Dyspnea: Pathophysiology, Measurement and Management in Palliative Care

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Disclosures
Margaret Campbell has no real or perceived conflicts of interest that relate to this presentation.

Objectives
1) Identify the prevalence of dyspnea
2) Describe the most common tools for assessing dyspnea
3) Describe the significance of cognitive impairment on dyspnea reporting
4) Describe the RDOS
5) Describe evidence-based interventions to reduce or eliminate dyspnea
Definitions

1) Dyspnea – a person’s awareness of uncomfortable or distressing breathing that *can only be known through the person’s report*

2) Respiratory distress* – an *observed* corollary to dyspnea; the physical and emotional distress associated with respiratory dysregulation

* Campbell, Crit Care Clinics, 2004

Physiology/pathophysiology

- Phylogenetically ancient response
  - Developed when species moved from water to air respiration
  - Redundant brain areas respond to an asphyxial threat; survival is threatened
    - Blood gas abnormalities
    - Airflow alterations
    - Stretch receptors
  - Autonomic, cognitive and affective stimulation
    - Awareness of altered breathing; positive or negative
    - Emotional reactivity (suffocation fear)
    - Pulmonary stress behaviors

Prevalence of dyspnea across terminal illnesses (Solano et al. 2006)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Prevalence %</th>
<th># of studies</th>
<th>N</th>
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<tr>
<td>Cancer</td>
<td>10-70</td>
<td>20</td>
<td>10,029</td>
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<td>AIDS</td>
<td>11-62</td>
<td>2</td>
<td>504</td>
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<tr>
<td>Heart disease</td>
<td>60-88</td>
<td>6</td>
<td>948</td>
</tr>
<tr>
<td>COPD</td>
<td>90-95</td>
<td>4</td>
<td>372</td>
</tr>
<tr>
<td>Renal disease</td>
<td>11-62</td>
<td>2</td>
<td>334</td>
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</table>
Trajectory of dyspnea by diagnosis


- Consecutive cohort study
  - n = 5862
  - Numeric Rating Scale measured at every clinical encounter
  - Average 86 days until death
  - Diagnoses
    - Lung cancer
    - Metastasis to lung
    - Heart failure
    - COPD

Results

- Dyspnea measured at 3 time points before death in days
  - 60-53
  - 30-23
  - 7-0
- Dyspnea was highest in non-cancer at all time points
- Dyspnea increased significantly in cancer

Patient (in)ability to self-report dyspnea when near death

(Campbell, et al., J Pall Med, 2009)

- 89 patients near death from one or more of
  - Lung cancer
  - COPD
  - CHF
  - Pneumonia
- Asked “Are you short of breath?”, asked to point to a VAS
  - 54% could not respond to query
  - 78% could not use VAS
- Inability to self-report associated with
  - Consciousness (p<.01)
  - Cognition (p<.01)
  - Nearness to death (p<.01)
  - Hypoxemia (p=.07)
Cognitive skills necessary for symptom reporting

- Able to interpret sensory stimuli
- Able to pay attention to instructions and concentrate to form a report
- Able to communicate
- Able to remember previous report

Common dyspnea assessment tools

- Yes or No query: Are you short of breath?
- Numeric rating system: 0-10
- Visual analog scale: vertical or horizontal line anchored from 0-10 or 0-100 mm
- Modified Borg: category-ratio scale using descriptive terms to anchor responses to dyspnea after exercise

Vertical Dyspnea Visual Analog Scale
A review of quality of dyspnea assessment

- Most instruments are one-dimensional
  - Quantify dyspnea at a particular moment
    - Numeric rating scale*
    - Visual analog scale
    - Modified Borg dyspnea scale
  - Quick and easy to administer
  - Not comprehensive
  - Require cognitive skills

* Most suitable for palliative care

Mularski et al., Am J Respir Crit Care Med, 2010

Measuring respiratory distress in patients with cognitive impairment

- Gold standard instruments
  - Numeric report
  - Dyspnea visual analog scale
  - Modified Borg

- Observation tools
  - Respiratory Distress Observation Scale

A theoretical model of respiratory distress

Campbell, Heart & Lung, 2008
Respiratory Distress Observation Scale©

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 points</th>
<th>1 point</th>
<th>2 points</th>
<th>Total</th>
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<tbody>
<tr>
<td>Heart rate per minute</td>
<td>&lt;90 beats</td>
<td>90-109 beats</td>
<td>≥110 beats</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate per minute</td>
<td>≤18 breaths</td>
<td>19-30 breaths</td>
<td>&gt;30 breaths</td>
<td></td>
</tr>
<tr>
<td>Restlessness: non-purposeful movements</td>
<td>None</td>
<td>Occasional, slight movements</td>
<td>Frequent movements</td>
<td></td>
</tr>
<tr>
<td>Accessory muscle use: rise in clavicle during inspiration</td>
<td>None</td>
<td>Slight rise</td>
<td>Pronounced rise</td>
<td></td>
</tr>
<tr>
<td>Paradoxical breathing pattern</td>
<td>None</td>
<td>Present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal flaring: involuntary movement of nose</td>
<td>None</td>
<td>Present</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Look of fear</td>
<td>None</td>
<td>Open wide eyes, facial muscles tense, brow furrowed, mouth open</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reliability and Validity

- Inter-rater reliability ($r = 1.0$)
- Scale reliability ($\alpha = .78, .64, .85$)
- Construct validity
  - RDOS – $SpO_2$
    - ($r = -.369, p < .01, n = 85$)
    - ($r = -.688, p < .01, n = 210$)
- Convergent validity
  - RDOS – patient report ($r = .740, p < .01, n = 210$)
- Discriminant validity
  - RDOS – pain ($F(2,207) = 119.84, p < .01$)
- Cut-point = 3
Assessment summary

- **Self-report should be elicited whenever possible using the simplest measure**
  - Yes or No response to query
  - NRS or VAS
- RDOS when patient is unable to self-report
- Proxy opinion
  - Clinicians
  - Patient’s family
- RDOS may be more reliable than proxy opinion

Dyspnea Treatment

- Disease-modifying treatments when possible (consistent with goals of care)
  - Paracentesis, thoracentesis, diuresis
  - Antibiotics
  - Mechanical ventilation, invasive or non-invasive
- Maintain supportive treatments
  - Bronchodilators, anti-cholinergics
  - Inotropes, diuretics

Medications to treat dyspnea

- Opioids
  - Morphine
  - Fentanyl
- Benzodiazepines
- Furosemide (investigational)
Opioids

- Potent μ agonist
- Routes
  - Oral, immediate and sustained release
  - Parenteral
  - Nebulized
- Indicated and approved for the treatment of severe pain
- Less often employed for dyspnea

Proposed mechanisms of action in dyspnea


Dyspnea: Opioids

- A systematic review of the use of opioids in the management of dyspnea (Jennings et al. Thorax, 2003)
  - 18 studies reviewed: double-blind, randomized, placebo-controlled trials
    - COPD = 14, ILD = 1, CHF = 1, Cancer = 2
  - Statistically positive effect of opioids by oral and parenteral routes
    - No statistically significant effect when nebulized
    - Insufficient evidence to rule out nebulized
  - All small, underpowered studies
**Doses**

- High variability across studies
- Optimal dosing has not been established
  - Once daily sustained release (10 – 30 mg) is safe and effective for those who respond (Currow et al. J Pain Symptom Manage, 2011)
- Expert recommendation (Thomas and Von Gunten, Lancet Oncol, 2002)
  - Immediate release morphine 5 mg orally (2 mg IV) q4 h
  - Equivalent breakthrough dose q1 h prn
  - Titrate in 50-100% increments
- More dose studies are needed

**Adverse effects**

- Constipation – never abates
- Itching – not an allergic response
- Nausea/vomiting – generally abates in 3 days
- Sedation
- Respiratory depression – not seen in any of the 18 studies in Cochrane review (Jennings, 2002); not seen in safety study (Currow, 2011)

**Benzodiazepines as adjunct**

  - Group 1 = ATC morphine with midazolam rescue
  - Group 2 = ATC midazolam with morphine rescue
  - Group 3 = ATC morphine and midazolam with morphine rescue
- Group 3 had best overall results
  - Does the benzodiazepine minimize fear associated with dyspnea?
Furosemide

• Diuretic – chloride channel blocker

• Inhaled furosemide
  – Protects against bronchospasm
  – Inhibits cough reflex
  – Reduces dyspnea
  – Absorbed systemically to produce diuresis

• Promising small clinical studies
  – Mixed results
  – Laboratory induced – healthy participants

Oxygen benefits

• Correct hypoxemia

• Reduce dyspnea

• Prolong life

COPD and long-term oxygen

• > 15 hours/day
• Increased survival of patients with resting dyspnea
• $\text{PaO}_2 < 55 \text{ mm Hg}$
• $\text{SaO}_2 < 88\%$

Global Initiative for Chronic Obstructive Lung Disease, 2013
**Oxygen burdens**

- Decreased mobility
- Nasal drying
  - Nosebleed
- Feeling of suffocation
- Prolongs dying
  - Extends caregiver days
  - Increases health care costs
- Flammable

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**Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnea: a double-blind, randomized controlled trial (Abernethy et al., 2010)**

- 239 terminally ill patients with refractory dyspnea
  - Outpatient clinics in Australia, US, and UK
  - Life-limiting illness
  - Refractory dyspnea
  - PaO$_2$ > 55 mmHg

- Nasal oxygen or medical air at 2 l/min for 15 hours/day x 7 days

- NRS q morning and evening

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**Results**

- No differences between oxygen and medical air
  - Clinically insignificant decrease in dyspnea
  - No differences in side effects
    - Drowsiness
    - Nasal irritation
    - Nosebleed
**Oxygen is non-beneficial for most patients who are near death** (Campbell, et al. J Pain Symptom Manage, 2013)

- Repeated measures, double – blinded, randomized cross-over, using the patient as his/her own control
- Patients who were near death and at risk of experiencing dyspnea
  - n = 32 (effect size 0.25, significance 0.05, power 0.80, correlation coefficient between measures 0.30)
  - Near death – Palliative Performance Scale ≤ 30
  - At risk for dyspnea but in no distress
    - COPD
    - Heart failure
    - Lung Cancer
    - Pneumonia

**Results**

- 27 (84%) had oxygen flowing at baseline
  - Reason for oxygen not measured
- 29/32 (91%) patients experienced no distress during the protocol
  - 3 patients were restored to baseline oxygen
- 1 patient died during the protocol

**Conclusions**

- Declining oxygen saturation is naturally occurring and expected
- Declining oxygen saturation may *predict* but *does not signify* respiratory distress
- The routine application of oxygen to most patients who are near death is not supported
- An n of 1 trial of oxygen is appropriate in the face of respiratory distress
Summary

- Objective assessment must be done to guide treatment
  - Yes or No query is simplest measure
  - NRS or VAS useful for trending
  - RDOS useful in cognitive impairment
- Opioids are the only evidence-based effective treatment for refractory dyspnea
  - Parenteral or oral routes
  - Morphine or fentanyl
- Benzodiazepines require further study
- Oxygen is useful in awake patients with hypoxemia
  - Oxygen is not useful when death is imminent
- Promising agents are under investigation

Case study

- John is a 69 year old with a 100 pack/year smoking history, lung cancer, and COPD
  - He has been on home oxygen for several years at 3 l/min for most of the day/night
  - He is restricted to the first floor of his home; too dyspneic to walk upstairs
  - Recent weight loss, decreased activity, and worsening dyspnea are the hallmarks of transition to the terminal stage
  - Spends most of the day/night in a recliner with a chair-side commode and urinal
  - Reports dyspnea at rest; 8/10 on a 0-10 scale

Palliative Performance Scale

Anderson, et al., J Pall Care, 1996
Refractory dyspnea treatment

- John is optimized with his bronchodilator/anticholinergic regimen
- No evidence on physical exam for obstruction or pleural effusion or pulmonary edema
- Optimal position is upright which he has achieved by forgoing his bed for the recliner
- Balance rest with activity – he is already minimally active
- Oxygen at 3 l/min produces an SpO₂ of 89-90%

Global dyspnea treatment

- Morphine immediate release 20 mg/ml po
  - Begin with 5 mg
  - Wait 15-20 minutes for peak effect
  - Repeat with 5 mg every 15-20 minutes until relief
  - Calculate total dose and prescribe q4 hours
  - Use 5 mg dose for breakthrough dyspnea q1 hour
- Lorazepam 0.5 mg po q6 hours prn anxiety
- Continue oxygen at 3 l/min
- Add bowel regimen
Case study continues

- A week later
  - John is hypersomnolent, rouses briefly
  - Unable to give a dyspnea self-report
  - Wife reports infrequent use of breakthrough morphine, no use of lorazepam
  - Not eating, occasional sips of water

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**Palliative Performance Scale**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Total Care</th>
<th>Mobility</th>
<th>Self Care</th>
<th>Health Status</th>
<th>Communication</th>
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<td>Poor</td>
</tr>
</tbody>
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Wang, et al., J Pain Symptom Manage, 2009
Global dyspnea treatment – near death

- Change MDI to aerosol delivery
- Change morphine to prn, teach wife buccal administration
- Evaluate need for oxygen
  - Turn oxygen off
  - Stand by to observe for respiratory distress
  - Resume oxygen if respiratory distress is noted
- Discontinue oral medications

Global dyspnea treatment – imminent death

- Three days later
  - John is unresponsive
  - Respirations are shallow, slow with periods of apnea
  - No intake
  - PPS = 10, median survival = 3 days
- Discontinue aerosol treatments
- Discontinue oxygen
- Continue morphine prn buccal space