Respiratory Issues in Palliative Care: Dyspnea and Cough

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Palliation of Dyspnea

- Mechanisms of dyspnea
  - Treat reversible causes
  - Palliation of refractory dyspnea
Dyspnea

- Analogous to pain
  - “Dyspnea is whatever the patient says it is”
- Total dyspnea (total pain)
  - physical, psychological, interpersonal and existential dimensions
- Same areas of brain activated
- Breakthrough dyspnea (breakthrough pain)
  - common (80%), frequent (5-6 times per day), brief (5 min)
- Role of endorphins
Dyspnea

- Different than pain
  - More primal
  - Less well-characterized neuro-physiologically
Mechanisms of dyspnea

- Chemoreceptors (pH, pCO2, pO2)
- Mechanoreceptors (Stretch receptors)

- Brain cortex
- Medullary Respiratory Center

Davenport et al. REsp Physiol Neurobiol 2009;167:72-86

CHEST 2010;138(5):1196-1201;
Increased deadspace

Increased airway resistance

Decreased lung compliance

Resp muscle weakness

CHEST TIGHTNESS

Increased ventilatory demands

INCREASED WORK OF BREATHING

Reduced ability to respond to ventilatory needs

AIR HUNGER

Increased ventilatory demands

Reduced ability to respond to ventilatory needs

Emotion

Dyspnea

Mechanisms of dyspnea

- Treat reversible causes
  - Palliation of refractory dyspnea
Potentially reversible causes of dyspnea

- Airway obstruction
- COPD, asthma
  - ☑ Bronchodilators
  - ☑ Steroids
  - ± Antibiotics for bronchitis
  - ± Mucolytics
Potentially reversible causes of dyspnea

- Airway obstruction
  - COPD, asthma
- Endobronchial obstruction
  - Endoscopic interventions
    - Bronchoscopy
    - Laser debulking
    - Stenting
    - Palliative radiation
Potentially reversible causes of dyspnea

- Pleural effusion
  - Thoracentesis
    - Removal of 300-400 mL relieves dyspnea
  - Options for recurrence
    - Repeated thoracentesis
    - Pleural sclerosis (> 6 mos survival)
    - Indwelling pleural catheter
Potentially reversible causes of dyspnea

- Pneumothorax
  - Pleural catheter
  - Pleurodesis
Potentially reversible causes of dyspnea

- Pneumonia
  - Antibiotics
  - Bronchodilators
  - Steroids
Potentially reversible causes of dyspnea

- Pulmonary edema
- Diuretics
- Positive pressure support
  - CPAP / BiPAP
  - Invasive ventilation
Potentially reversible causes of dyspnea

- Anemia
Potentially reversible causes of dyspnea

- Airway obstruction
  - COPD, asthma
  - Endobronchial obstruction
- Pleural effusion
- Pneumothorax
- Pneumonia
- Pulmonary edema
- Anemia
Potentially treatable causes of dyspnea

- Ascites
- SVC syndrome
- Carcinomatous lymphangitis
- Radiation pneumonitis
- Pericardial effusion
Palliation of Dyspnea

- Mechanisms of dyspnea
- Treat reversible causes
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Palliation of Dyspnea

- Mechanisms of dyspnea
- Treat reversible causes
- Palliation of refractory dyspnea
Mechanoreceptors

Chemoreceptors (pH, pCO2, pO2)

Brain cortex (insula, cingulate gyrus, amygdala)

DYSPNEA

Opioids

Medullary Respiratory Center

Mechanoreceptors Stretch receptors

Brain cortex (insula, cingulate gyrus, amygdala)

DYSPNEA

Opioids

Mechanoreceptors Stretch receptors

Chemoreceptors (pH, pCO2, pO2)
Opioids for refractory dyspnea

- Systemic opioids (oral, iv, sc) found effective in systematic reviews & meta-analysis
  - Total 256 cancer patients
  - Small studies, some negative
  - Morphine & dihydrocodeine
  - No respiratory adverse effects

Viola et al. Support Care Cancer 2008; 16:329-337
Opioids for refractory dyspnea

Dosing opioids for dyspnea

- Double-blind, controlled, cross-over trial
- 48 opioid-naïve patients (42 with COPD) SOB at rest
- Received MS Contin 20 mg qday or placebo for 4 days, then cross-over to alternate (no washout)
- Dyspnea assessed by VAS
- Results
  - 10 withdrew during study, 4 due to opioids
  - MS Contin associated with less dyspnea (morning and night), better sleep, more constipation (despite laxatives)

Abernethy et al, BMJ 2003;327:523-8
Opioids for refractory dyspnea

Dosing opioids for dyspnea

- Phase II open-label dose increment study
- 83 opioid-naïve with severe dyspnea (45 COPD, 24 cancer, 10 ILD), followed for mean 142 days
- Received MS Contin 10 mg/day, increased by 10 mg qweek to max 30 mg/day
- Dyspnea assessed by VAS, goal 10% improvement

Currow et al, J Pain Symp Manage 2011; 42::388-99
Opioids for refractory dyspnea

83 opioid-naïve with refractory SOB
Morphine dose mean 16.5 mg, median 10 mg

52 with at least 10% improvement and no intolerable side-effects

24 with sustained-benefit at 3 months

Currow et al, J Pain Symp Manage 2011; 42::388-99
Opioids for refractory dyspnea

- **Safety**
  - Concerns from acute effects of opioids on opioid-naïve patients in acute care setting\(^1\)
  - Systematic review of opioids for dyspnea\(^2\)
    - No change in pO2 or pCO2
    - No evidence of respiratory compromise (RR, SpO2, or pCO2) with scheduled low-dose opioids
  - Endorsed by ACCP 2010 Consensus Statement\(^3\)

2. Jennings et al. Cochrane Database Sys Rev 2010(1) CD002066;
3. Mahler et al. CHEST 2010;137:674-691
Anxiolytics for refractory dyspnea

- No benefit of clorazepate, alprazolam or diazepam as single agents\(^1\)
- Modest improvement with midazolam added to morphine at end of life in cancer patients\(^2\)
- One study showing oral midazolam equal or better than oral morphine for SOB in 63 ambulatory cancer patients\(^3\)
  - Exclusions: COPD, CHF, severe renal or hepatic failure, hypoxemia
  - AE: Somnolence in 50%, not requiring d/c of meds

Non-opioids for refractory dyspnea

Nebulized furosemide

- Speculated mechanisms (animal and in-vitro)
  - protective effect again cholinergic, non-cholinergic and nonadrenergic contraction of smooth muscles
  - inhibition of cough reflex
  - preventing bronchoconstriction in asthma
  - possible indirect effect on airway epithelial nerve endings and stretch receptors

- Benefit in asthma patients
  - not better than bronchodilators

Non-opioids for refractory dyspnea

Nebulized furosemide in healthy volunteers

- 3 randomized placebo-controlled trials in healthy volunteers with induced air hunger
- trend towards reduced SOB by VAS ($p=.05$)
- rapid onset, short-duration (1 h)
- diuretic effect

Moosavi et al. Resp Phys Neurobiol 2007;156-1-8
Nishino et al. AJRCCM 2000; 161:1963-7
Minowa et al. Pulm Pharmacol Ther 2002;154:363-8
Non-opioids for refractory dyspnea

Nebulized furosemide in COPD

- one randomized placebo-controlled trial in 19 COPD patients using exercise testing
- improved SOB by VAS (9 mm, p=0.014)
- improved FEV1 and FVC

Ong et al. AJRCCM 2004;169:1028-1033
Non-opioids for refractory dyspnea

Nebulized furosemide in cancer

- Double-blind cross-over study in 7 advanced CA patients (5 lung CA) with SOB at rest (reported in Letter to Editor)
- Asthma excluded
- No significant difference in distress of breathing \( p=0.06 \) or difficulty breathing \( p=0.09 \) using VAS up to 2 hrs after neb treatment
- Trend for furosemide to worsen symptoms

Non-opioids for refractory dyspnea

Nebulized furosemide in cancer

- Double-blind cross-over study in 15 thoracic CA patients with refractory SOB at rest
  - excluded asthma, recent chemo or XRT, cardiac disease that would affect exercise
- Interventions
  - nebulized furosemide 40 mg, saline, or no treatment for 3 consecutive days
  - number reading test or arm exercise
- Assessments
  - dyspnea exertion scale
  - spirometry

Non-opioids for refractory dyspnea

Nebulized furosemide in cancer

- Results
  - no significant differences between duration of arm exercise or SOB at maximum exercise
  - fall in FEV1 (8%) after saline, 7% after furosemide
  - no difference in urine output, no adverse effects
  - changes in perceived SOB with nebulizer
    - 9 no improvement
    - 3 preferred saline
    - 1 preferred furosemide
    - 2 felt both equal

Therapies without proven benefit

Oxygen

- proven benefit on survival in severe chronically hypoxemic COPD
- more than 70% of physicians use for palliation of dyspnea
Therapies without proven benefit

Oxygen for dyspnea

- Systematic review > 8 RCTs (O2 vs air)
  - primary or met lung CA, heart failure (not COPD)
  - studies small, underpowered, rest vs exercise, high vs low flow O2
  - no consistent effect, but some patients may benefit (e.g. some hypoxemic terminally ill patients)

J Clin Oncol 2008; 26:2396-2404
Therapies without proven benefit

Oxygen for dyspnea in COPD

- systematic review of RCTs comparing oxygen and air in mildly hypoxemic and non-hypoxemic patients with COPD
- continuous but not “short-burst” oxygen improved dyspnea

Therapies without proven benefit

Oxygen for dyspnea in cancer

- randomized controlled cross-over study in non-hypoxemic advanced cancer
  - 33 patients with dyspnea at rest (or mild exertion) from cancer
  - O2 or air @ 5 LPM by NC
  - assessed DOE during 6 min walk
  - no difference in dyspnea or distance walked

Therapies without proven benefit

Oxygen for dyspnea in cancer

- randomized controlled cross-over study in non-hypoxemic advanced cancer
  - 51 patients with SOB at rest from cancer
  - O2 or air @ 4 LPM by NC for 15 min, 30 min washout, then cross-over
  - patients improved with both air and O2
  - no significant difference in dyspnea or preference (air vs O2)
  - no correlation between SpO2 and dyspnea

Philip et al. J Pain Symptom Manage 2006:32;541-50
Therapies without proven benefit

Oxygen for dyspnea in cancer

- international, multicenter, double-blind randomized trial of 239 patients with refractory dyspnea without hypoxemia
- gas @ 2 LPM provided at home by “concentrator”, advised to use > 15 h/d
- dyspnea improved after delivery of “concentrator” but was not associated with gas used
- most improvement within first 3 days
- patients with more severe SOB improved more with either gas

Abernethy et al, Lancet 2010;376:784-93
Oxygen for dyspnea in cancer

- possible benefit for SOB in cancer if hypoxemic
- only 40% of patients with advanced cancer and SOB are hypoxemic

Non-pharmacologic therapies

- Blowing air on face / in nose
  - cold air on face reduces induced dyspnea\(^1\)
  - randomized cross-over trial of handheld fan on face or leg for 5 min in 50 patients
    - significant decrease in dyspnea from air on face
    - persistence of effect after use of fan

Non-pharmacologic therapies

- **Blowing air on face / in nose**
  - Randomized controlled trial of use of fan in 70 (of 109) patients
  - Inclusions:
    - advanced lung cancer or COPD
    - SOB impacting daily life
  - Block randomized by disease
  - Fan vs “breathe easy” wristband
  - Primary outcome: use after 2 mos
  - Secondary outcomes:
    - Perceived helpfulness after 2 mos
    - Change in SOB after 2 mos

Bausewein et al. BMC Palliat Care 2010;9:22
Non-pharmacologic therapies

- Blowing air on face / in nose
  - Attrition over six months
    - 29% in fan group, 41% in wristband group
  - Two month results
    - 16/33 (48%) fan and 5/25 (20%) wristband using (p= 0.2)
    - No difference in Borg scores
  - Perception as positive experience
    - 13/38 (34%) fan users
    - 5/32 (16%) wristband users

Bausewein et al. BMC Palliat Care 2010;9:22
Non-pharmacologic therapies

- Blowing air on face / in nose
- Muscle strengthening (↓ ventilatory needs)
- Pursed lip breathing
- Chest-wall vibration
- Positional therapy
- Aids to support accessory muscles of respiration
- Acupuncture / acupressure
- Non-invasive ventilation
Non-pharmacologic therapies

- Acupuncture / acupressure
  - 47 cancer patients (lung and breast)
  - single treatment and placement of acupuncture studs for self treatment
  - daily true acupuncture associated with slightly worse SOB over one week

Non-pharmacologic therapies

Non-invasive ventilation

- Strong evidence for benefit in
  - acute resp failure in COPD exacerbation
  - hypoxic resp failure in immunocompromised
  - acute resp failure in cardiogenic pulmonary edema
- Observation studies suggesting benefit for neuromuscular diseases

Crit Care Med 2007;35:932-939
Non-pharmacologic therapies

Non-invasive ventilation

- Limited studies indicating reduced dyspnea in
  - acute resp failure from COPD
  - advanced cancer and resp failure
  - stable chronic resp failure from COPD

2. Eur Respir J 2007;30:293-306
Non-pharmacologic therapies

Non-invasive ventilation

- No studies comparing benefit to harm
- Potential for relief of dyspnea offset by discomfort from mask
- No studies comparing NPPV to opioids

2. Eur Respir J 2007;30:293-306
## Palliation of refractory dyspnea

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids, systemic</td>
<td>😊😊😊</td>
</tr>
<tr>
<td>Opioids, nebulized</td>
<td>😞</td>
</tr>
<tr>
<td>Inhaled furosemide</td>
<td>😐</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>😞</td>
</tr>
<tr>
<td>Oxygen - hypoxemic</td>
<td>😊😊</td>
</tr>
<tr>
<td>Oxygen - normoxemic</td>
<td>😐</td>
</tr>
<tr>
<td>Fan</td>
<td>😊😊</td>
</tr>
<tr>
<td>Pulmonary rehabilitation</td>
<td>😊😊</td>
</tr>
</tbody>
</table>

Palliation of Cough
Palliation of Cough

- Cough
  - Essential respiratory defense
  - Abnormal cough disrupts quality of life
    - Physical symptoms
      - Chest & abdominal pain
      - Vomiting
      - Loss of appetite
      - Headaches
      - Dizziness
      - Sweating
      - Insomnia
      - Exhaustion
Palliation of Cough

- Cough
  - Essential respiratory defense
  - Abnormal cough disrupts quality of life
    - Physical symptoms
    - Psychosocial issues
      - Family distress
      - Difficulty speaking on telephone
      - Embarrassment / self-consciousness
      - Social isolation
Palliation of Cough

- Cough
  - Essential respiratory defense
  - Abnormal cough disrupts quality of life
    - Physical symptoms
    - Psychosocial issues
  - Prevalent in lung cancer
  - Difficult to measure objectively
  - Limited evidence regarding palliative treatment
Mechanisms of Cough

Differential diagnosis of cough in palliative care

- Potentially treatable causes
  - Medications
    - (ACE inhibitors)
  - Asthma, COPD
  - Eosinophilic bronchitis
  - GERD
  - Post-nasal drip
  - Pleural effusion

- Less reversible causes
  - Endobronchial tumor
  - CNS / neuromuscular dz
  - End-stage cardiopulmonary
  - Interstitial disease
    - Lymphangitic
    - Radiation
    - Chemotherapy
    - Recurrent aspiration

Palliation of refractory cough: pharmacologic

- Central action (brainstem)
  - Dextromethorphan 15 – 30 mg po q 4-8 hours
    - 120 mg/d max
  - Codeine 20 mg po q 4 h prn
  - Hydrocodone 5 – 10 mg po q 4-6 hours prn
  - Gabapentin 100 mg po tid (starting dose)
  - Paroxetine 10 mg po qday (starting dose)
Palliation of refractory cough: pharmacologic

- Peripheral action (airway afferent receptors)
  - Sodium cromoglycate 20 mg inhaled bid – qid
  - Benzonatate 100 mg po tid (600 mg/d max)
  - Nebulized / spray lidocaine (100 mg)
  - Glycopyrrolate 1 mg po tid (8 mg/d max)
  - Thalidomide up to 100 mg per day
  - Ipratropium bromide

- Others
  - Sweet syrups
  - Antihistamines
  - Expectorants (guiafenesin)

Haas AR. Am J Hosp Pall Med 2007; 24:144-51
Palliation of refractory cough: pharmacologic

- **EXPERIMENTAL**
  - Carbamazepine,
  - Thalidomide, gabapentin,
  - Baclofen amitriptyline

- **LOCAL ANAESTHETICS**
  - Nebulised lidocaine/bupivacaine; benzonatate
  - PERIPHERALLY-ACTING ANTITISSIVES
  - Levodropropizine*, morguiste*, levocloperastine

- **OPIOIDS**
  - Morphine, methadone linctus
  - Dextromethorphan*, codeine, pholcodine, hydrocodone*

- **CONSIDER ORAL STEROID TRIAL**
  - (If appropriate) - 2 weeks

- **Simple linctus/glycerol**

- **CANCER SPECIFIC**
  - Systemic chemotherapy/RT endobronchial therapy,
  - Photodynamic therapy, paliative radiotherapy.

- **CO-MORBIDITIES**
  - COPD, reflux, asthma, infections.
  - Medication review

Molassiotis et al. Cough 2010, 6:9
Palliation of refractory cough: non-pharmacologic

- Positioning
- Chest physiotherapy
- Nebulized saline

Haas AR. Am J Hosp Pall Med 2007; 24:144-51
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