How to decrease heart dysfunction with suitable therapy of pulmonary diseases?

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HEALTHY AGEING RESEARCH CENTRE (HARC)
Financial disclosures

- Lecture fees and travel grants from Novartis, Boehringer-Ingelheim and GSK
- Gratification for clinical trials – GSK, BI
Lecture plan

- COPD – definition, classification, epidemiology, why COPD?
- Treatment strategy – pharmacological and non-pharmacological
- Possible mechanisms of heart dysfunction in respiratory diseases
- Oxygen therapy
- Influence of pharmacological treatment (data from clinical trials)
- How to decrease lung dysfunction with suitable therapy of heart diseases?
- Conclusions
Lecture plan

- COPD – definition, classification, epidemiology, why COPD?
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Chronic bronchitis and emphysema
Definition

- Common
- Preventable and treatable
- Persistent airflow limitation
- Usually progressive
- Enhanced inflammatory response to noxious particles and gases
- Exacerbations
- Comorbidities
Persistent airflow limitation

- $\text{FEV}_1/\text{FVC} < 0.7$ after bronchodilation
Why COPD?

- Fourth leading cause of death in the world
- 65 million people with moderate to severe stage of the disease
- More than 3 million people died in 2005
- Third leading cause of death worldwide in 2030.
COPD prevalence and age

Niżankowska-Mogilnicka E.
FEV₁ as an independent risk factor for cardiovascular mortality

FEV₁ < 50% pred

Shibata Y et al. PLOS One 2013
COPD stages

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>≥80</td>
</tr>
<tr>
<td>II</td>
<td>50-79</td>
</tr>
<tr>
<td>III</td>
<td>30-49</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

FEV<sub>1</sub>/FVC must be < 0.7 !!!
C

D

A

B

High risk

Low risk

Less symptoms

More symptoms

GOLD 2016 updated
Model-based adjusted survival curves, per GOLD stage A, B, C, D and D.
Death causes (TORCH study)

- Cardiovascular: 26
- Respiratory: 21
- Cancer: 35
- Others: not assessed
- Not assessed: not available

Comorbidome in COPD
Lecture plan

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## Recommended drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>First choice</th>
<th>Alternative choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA/SAMA</td>
<td>A B C D</td>
<td></td>
</tr>
<tr>
<td>LABA</td>
<td>A B C D</td>
<td></td>
</tr>
<tr>
<td>LAMA</td>
<td>A B C D</td>
<td></td>
</tr>
<tr>
<td>iGKS</td>
<td>C D</td>
<td></td>
</tr>
<tr>
<td>Methylxantines</td>
<td>A B C D</td>
<td></td>
</tr>
<tr>
<td>PDE-4 inhibitors</td>
<td>CD</td>
<td></td>
</tr>
<tr>
<td>Carbocysteine</td>
<td>CD</td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>CD</td>
<td></td>
</tr>
</tbody>
</table>

GOLD 2016 updated
To date, none of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function.
Non-pharmacological treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Smoking cessation strategy</th>
<th>Rehabilitation</th>
<th>Vaccination</th>
<th>Surgical &amp; non-surgical LVR</th>
<th>Domiciliary oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / -</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / -</td>
</tr>
<tr>
<td>D</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Treatment goals

- Relieve symptoms
- Improve exercise tolerance
- Improve health status

- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

REDUCE SYMPTOMS

REDUCE RISK
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Alveolar hypoxia

Pulmonary vascular bed remodeling

Cor pulmonale

RIGHT HEART DYSFUNCTION

Systemic hypoxia

Cellular hypoxia & mitochondrial dysfunction

Heart muscle dysfunction

LEFT HEART DYSFUNCTION
COPD and HF

- Prevalence of COPD among HF patients - 20-32%
- Prevalence of HF among COPD patients – 10%
- The risk of developing HF in COPD is 4.5 times higher
- Prevalence of bronchial obstruction in HF is >37%
- Prevalence of ventricular dysfunction in COPD is >17%

De Miguel Diez J et al. Int J COPD 2013
Potential causes of FEV1 decline in HF

- Hyperemia and oedema of bronchial mucosa
- Interstitial oedema
- Pulmonary congestion
- Heart enlargement
- Pleural effusion
- Attenuated thoracic muscle function
- Non-selective beta-blocking agents
Acute effects of saline infusion on lung spirometry and PEFR in patients with LVD. Comparison of results between preinfusion and 1 hour postinfusion values was made by paired Student’s t test analysis.

COPD – systemic inflammation

- Cigarette smoke
- Biomass fuel
- Pneumonia
- Lung cancer
- Peripheral lung inflammation
- "Spill-over"

**Systemic Inflammation**
- Cytokines: IL-β, IL-6, TNF-α, GM-CSF
- Acute-phase proteins: CRP, SAA
- Abnormal leukocytes

**Cardiovascular diseases**
- IHD, CHF, hypertension

**Metabolic diseases**
- Diabetes
- Metabolic syndrome
- Renal disease

**Bone disease**
- Osteoporosis
- Osteopenia

Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes

Judith García-Aymerich,1,2,3,4 Federico P Gómez,5,6 Marta Benet,1,2,4 Eva Farrero,7 Xavier Basaganya,1,2,4 Angel Gayete,8 Carles Parè,9 Xavier Freixa,9 Jaume Ferrer,6,10 Antoni Ferrer,2,6,11,16 Josep Roca,5,6 Juan B Gáliz,12 Jaume Saulela,6,13,14 Eduard Monsó,6,11,15 Joaquim Geya,2,3,6,16 Joan A Barberà,5,6 Àlvar Agustí,5,6,14 Josep M Antó,1,2,3,4 on behalf of the PAC-COPD Study Group

- **Group 1:** severe airflow limitation, worse performance in respiratory domains

- **Group 2:** milder airflow limitation

- **Group 3:** milder airflow limitation, comorbidities (CVD, obesity, DM) and systemic inflammation

27%
hypoxia

Altered myocyte cell metabolism

↓ ventricular relaxation  ↓ ventricular contraction

↑ HR

Adrenergic stimulation

Pulmonary vascular remodeling
Atherosclerosis

↓ arterial distensibility

↑ central arterial pressure

↑ LV afterload

↓ coronary reserve

LV diastolic dysfunction
Ventricular interdependence

- RV volume overload
- ↑ RV pressure

→ Shift of interventricular septum towards LV

↓ distensibility and filling of LV
Emphysema

Hyperinflation

High intrinsic positive end-expiratory pressure

- ↓ end-systolic volumes of LV
- ↓ end-diastolic volumes of LV
- ↓ cardiac index
- ↓ stroke volume
Guttenberg Health Study

15010 individuals
Age 55±11
Men 50.5%

Lung function tests
Echocardiography
Biomarkers

RESULTS

FEV₁ and FVC associated with hsTnI (p<0.001) and NT-proBNP (p<0.001)

FEV₁/FVC associated with hsTnI (p<0.004) and NT-proBNP (p<0.001)

FEV₁, FVC and FEV₁/FVC associated with LVESD, E/e', SV and EF

Baum C et al. Int J Cardiol 2016, May
Lecture plan

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Long-term Domiciliary Oxygen in Chronic Bronchitis with Pulmonary Hypertension

R. D. STARK, P. FINNEGAN, J. M. BISHOP

British Medical Journal, 1973, 3, 467-470

Summary

Five patients with chronic bronchitis and pulmonary hypertension were treated with oxygen in their homes for periods of between 8 and 24 months. Oxygen was supplied for 15 hours daily from cylinders or from an oxygen concentrator and few practical difficulties arose. After 23 to 59 weeks of treatment there were significant decreases in pulmonary arterial pressure and vascular resistance, and four of the five patients no longer had pulmonary hypertension at rest. Two of these patients had shown little response after three weeks of treatment. There was a reduction in the number of episodes of congestive cardiac failure compared with the corresponding period before treatment. Two of the patients improved enough to return to work. These results are encouraging enough to justify a controlled trial of the treatment in a large number of patients.

Methods

Five patients with chronic bronchitis and pulmonary hypertension underwent treatment with oxygen in their homes for periods of between six months and two years. The responses after three to six weeks in three of these patients were reported previously (Stark et al., 1972). The principal criteria for selection were hypoxaemia, a history of episodes of congestive cardiac failure, and willingness to participate in the study. The reliability of the patient was an important factor, and though few problems arose the arrangement and situation of the house helped to determine the practicability of treatment with oxygen at home.

Before admission to the trial a full explanation of the treatment was given to the patient on at least two occasions. It was made clear that the treatment was experimental and that we hoped to follow their response by tests of pulmonary function.
COPD prevalence 10% >40 years of age

COPD - 10 000/100 000

LTOT – 50/100 000

1 LTOT per 200 patients with COPD
Oxygen therapy in HF

Coronary blood flow

Coronary vascular resistance
Dynamic hyperinflation

- PL = translung pressure, V = ventilation

Dynamic Hyperinflation During Exercise

Healthy at Rest
- TLC
- IC
- IRV
- VT
- FRC
- ERV
- RV

Healthy During Exercise

COPD During Exercise

RV

= Hyperinflation
Lung volume reduction
Conclusions:

LV functions is impaired in patients with severe emphysema due to small end-diastolic dimensions.

LVRS increases LV end-diastolic dimensions and filling, and improves LV function.
Improvements in lung function, quality of life and exacerbations

No significant impact on rate of FEV$_1$ decline
Cardiac safety of tiotropium in patients with cardiac events: a retrospective analysis of the UPLIFT® trial

Donald P Tashkin, Inge Leimer, Norbert Metzdorf and Marc Decramer
Effects of tiotropium and formoterol on dynamic hyperinflation and exercise endurance in COPD

Danilo C. Berton a,b,d,*, Michel Reis a, Ana Cristina B. Siqueira a, Adriano C. Barroco a, Luciana S. Takara a, Daniela M. Bravo a, Solange Andreoni c, J. Alberto Neder a,e,*

A

B

C

Baseline FOR-PLA Baseline FOR-TIO

Tlim (% of change)

p = 0.038

p = 0.55

p = 0.02

p = 0.74

p = 0.04

p = 0.78

p = 0.09

Tlim (% of change from baseline)

p = 0.038

p = 0.55

p = 0.02

p = 0.74

p = 0.04

p = 0.78

p = 0.09

IC (% change from baseline)
Effects of Inhaled Tiotropium on Left Ventricular Diastolic Function in Chronic Obstructive Pulmonary Disease Patients after Pulmonary Resection

Takashi Nojiri, MD, Kazuhiro Yamamoto, MD, PhD, Hajime Maeda, MD, PhD, Yukiyasu Takeuchi, MD, PhD, Yasunobu Funakoshi, MD, PhD, Ryoji Makura, MD, PhD, and Meinoshin Okamura, MD, PhD

![Graph showing changes in PASP and E/e']

**Fig. 1** Changes in pulmonary arterial systolic pressure (PASP) and early transmitral velocity/tissue Doppler mitral annular early diastolic velocity (E/e') before and after treatment with inhaled tiotropium. Each point with bars shows the mean ± SD. PASP and E/e' are improved from 38.5 ± 5.6 mmHg and 8.97 ± 1.6, respectively, before treatment, to 33.0 ± 3.6 mmHg and 7.59 ± 1.4, respectively, 3 months after treatment (P <0.01 and P <0.001).
Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Jørgen Vestbo, Julie A Andersen, Robert D Brock, Peter M A Calverley, Bartolome R Celli, Courtney Crim, Fernando Martinez, Julie Yates, David E Newby, on behalf of the SUMMIT Investigators.

SUMMIT study - results

- **Effect on composite CV events:**
  - Combination HR 0.93 [95%CI 0.75-1.14]
  - Fluticasone HR 0.90 [95%CI 0.72-1.11]
  - Vilanterol HR 0.99 [95%CI 0.80-1.22]

- **Adverse cardiac events:**
  - 17% - placebo
  - 18% - combination
  - 17% fluticasone
  - 17% vilanterol

Effect of indacaterol on lung deflation improves cardiac performance in hyperinflated COPD patients: an interventional, randomized, double-blind clinical trial

**RESULTS**

- Increased VC, IC, FEV1
- Reduced TLC, RV, ITGV, sRAW
- Increased TAPSE, DT-TR
- Decreased HR

**Conclusion:** Indacaterol significantly reduces lung hyperinflation in acute conditions, with a clinically relevant improvement of dyspnea. These modifications are associated with a significant increase of the right ventricular compliance indexes and may have a role in improving left ventricular preload leading to a reduction in cardiac frequency.

TAPSE – tricuspid annular plane systolic excursion
DT-TR – tricuspid E-wave deceleration time
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Beta-blockers in COPD

Beta-blocker use and COPD mortality: a systematic review and meta-analysis

Mahyar Ehtminan, Slavash Jafari, Bruce Carleton and John Mark FitzGerald

RESEARCH ARTICLE

Odds Ratio

Study or Subgroup | log(Odds Ratio) | SE | Weight | IV, Random, 95% CI
--- | --- | --- | --- | ---
Au 2004 | -0.56 | 0.225 | 5.3% | 0.67 [0.37, 0.89]
Chen 2001 | -0.155 | 0.079 | 14.0% | 0.86 [0.73, 1.00]
Dransfield 2007 | -0.95 | 0.48 | 1.5% | 0.39 [0.15, 0.99]
Gottlieb 1998 | -0.51 | 0.022 | 17.9% | 0.60 [0.58, 0.63]
Hawkins 2009 | -0.3 | 0.04 | 17.0% | 0.74 [0.68, 0.80]
Rutten 2007 | -0.39 | 0.105 | 11.9% | 0.68 [0.55, 0.83]
Short 2011 | -0.244 | 0.08 | 13.9% | 0.78 [0.67, 0.92]
Staszewsky 2007 | -0.59 | 0.2 | 6.2% | 0.55 [0.37, 0.82]
Van Gestel 2008 | -0.32 | 0.1 | 12.3% | 0.73 [0.60, 0.88]

Total (95% CI) | 100.0% | 0.89 [0.62, 0.87]

Heterogeneity: Tau² = 0.02; Chi² = 44.80, df = 8 (P < 0.00001); I² = 82%

Test for overall effect: Z = 5.94 (P < 0.00001)
Beta-blockers in COPD

Mortality

Exacerbations

Du Q et al. PLOS one 2014
**RESEARCH PAPER**

Statin use in COPD patients is associated with a reduction in mortality: a national cohort study


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**Table 1. Characteristics of patients at discharge from hospital.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statin use</th>
<th>No (n=1,091)</th>
<th>Yes (n=596)</th>
<th>Total (n=1,687)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>562 (51.5%)</td>
<td>248 (41.6%)</td>
<td>810 (48.0%)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>529 (48.5%)</td>
<td>348 (58.4%)</td>
<td>877 (52.0%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td>167 (15.3%)</td>
<td>45 (7.6%)</td>
<td>212 (12.6%)</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td>331 (30.3%)</td>
<td>197 (33.1%)</td>
<td>528 (31.3%)</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td>593 (54.4%)</td>
<td>354 (59.4%)</td>
<td>947 (56.1%)</td>
</tr>
<tr>
<td><strong>Median age (years)</strong></td>
<td></td>
<td>70.1</td>
<td>71.6</td>
<td>70.6</td>
</tr>
<tr>
<td><strong>History of CVD</strong></td>
<td></td>
<td>274 (25.1%)</td>
<td>349 (58.6%)</td>
<td>623 (36.9%)</td>
</tr>
<tr>
<td><strong>History of diabetes</strong></td>
<td></td>
<td>127 (11.6%)</td>
<td>211 (35.4%)</td>
<td>338 (20.0%)</td>
</tr>
<tr>
<td>Dispensed frusemide</td>
<td></td>
<td>267 (24.5%)</td>
<td>284 (47.7%)</td>
<td>551 (32.7%)</td>
</tr>
<tr>
<td>Dispensed β-blocker</td>
<td></td>
<td>124 (11.4%)</td>
<td>224 (37.5%)</td>
<td>348 (20.6%)</td>
</tr>
<tr>
<td>Undergoing cancer treatment</td>
<td></td>
<td>112 (10.3%)</td>
<td>86 (14.4%)</td>
<td>198 (11.7%)</td>
</tr>
<tr>
<td>Death during follow-up</td>
<td></td>
<td>429 (39.3%)</td>
<td>242 (40.6%)</td>
<td>671 (39.8%)</td>
</tr>
</tbody>
</table>

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**Figure 1.** Cox modelled survival plot of statin users vs. statin non-users for those receiving cancer treatments and not receiving cancer treatments*

**HR=0.69, 95%CI 0.58-0.84**
The effect of statins on chronic obstructive pulmonary disease exacerbation and mor systematic review and analysis of observation.

Forest plot showing effect of statins on COPD exacerbation with or without hospitalization.
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- How to decrease lung dysfunction with suitable therapy of heart diseases?
- Conclusions
conclusions

- Suitable treatment of COPD may decrease heart dysfunction by several mechanisms:
  - Improving oxygenation
  - Decreasing right heart overload
  - Improving left heart function

- Improvement of LV diastolic function through reduction of hyperinflation seems to be a key point

- Suitable treatment of heart disease may have a positive impact on respiratory outcomes