid therapy for cough

- Benzonatate
  - butylamine, chemically related to other ester local anesthetics such as procaine and tetracaine
  - Theoretically decreases sensitivity of lower airway mechanoreceptors
  - No RCTs exist comparing or demonstrating effectiveness on cough

- Dextromethorphan
  - Multiple receptor mechanism of action
  - Dissociative hallucinogenic side effects at higher doses
  - May have role in treatment of cough related to inhalation of particles
  - Trial comparing efficacy vs placebo in childrens’ cough showed no difference

- Expectorants
  - Generally not useful in cough caused by ILD

Summary

- Physiology of restrictive parenchymal lung disease drives symptoms
- Dyspnea is multifactorial
- Airway sensitivity and cough are increased in patients with advanced parenchymal lung disease
- Symptom management requires assessment and reassessment of symptoms
- Responsibly used opioid medications are critical backbone for management of dyspnea and cough in advanced ILDs