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‘It’s funny, but you never think much about breathing.
Until it’s all you ever think about.’

‘Breath’
Two specific goals in breathlessness by 2020:

1. A medication registered for the symptomatic treatment
2. An ability to correlate underlying pathophysiology, descriptors or both with specific interventions
…the sensation

- ‘Neuroventilatory dissociation’
- ‘Efferent / reafferent dissociation’
- ‘Mismatch theory’

- Afferent stimuli (mechanical, chemical) generate an efferent response that does not sufficiently reduce the afferent stimuli


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1. Population science
2. Basic science
3. Clinical science
1. Population science
2. Basic science
3. Clinical science

Population estimates of...
- Dyspnoea
- Constipation
- Pain
- Fatigue
(Not possible in areas such as cachexia)
Population estimates of dyspnoea:

The background rate determines the percentage of people coming to hospice / palliative care services with long term dyspnoea

Magnitude of problem – whole of population

Population estimates of dyspnoea that do not rely on health service attendance

3 studies spread over >50 years (because rates and risk factors have changed)

Magnitude of problem – whole of population

E. Cuyler Hammond (1912-1986)

Hammond EC. Am J Publ Health 1964;54(1):11-23
Magnitude of problem – whole of population

E. Cuyler Hammond
Enrolled 1,064,004 participants >30y.o.
68,116 volunteers (representative of the demographics of the country*) in 25 states and 1,121 counties.

October 1, 1959 – February 15, 1960

*literate, not a ‘migrant worker’

Hammond EC. Am J Publ Health 1964;54(1):11-23

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Magnitude of problem – whole of population

E. Cuyler Hammond

Breathlessness increased with age
25.3% of men were breathless
(16.2% 30-34y.o.; 33.1% 80-84y.o.; on a plateau from age 60 at >30%)

#5 of 24 symptoms in the general community

Hammond EC. Am J Publ Health 1964;54(1):11-23
**Magnitude of problem – whole of population**

**E. Cuyler Hammond**

Breathlessness increased with age
- 22.5% of women were breathless
  - (19.4% 30-34y.o.; 33.8% 80-84y.o.; plateau up to age 64 at <23%)
- #7 of 26 symptoms in the general community

Hammond EC. Am J Publ Health 1964;54(1):11-23

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<table>
<thead>
<tr>
<th>Factor</th>
<th>Mortality Ratio</th>
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</thead>
<tbody>
<tr>
<td>Loss of weight</td>
<td>2.24</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>2.14</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>2.08</td>
</tr>
</tbody>
</table>

Hammond EC. Am J Publ Health 1964;54(1):11-23
Dyspnoea

Magnitude of problem – whole of population

Breathlessness in the community

2,819 were contactable in 1997 of whom 2,405 had a physical exam.
2,306 had a completed SF12

Bergen, Norway

‘Changes in respiratory symptoms’

Voll-Aanerud M et al. Chest 2007;131:1890-1897

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>Never</td>
<td>74.8%</td>
<td>84.2%</td>
</tr>
<tr>
<td>Incident</td>
<td>13.6%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Remission</td>
<td>4.7%</td>
<td>3.8%</td>
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<tr>
<td>Persistent</td>
<td>6.9%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Voll-Aanerud M et al. Chest 2007;131:1890-1897
Magnitude of problem – whole of population

Breathlessness - Gender differences
Symptom perception theory
For similar levels of morbidity, higher rates of reported symptoms including breathlessness
Gender differences disappear when controlled for mood


What can we find from the whole population?

The South Australian Health Omnibus – a random, population-based, annual, face-to-face survey
South Australian Health Omnibus

Run September – December each year

Trained interviewers; face-to-face

Approximately 200 questions about health

Statewide sample randomly selected directly standardised to the whole population; macro for combining years

Overall participation rate – 77.9%

Magnitude of problem – whole of population

n = 8,396

Modified Medical Research Council Scale
- 8.9% overall at ≥ 2

- 1% of the population had chronic disabling dyspnoea (mMRC ≥ 3).

- 0.3% of people were housebound by breathlessness

Currow et al. J Pain Symptom Manage, 2009
**Magnitude of problem – whole of population**

**Multifactor analysis**
Demographic associations with significant breathlessness (MRC ≥ 2)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low income</td>
<td>2.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Work related injury</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Currow et al. J Pain Symptom Manage 2009

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**Magnitude of problem – whole of population**

Multifactor analysis; n=5331
Including smoking, age, gender, living circumstances, social disadvantage, physical activity and obesity
That included Demographic associations with significant breathlessness (MRC ≥ 2)
Age, marital status, physical activity, obesity, gender, social disadvantage all significant

**Smoking was not a significant predictor**

Bowden et al. BMC Public Health 2011
Magnitude of problem – whole of population

Health Omnibus; n=4432
To what do people attribute their breathlessness?

If breathless (mMRC ≥1), then 65% of people attributed their dyspnoea to lung disease

If attributed to lung disease, it was likely that breathlessness had been with them for significantly longer –
13.8 yrs vs 5.7 yrs; p<0.001


Palliative populations

How does the prevalence and intensity of breathlessness change over time?

Currow DC et al. J Pain Symptom Mange 2010
Magnitude of problem – palliative populations

Silverchain palliative care service Perth
n=5,862

Consecutive cohort with point of care data collection in a large community service

116982 data points

Incidence, prevalence and severity (including by diagnosis)

Currow DC et al. J Pain Symptom Mange 2010

Currow et al JPSM.
2010;39(4):680-690
116,982 data points in 5,862 people


1. Population science
2. Basic science
3. Clinical science
von Leopoldt et al. Neural processing of respiratory sensation when breathing becomes more difficult and unpleasant. Frontiers in Physiology 2011;1:1-5

Figure 2. Brain activations associated with the perceived unpleasantness of resistive load-induced dyspnea. Results represent the difference in cortical activity between dyspnea-negative and baseline-negative conditions compared with the difference in cortical activity between dyspnea-positive and baseline-positive conditions. Group results are presented as statistical maps superimposed onto the group mean structural T1-weighted magnetic resonance image from a transverse view (z = –12, left), a coronal view (y = 18, middle), and a coronal view (y = 9, right). Signal intensity is coded by the inserted color scale (thresholded at T = 3.9, P < 0.001 uncorrected). Main activation areas (P < 0.05 corrected for multiple comparisons) are seen in the right anterior insular cortex (IC) and right amygdala (AM). A 5 anterior; L 5 left side of brain; R 5 right side of brain.

...the sensation

Intensity of breathlessness is probably what we ask patients

But there is good evidence that the intensity may be less important than how unpleasant the sensation is

Intensity and unpleasantness may potentially even respond differently to symptom control interventions.


Dyspnoea Opioid therapy

- Mahler et al Eur Resp J 2009

D - Double blind, randomised crossover
P - 17 people with moderate to severe COPD
I - Naloxone 10mg i.v. before constant intense work rate on treadmill for a minimum of 10 minutes
C - Normal saline
O - Oxygen use / breathlessness regression curve; breathlessness scores

Results – significantly increased breathlessness / oxygen consumption regression curve in naloxone group; significantly less breathlessness in saline group
Minimum clinically important difference in dyspnoea intensity

In the acute care setting – a 2 point difference on a 0-10 numerical rating scale may be required for patients to feel that there is any difference to the relief of their breathlessness.


Minimum clinically important difference in dyspnoea intensity

In the chronic setting, it is thought that the threshold for patient-defined differences may 1 on a 0-10 numerical rating scale.


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Two reciprocal regression lines (average NRS for breathlessness intensity) compared to a single point in time global impression of change in chronic heart failure

Thanks to Dr Miriam Johnson of Hull York Medical School for this graph

Opioid therapy
Currow et al. J Pain Symptom Manage 2011
D - Phase II dose ranging; Phase IV long term effectiveness / safety
P - Opioid naïve palliative care patients with dyspnoea
I - Sustained release morphine 10mg / 24 hours titrated until response up to 30mg / 24 hrs
C - none
O - 31 participant/years of data from 85 participants (1-660 days)

Number needed to treat 1.6 (2.1 at 3/12)
Of responders, 92% responded at or below 20mg / 24 hours.
Number needed to harm 4.5
Changes in VAS in people who have responded to dose titration on sustained release morphine for refractory breathlessness. Secondary analysis of dose ranging study

Change in VAS per day

Day 8 increment from 10mg to 20mg; n = 13

Day 15 increment from 20mg to 30 mg; n=4

Days pre/post of incremental response

Reduction in VAS due to response = 10.7 mm (p<0.001)
Reduction in VAS/day after response is 2.2mm (p<0.001)

Titrate to effect
Changes in VAS in people who have responded to dose titration on sustained release morphine for refractory breathlessness. Secondary analysis of dose ranging study.

Maximal effect not for several days after a marked response once it occurs.
Dyspnoea in hospice / palliative care

1. Population science
2. Basic science
3. Clinical science

What were we saying a decade ago?

- Oxygen therapy in ‘hypoxemic and nonhypoxemic patients’
- Transfusion therapy ‘controversial’
- Oral, parenteral opioids but not nebulized
- Benzodiazepines ineffective in 4/5 trials
- Focus on breathlessness as a symptom rather than a function simply of gas exchange
- Use allied health interventions

Prevalence of pathology

100 consecutive patients with cancer

- Median VAS dyspnoea 53mm
- Spirometry abnormal 93%
  5% obstructive; 41% restrictive; 47% mixed
- Mean max. inspiratory pressure 16cm H$_2$O
  >80 – no significant weakness
  <50 – impaired ability to generate cough to clear secretions
- No chest x-ray abnormality 35%
- Recent ischaemia, infarct or AF 29%

Prevalence of potentially contributing / reversible causes

100 consecutive patients with cancer

- Median of 5 likely contributing causes

- Potentially correctable causes
  - hypoxaemia 40%
  - anaemia 20%
  - bronchospasm 52%


Pharmacology of breathlessness

No medication registered with EMEA / FDA / TGA for the treatment of symptomatic refractory or intractable breathlessness.

Evidence supports efficacy and safety of opioids for symptomatic breathlessness.

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- 1999 ‘Despite the beneficial effects of opiates, for acute dyspnoea there is insufficient evidence to recommend their regular use in the longterm management of dyspnea.’

- 2012 ‘Short term administration of opioids reduces breathlessness in patients with a variety of conditions…’


Opioid therapy

Jennings et al Thorax 2002
- Cochrane review of double-blind randomized placebo-controlled trials of opioids in refractory dyspnoea.
  9 studies with 116 participants
D - Meta-analysis
P - Dyspnoea due to any cause
I - Parenteral / oral opioids
C - Placebo
O - Dyspnoea intensity

Results - Dyspnoea intensity reduced by 8mm on 0-100mm scale with a mean starting point of 50mm (16% improvement)
Magnitude of benefit maintained for people with COPD
Opioid therapy

D - Double-blind randomised cross-over
P - 48 opioid naïve patients with dyspnoea due to any cause*
I - Morning sustained release morphine 20mg / 24 hours
C - Placebo
O - Dyspnoea intensity at day 4

Results - Dyspnoea intensity reduced by 7 to 10 mm on 0-100mm scale.
(Mean starting point of 47mm; 15 - 22% improvement)

*88% had COPD as their primary cause of breathlessness

Adequately powered randomised controlled trials versus meta-analyses

- Similar populations being studied
- Same direction and order of magnitude in absolute and relative terms

Gives us confidence in both methods of answering key clinical questions
Deconstructing Dyspnoea

Pharmacological treatments - Non-opioids

Benzodiazepines – meta-analysis – no benefit to date

**Nebulised frusemide – systematic review – potential benefit**
(not principally a diuretic effect)

**SSRIs – 3 pilot RCTs, 3 case series – potential benefit**

Promethazine – one small RCT – benefit in cancer during exercise


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Khan et al. *BMC Pulm Med 2004*

D - Single blind assessment of sham versus effective administration of nebulised saline at 10 minutes

P - 40 patients FEV₁ 30%, in hospital with acute exacerbation

I - Nebulised saline

C - Ineffectively nebulised saline

O - Intensity of breathlessness on a Likert scale

No significant difference in FEV₁

Can be used as a control arm in bronchodilator studies

4% vs 23% improvement in breathlessness (p=0.0001)

5% vs 65% improvement in mucous expectoration (p<0.0001)

Cannot be used as a placebo arm in studies of nebulised medications.
Non-pharmacological interventions

2532 participants in 47 studies:

walking aids (7); music (6); chest wall vibration (5);
acupuncture / acupressure (5); relaxation (4);
neuro-electrical muscle stimulation (3); fan (2);
counselling (6); breathing training (3); counselling
and support (2); case management (2);
psychotherapy (2).

Bausewein et al Cochrane Collaboration, 2008

Non-pharmacological interventions

2532 participants in 47 studies:
Strong evidence of benefit:
- chest wall vibration (5);
- neuro-electrical muscle stimulation (3).

Moderate strength of evidence:
- walking aids (7); - breathing training (3).

Bausewein et al Cochrane Collaboration, 2008
"Nurse Wilson you've mixed up the helium and oxygen bottles again haven't you?"

Oxygen therapy

- Uronis et al Cochrane database of systematic reviews 2011
  Mean study quality score 2.9

D - Cochrane review of symptomatic benefit of oxygen in people with COPD of 18 studies and 321 participants

P - People with COPD (mean FEV$_1$ 0.9l) who do NOT qualify for domiciliary O$_2$

I - Oxygen therapy (short burst and long term)

C - Medical air

O - Breathlessness (visual analogue, numerical rating or Borg)

Results. Reduced standardised mean difference of breathlessness -0.41 (95% CI -0.52 to -0.33). All studies had reduced breathlessness in the intervention arm.
Drug therapy to palliate breathlessness

1. Evidence and clinical practice

2. Current evidence

3. Future directions for:
   (a) generating new evidence
   (b) translating into practice

The situation of Mount Lyttle was found from hence and from some other bearings, to be 34°59' south and 138°42' east. No land was visible so far to the north as where the trees appeared above the horizon, which showed the coast to be very low, and our soundings were fast decreasing. From noon to six o'clock we ran thirty miles to the northward, skirting a sandy shore at the distance of five, and thence to eight miles; the depth was then 5 fathoms, and we dropped the anchor upon a bottom of sand, mixed with pieces of dead coral.

Oxygen therapy

- Uronis et al Br J Cancer 2008

  Mean study quality score 2.1

D - Cochrane review of symptomatic benefit of oxygen in people with cancer who do not qualify for domiciliary oxygen

P - People with cancer who DO NOT qualify for domiciliary O₂ (Mean pulse oximetry 93%)

I - Oxygen therapy (short burst and long term)

C - Medical air

O - Breathlessness (visual analogue, numerical rating or Borg)

Results. Reduced standardised mean difference of breathlessness (SMD 0.08, 95% CI -0.22 to 0.05; p=0.24).
Oxygen for breathlessness in lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (SE)</th>
<th>SMD (fixed 95% CI)</th>
<th>Weight (%)</th>
<th>SMD (fixed 95% CI)</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beam</td>
<td>-0.1602 (0.3128)</td>
<td>-0.16 [-0.357, 0.02]</td>
<td>9.06</td>
<td>-0.16 [-0.357, 0.02]</td>
<td>D</td>
</tr>
<tr>
<td>Booth</td>
<td>-0.1200 (0.3900)</td>
<td>-0.12 [-0.329, 0.08]</td>
<td>67.95</td>
<td>-0.12 [-0.329, 0.08]</td>
<td>D</td>
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<tr>
<td>Philip</td>
<td>-0.0928 (0.4100)</td>
<td>-0.09 [-0.18, 0.00]</td>
<td>22.19</td>
<td>-0.09 [-0.18, 0.00]</td>
<td>D</td>
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<tr>
<td>Total</td>
<td>-0.07</td>
<td>100.00</td>
<td>-0.07 [-0.21, 0.07]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2=1.8$, df=2 (P=0.38), $I^2=0$

Test for overall effect: $Z=1.7$ (P=0.03)

Dyspnoea

1. The evidence base has grown substantially in the last decade

2. We have very specific challenges for the years ahead if we are going to make difference (especially for the people who are NOT referred to specialist hospice / palliative care services)
"Anything else besides shortness of breath?"
"How about that — they must have developed a resistance to oxygen!"