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 EFL^{High} patients compared to both EFL^{None} and $EFL^{Intermediate}$ (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 EFL^{High} patients compared to EFL^{None} and $EFL^{Intermediate}$ (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 $EFL^{Intermediate}$ when compared to EFL^{None} (0.19 vs 0.09 kPa/L/s, p=0.01, supplementary table 3). Furthermore, X5 was more negative in EFL^{High} patients compared to both EFL^{None} 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 EFL^{High} compared to EFL^{None} 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 (%)	EFL^{None} (n=24) n (%)	EFL^{Intermediate} (n=12) n (%)	EFL^{High} (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	27	9 (37.5)	3 (25.0)	14 (42.4)	0.57

osteoporosis	(38.6)				
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 EFL^{High} ($\Delta X5 \geq 0.28$ kPa/L/s), $EFL^{Intermediate}$ ($\Delta X5$ 0.10-0.27 kPa/L/s) and $\geq EFL^{None}$ ($\Delta X5 < 0.10$ kPa/L/s).

[a] = $p<0.05$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs EFL^{High}

[b] = $p<0.05$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs $EFL^{Intermediate}$

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)

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

Characteristic	EFL^{None} (n=24)	$EFL^{Intermediate}$ (n=11)	EFL^{High} (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
FEV_1 reversibility (%)	10.0 (6.6-13.3)	11.9 (5.3-18.4)	17.6 (9.2-26.0)	0.14
FEV_1 reversibility (mls)	165.8 (112.4-219.3)	159.1 (90.8-227.4)	194.2 (110.0-278.4)	0.75
FEV_1/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
ΔX5 (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 EFL^{High} ($\Delta X5 \geq 0.28$ kPa/L/s), $EFL^{Intermediate}$ ($\Delta X5$ 0.10-0.27 kPa/L/s) and EFL^{None} ($\Delta X5 < 0.10$ 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 EFL^{None} vs EFL^{High}

[c] = $p<0.05$, [c c] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for EFL^{None} vs $EFL^{Intermediate}$

[d] = $p<0.05$, [d d] = $p<0.01$ (using Tukey's or Dunns post-hoc test) for $EFL^{Intermediate}$ vs EFL^{High}

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, $\Delta X5$, difference in total reactance between inspiration and expiration;