Physiological Characteristics and Phenotypes

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OUTLINE

- Physiological heterogeneity in COPD
- Small airway dysfunction
- Effect of mucus hypersecretion
- The pulmonary microcirculation
- Lung hyperinflation
- Mapping COPD Characteristics
GOLD stage:
- III/IV
- II
- I
n=2,265

Phenotypes: Definition

Clinical Commentary

Chronic Obstructive Pulmonary Disease Phenotypes
The Future of COPD


Am J Respir Crit Care Med 2010; 182: 598-604.

“a single or combination of physiological attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exercise capacity, exacerbations, rate of disease progression, or death).”
Physiological COPD “Phenotypes”

- Small airways dysfunction dominant
- Lung hyperinflation dominant
- The “isolated” reduced $D_L$CO
- “Chronic bronchitis” dominant [hypoxemia]
- The rapid decliner
- The asthma / COPD overlap [ACOS]
- The obese COPD / OSA overlap
- Mixed pattern
Clinical COPD Phenotypes

The Blue Blaster

The Pink Puffer

AC Dornhorst 1955
<table>
<thead>
<tr>
<th>“Type B”</th>
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<tbody>
<tr>
<td>Overweight</td>
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<td>Normal $D_LCO$</td>
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<td>Milder dyspnea</td>
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<td>Severe dyspnea</td>
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<tr>
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</tr>
<tr>
<td>Decreased CO$_2$ sensitivity</td>
<td>Emphysema</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Normal ABG at rest</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>$O_2$ desaturation during exercise</td>
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GOLD 2011: Combined Assessment of COPD

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<tr>
<th>Risk classification of airflow obstruction</th>
<th>Risk history</th>
</tr>
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<tbody>
<tr>
<td>mMRC 0-1 CAT &lt; 10</td>
<td>mMRC ≥ 2 CAT ≥ 10</td>
</tr>
<tr>
<td>0</td>
<td>≥ 2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
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Symptoms

(A) mMRC 0-1 CAT < 10
(B) mMRC ≥ 2 CAT ≥ 10
(C) mMRC 0-1 CAT ≥ 10
(D) mMRC ≥ 2 CAT < 10
Dyspnea $\rightarrow$ Activity $\rightarrow$ $\geq 3$ $\geq 3$
Small Airway Dysfunction
Physiological Impairment in Mild COPD

- Premature airway closure
- Heterogeneous mechanical time constants (increased lung compliance and airway narrowing)
- Mal-distribution of ventilation
- Disruption of pulmonary gas exchange
- Increased pulmonary gas trapping

Measurement of Small Airway Function

- $C_{dyn}$ (frequency dependence)
- Partial F-V loop
- Pst – maximal expiratory flow
- Maximal F-V loops ± heliox
- Shape of maximal F-V loop
- N$_2$ washout: closing volume, LCI
- Forced / impulse oscillometry
COPD Challenge Test!
To the COPD patient, this is a breathtaking view.
Ventilatory Inefficiency in Mild COPD

\[ \frac{\dot{V}_E}{\dot{V}_{CO_2}} = \frac{863}{PaCO_2 \times (1-V_D/V_T)} \]

Operating Lung Volumes during Exercise

Exertional Dyspnea Intensity

Values are means ± SEM.
Mild > Normal slopes (p<0.05).

Mucus Hypersecretion
Cough → Sputum → ≥ 3

≥ 3
William Stokes and William Wilde sharing a bottle of beer.
William Stokes, 1837
in “Diseases of the Lung and Windpipe”

Chronic bronchitis:
“we observe the expectoration ...of opaque albuminous matter, of a whitish colour, and without any tendency to a purulent character”

Obliteration of the minute tubes occurred due to local hypertrophy of the mucus membranes and secretions

Just at the commencement of the obliteration a cul de sac existed beyond which, the tube was converted into a solid fibrous cord

In the neighbourhood of the obliterated canals the air cells were
<table>
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<tr>
<th></th>
<th>Chronic Bronchitis (GOLD grade 1B)</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female, n</td>
<td>11:9</td>
<td>11:9</td>
</tr>
<tr>
<td>Age, years</td>
<td>69 ± 2</td>
<td>64 ± 2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 ± 2</td>
<td>167 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 ± 4</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29 ± 1.3</td>
<td>27 ± 0.6</td>
</tr>
<tr>
<td>BDI focal score (0-12)</td>
<td>7.7 ± 0.4*</td>
<td>11.6 ± 0.2</td>
</tr>
<tr>
<td>MRC score (1-5)</td>
<td>2.4 ± 0.1*</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>CAT score (0-40)</td>
<td>17 ± 1.7*</td>
<td>3 ± 0.6</td>
</tr>
<tr>
<td>Oxygen cost diagram (0-100 mm)</td>
<td>65 ± 4*</td>
<td>93 ± 2</td>
</tr>
<tr>
<td>FEV₁ post-bronchodilator, %pred</td>
<td>93 ± 3 *</td>
<td>122 ± 2</td>
</tr>
<tr>
<td>FEV₁/FVC post-bronchodilator, %</td>
<td>62 ± 2 *</td>
<td>77 ± 1</td>
</tr>
</tbody>
</table>

Elbeihairy A, et al. 2013 (in review)
**Chronic Bronchitis vs Healthy Control**

- **Resistance (cmH₂O L⁻¹ sec⁻¹)**

  - **Frequency (Hz)**: 0 5 10 15 20 25
  - **Resistance Values**: 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0

- **R5 - R20**

  - Values: -10, 0, 10, 20, 30, 40, 50, 60

- **Graphs**
  - *Chronic Bronchitis* vs *Healthy Control*
  - Significant differences marked with *.

- **Reference**
  - Elbeihary A, et al. 2013 (in review)
Elbeihairy A, et al. 2013 (in review)
Additional Risks Associated with Cough and Sputum

COPD patients with cough and sputum are more likely to have:

– Increased airway inflammation
– Steeper decline in FEV$_1$
– Increased risk of recurrent AECOPD
– Increased risk of mortality
– Selective response to PD4 inhibitors

Oxygen Saturation during CWR Cycle Exercise: Effects of Roflumilast Treatment in COPD

Diffusing Capacity for Carbon Monoxide

- A measure of the surface area available for gas exchange
- A measure of alveolar-capillary integrity
- Correlates with structural emphysema, dyspnea, arterial $O_2$ desaturation and exercise intolerance

Dyspnea in Patients with Severe COPD: Physiologic Correlations

SB = severely breathless
MB = mildly to moderately breathless

Impairment in Lung Diffusion Contributes to Activity-Related Dyspnea

The Role of Abnormal $D_{LCO}$ in Ex-smokers Without Airflow Limitation

<table>
<thead>
<tr>
<th></th>
<th>Normal diffusion (ND, n=19)</th>
<th>Abnormal diffusion (AD, n=19)</th>
<th>Stage 1 COPD (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ %predicted</td>
<td>107</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>FEV$_1$/FVC, %</td>
<td>80</td>
<td>80</td>
<td>63 *</td>
</tr>
<tr>
<td>RV, %predicted</td>
<td>103</td>
<td>107</td>
<td>114</td>
</tr>
<tr>
<td>$D_{LCO}$, %predicted</td>
<td>89 *</td>
<td>59</td>
<td>68</td>
</tr>
<tr>
<td>6-min walk distance, m</td>
<td>430 *</td>
<td>341</td>
<td>417 *</td>
</tr>
<tr>
<td>CT: relative area with attenuation &lt;950 HU</td>
<td>1.36</td>
<td>1.60</td>
<td>5.50</td>
</tr>
<tr>
<td>CT: wall area %</td>
<td>57</td>
<td>59</td>
<td>58</td>
</tr>
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*p<0.05 vs AD

Reduced Lung Diffusing Capacity Contributes to Exercise Intolerance in COPD

\[
r^2 = 0.57, \quad p < 0.0005
\]

Reduced Lung Diffusing Capacity Contributes to Ventilatory Inefficiency in COPD

\[ r = -0.367 \]
\[ p < 0.0005 \]

Selective Loading of the Respiratory System in Mild COPD

Incremental Cycle Test with Added Dead Space

Chin RC, et al. AJRCCM 2013
Mild COPD: Significant constraints on tidal volume expansion with added dead space were associated with greater dyspnea.

Chin RC, et al. AJRCCM 2013
Lung Hyperinflation
Natural History of Lung Hyperinflation in COPD

Lung volumes (L)

Normal (n=128)  GOLD I (n=620)  GOLD II (n=1,129)  GOLD III (n=442)  GOLD IV (n=74)

Mapping COPD Characteristics

Pathology
- Small airway
- Large airways
- Blood vessels
- Parenchyma

Physiology
- ↑ Airway resistance
- ↑ Air trapping
- ↑ V/Q abnormalities
- Expiratory flow limitation

Compensation
- Respiratory muscle
- Mechanical
- Respiratory controller
- Autonomic NS
- Cardiac

Adaptation to physical conditions
- Behavioral
- Cognitive
- Psychological
- Social

Clinical expression

Pre-clinical
Asymptomatic

Compensatory phase

Dyspnea
Activity restriction
COPD Grade 1B [activity-related dyspnea]

\[(CAT \geq 10; \ mMRC \geq 2, \ BDI \leq 8)\]

- At risk for greater hospitalization and all cause mortality
- Poor quality of life
- Reduced exercise capacity (6MWD)
- Activity avoidance/restriction
- At risk for subsequent decline of pulmonary function

Relationship between patterns of $V_A/Q$ distribution and clinical classification