**Online Data Supplement**

**Expiratory flow limitation in a cohort of highly symptomatic COPD patients**

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# **Methods**

**Impulse Oscillometry (IOS)**

# Patients were required to support their cheeks and use a free-flow mouthpiece to depress the tongue while impulses were applied during tidal breathing for 30 seconds in a seated position - this process was repeated to achieve three technically acceptable and reproducible attempts of which the means were reported. IOS was performed prior to all other lung function measurements.

# **Results**

## **EFL and other IOS measurements at 6 months**

At 6 months R5 and AX were elevated in EFLHigh patients compared to both EFLNone and EFLIntermediate (0.72 vs 0.44 and 0.56 kPa/L/s, p=0.02 and <0.0001 and 0.02. 4.48 vs 1.03 and 2.12 kPa/L/s, p<0.001 and 0.04 respectively, supplementary table 3). R5-R20 was elevated in EFLHigh patients compared to EFLNone and EFLIntermediate (0.35 vs 0.09 and 0.19 kPa/L/s, p<0.0001 for both, supplementary table 3). R5-R20 was also higher in EFLIntermediate when compared to EFLNone (0.19 vs 0.09 kPa/L/s, p=0.01, supplementary table 3). Furthermore, X5 was more negative in EFLHigh patients compared to both EFLNone patients (-0.39 vs -0.17 kPa/L/s, p<0.0001, supplementary table 3).

## **EFL and lung volumes at 6 months**

At 6 months, 53 patients had technically acceptable data collected for both IOS and body plethysmography. RV/TLC ratio was significantly elevated in EFLHigh compared to EFLNone patients (0.55 vs 0.45 respectively, p<0.01, supplementary table 3). No differences in DLCO or KCO were observed between groups.

# **Tables**

**Supplementary table 1.** Baseline comorbidities, n=70

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **All**  **(n=70)**  **n (%)** | **EFLNone**  **(n=24)**  **n (%)** | **EFLIntermediate (n=12)**  **n (%)** | **EFLHigh**  **(n=33)**  **n (%)** | **p-value** |
| **Patients with at least one concomitant disease** | 66 (94.3) | 24 (100.0) | 11 (91.7) | 31 (93.9) | 0.41 |
| **Ischaemic heart disease** | 18 (25.7) | 8 (33.3) | 3 (25.0) | 7 (21.2) | 0.59 |
| **Myocardial ischaemia** | 13 (18.6) | 4 (16.7) | 2 (16.7) | 7 (21.2) | 0.89 |
| **Angina pectoris** | 7 (10.0) | 4 (16.7) | 0 | 3 (9.1) | 0.28 |
| **Myocardial infarction** | 10 (14.3) | 5 (20.8) | 2 (16.7) | 3 (9.1) | 0.45 |
| **Cardiac failure** | 0 | 0 | 0 | 0 | N/A |
| **Cardiovascular disease** | 52 (74.3) | 16 (66.7) | 10 (83.3) | 25 (75.8) | 0.53 |
| **Hypertension** | 32 (45.7) | 6 (25.0) | b 8 (66.7) | a 17 (51.5) | 0.04 |
| **Hypercholesterolemia** | 38 (52.3) | 13 (54.2) | 6 (50.0) | 18 (54.5) | 0.96 |
| **Coronary artery disease** | 0 | 0 | 0 | 0 | N/A |
| **Pulmonary hypertension** | 0 | 0 | 0 | 0 | N/A |
| **Peripheral vascular disease** | 5 (7.1) | 4 (16.7) | 1 (8.3) | 0 | 0.06 |
| **Cerebrovascular disease** | 0 | 0 | 0 | 0 | N/A |
| **Stroke (including transient ischaemic attack)** | 9 (12.9) | 2 (8.3) | 3 (25.0) | 4 (12.1) | 0.37 |
| **Irregular heartbeat** | 3 (4.3) | 1 (4.2) | 0 | 2 (6.1) | 0.68 |
| **Diabetes** | 8 (11.4) | 1 (4.2) | 3 (25.0) | 4 (12.1) | 0.09 |
| **Obesity** | 23 (32.9) | 4 (16.7) | 5 (41.7) | 14 (42.4) | 0.10 |
| **Obstructive sleep apnoea** | 1 (1.4) | 0 | 0 | 1 (3.0) | 0.57 |
| **Anaemia** | 4 (5.7) | 3 (12.5) | 0 | 1 (3.0) | 0.20 |
| **Osteoarthritis, osteopenia or osteoporosis** | 27 (38.6) | 9 (37.5) | 3 (25.0) | 14 (42.4) | 0.57 |
| **Gastro-oesophageal reflux disease** | 17 (24.3) | 6 (25.0) | 2 (16.7) | 9 (27.3) | 0.77 |
| **Psychological disturbances** | 23 (32.9) | 8 (33.3) | 5 (41.7) | 10 (30.3) | 0.79 |
| **Depression** | 19 (27.1) | 7 (29.2) | 4 (33.3) | 8 (24.2) | 0.81 |
| **Anxiety** | 9 12.9) | 3 (12.5) | 2 (16.7) | 4 (12.1) | 0.92 |
| **Insomnia** | 1 (1.4) | 0 | 1 (8.3) | 0 | 0.09 |

Data presented as n (%). p-value corresponds to a chi-squared test. EFL defined as EFLHigh (ΔX5 ≥0.28 kPa/L/s), EFLIntermediate (ΔX5 0.10-0.27 kPa/L/s) and ≥ EFLNone (ΔX5 <0.10 kPa/L/s).

a = p<0.05 (using Tukey’s or Dunns post-hoc test) for EFLNone vs EFLHigh

b = p<0.05 (using Tukey’s or Dunns post-hoc test) for EFLNone vs EFLIntermediate

**Supplementary table 2.** Summary of patients that were lost to follow-up between baseline and 6 month visits (n=15)

|  |  |
| --- | --- |
| **Reason for loss of follow up** | **Number of patients, n (%)** |
| Not contactable | 10 (66.6) |
| Unable to produce technically acceptable oscillometry results | 1 (6.7) |
| Withdrawn due toa change in medical circumstances | 4 (26.7) |

**Supplementary table 3.** 6 month characteristics in different EFL groups, n=54 a

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **EFLNone (n=24)** | **EFLIntermediate (n=11)** | **EFLHigh (n=19)** | **ANOVA**  **p-value** |
| **Post-BD FEV1 (% predicted)** | 74.8 (68.9-80.7) | 64.7 (51.9-77.5) | b  b 54.4 (46.3-62.5 | <0.01 |
| **Post-BD FEV1 (L)** | 2.0 (1.8-2.2) | 1.7 (1.3-2.1) | b  b 1.4 (1.1-1.6) | <0.01 |
| **Post-BD FVC (% predicted)** | 102.7 (92.3-114.1) | 99.8 (87.0-112.5) | 95.0 (84.0-106.1) | 0.60 |
| **Post-BD FVC (L)** | 3.4 (2.9-3.9) | 3.3 (2.7-3.9) | 3.1 (2.7-3.6) | 0.66 |
| **FEV1 reversibility (%)** | 10.0 (6.6-13.3) | 11.9 (5.3-18.4) | 17.6 (9.2-26.0) | 0.14 |
| **FEV1 reversibility (mls)** | 165.8 (112.4-219.3) | 159.1 (90.8-227.4) | 194.2 (110.0-278.4) | 0.75 |
| **FEV1/FVC ratio (%)** | 54.5 (48.3-60.6) | 52.4 (45.5-59.3) | b 43.8 (37.5-50.2) | 0.04 |
| **R5 (kPa/L/s)** | 0.44 (0.39-0.49) | 0.56 (0.47-0.65) | b  b, d 0.72 (0.63-0.81) | <0.01 |
| **R20 (kPa/L/s)** | 0.36 (0.32-0.40) | 0.37 (0.31-0.44) | 0.38 (0.33-0.42) | 0.77 |
| **R5-R20 (kPa/L/s)** | 0.09 (0.06-0.11) | c 0.19 (0.15-0.22) | b b, d  d 0.35 (0.28-0.41) | <0.01 |
| **AX** | 1.03 [0.10-2.64] | c 2.12 [0.62-4.22] | b b, d 4.48 [1.76-11.69] | <0.01 |
| **X5 (kPa/L/s)** | -0.17 [-0.27-(-0.07)] | -0.24 [-0.41-(-0.11)] | b  b -0.39 (-1.00(--0.07)] | <0.01 |
| **∆X5 (kPa/L/s)** | 0.01 [-0.07-0.09] | c  c 0.18 [0.11-0.25] | b  b 0.57 [0.29-1.55] | <0.01 |
| **TLC (L)** | 6.16 (5.56-6.76) | 5.99 (5.08-6.90) | 6.25 (5.58-6.91) | 0.89 |
| **TLC (% predicted)** | 103.00 (77.32-136.8) | 98.26 (65.05-130.08) | 99.85 (74.63-149.00) | 0.64 |
| **FRC (L)** | 3.43 [2.06-7.79] | 3.78 [2.24-5.23] | 4.25 [1.96-6.41] | 0.11 |
| **FRC (% predicted)** | 109.30 [74.00-196.80] | 124.80 [69.14-160.60] | 133.60 [69.00-266.00] | 0.08 |
| **RV(L)** | 2.61 [1.62-5.81] | 3.08 [1.92-4.34] | 3.61 [1.49-5.59] | 0.08 |
| **RV (% predicted)** | 121.10 [68.00-213.00] | 127.50 [92.00-106.80] | 146.60 [68.00-265.00] | 0.10 |
| **RV:TLC** | 0.45 [0.31-0.61] | 0.49 [0.35-0.73] | b 0.55 [0.34-0.69] | 0.03 |
| **DLCO (mmol/min/kPa)** | 4.50 [1.80-9.80] | 3.90 [2.80-7.0] | 4.0 [2.0-6.90] | 0.67 |
| **DLCO (% predicted)** | 55.0 [25.0-92.0] | 42.0 [34.0-90.0] | 48.0 [31.0-86.3] | 0.48 |
| **KCO (mmol/min/kPa/L)** | 0.96 [0.00-1.50] | 0.95 [0.53-1.54] | 0.85 [0.47-1.44] | 0.86 |
| **KCO (% predicted)** | 64.86 [54.31-75.41] | 71.39 [55.10-87.68] | 68.72 [58.00-79.45] | 0.73 |
| **VA (L)** | 4.61 [3.95-5.27] | 4.51 [3.62-5.40] | 4.41 [3.94-4.87] | 0.88 |
| **VA (% predicted)** | 81.0 [0.0-103.0] | 76.0 [58.0-106.0] | 76.0 [54.0-96.0] | 0.40 |

Data presented as mean (95% CI), median [range] or percentage as appropriate. p-value corresponds to one way ANOVA, Kruskal-wallis or chi-squared test as appropriate. EFL defined as EFLHigh (ΔX5 ≥0.28 kPa/L/s), EFLIntermediate (ΔX5 0.10-0.27 kPa/L/s) and EFLNone (ΔX5 <0.10 kPa/L/s).

a 1 patient did not produce technically acceptable results for lung volumes or spirometry

b = p<0.05, b b = p<0.01 (using Tukey’s or Dunns post-hoc test) for EFLNone vs EFLHigh

c = p<0.05, c c = p<0.01 (using Tukey’s or Dunns post-hoc test) for EFLNone vs EFLIntermediate

d = p<0.05, d d = p<0.01 (using Tukey’s or Dunns post-hoc test) for EFLIntermediate vs EFLHigh

Abbreviations: AX, reactance area; BD, bronchodilator; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; KCO, carbon monoxide transfer coefficient; RV, residual volume; R5, resistance at 5Hz; R20, resistance at 20Hz; TLC, total lung capacity; VA, alveolar volume; X5, reactance at 5Hz, ∆X5, difference in total reactance between inspiration and expiration;