The Peak Index: Spirometry Metric for Airflow Obstruction Severity and Heterogeneity

ONLINE DATA SUPPLEMENT

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Supplemental Methods

Spirometry Acquisition

We included subjects from a large multicenter study (COPDGene) that enrolled participants at 21 clinical centers. Participants included current and former smokers between the ages of 45 and 80 years. Spirometry was performed at enrollment using the ndd Easy-One spirometry (Easy-One spirometer; NDD, Andover, MA) according to the American Thoracic Society (ATS) criteria.[1] Spirometry was performed by trained personnel at each site. Approximately 12-20 minutes after administration of 180 mcg of albuterol HFA with a spacer (Aerochamber®, Monaghan Medical Corporation, Plattsburgh, NY), spirometry was repeated to obtain post bronchodilator values. The effort with the highest sum of FEV_1 and FVC was selected as the best effort for pre and post bronchodilator spirometry.

Spirometry Quality Control

Stringent quality control (QC) was performed in the COPDGene study at multiple levels. The primary QC was automated with quality grading according to the Quality grades based on the National Lung Health Education Program (NLHEP) and the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations for all tests.[1, 2] The three best efforts for both pre and post bronchodilator tests were stored at the clinical centers. Each center uploaded their spirometry database to a central depot located at the Data Coordinating Center for the Spirometry Core. Pre and post bronchodilator FEV_1 and FVC for all spirometries were reviewed and graded by the automated QC software as follows:

- Grade 4: fully met ATS criteria, reproducible to within 50 ml
- Grade 3: fully met ATS criteria, reproducible between 50 and 100 ml
- Grade 2: fully met ATS criteria, reproducible between 100 and 150 ml
- Grade 1: partly met ATS criteria and/or reproducible between 150 and 200 ml
- Grade 0: failed to meet ATS criteria and/or reproducible greater than 200 ml

In COPDGene, the average primary QC grades were 3.1 to 3.5 for pre and post bronchodilator spirometry. Primary QC grades of 1 or 0 were considered to be failing grades

and any grade of 2 or above were considered acceptable efforts for analysis. Those spirometries that failed primary QC were repeated at the test location, whenever possible.

In the event of inability to repeat spirometry, these efforts that failed primary QC were reviewed using a Secondary Spirometry Core QC process wherein non-representative efforts were excluded. Lastly, the COPDGene Spirometry Review Committee evaluated technical quality issues including zero-flow errors and spirometer malfunctions to determine if spirometry efforts should be repeated.

Extraction of Raw Data

The raw data points that comprise the flow-volume and volume-time curves are stored in "ByteArrays", one for Flow by Volume, and one for Volume over Time. The ByteArrays are strings of 2-byte integer values that can be parsed out into separate data points. For the Flow by Volume curve, the spacing of the data points is in increments of 30 ml volume. The listed values are flow values with a resolution of 10 ml/s per bit. For the Volume over Time curve, the spacing is in increments of 60 ms. The listed values are volume values with a resolution of 10 ml per bit.

Supplemental Results

Supplemental Table E1: Baseline Demographics with inclusion of PRISm

		COPD Severity Stages				
Parameters	**PRISm** (n=1194)	**GOLD 0** (n=4145)	**GOLD 1** (n=749)	**GOLD 2** (n= 1825)	**GOLD 3** (n= 1102)	**GOLD 4** (n= 569)
Age (years)	57.3 (8.3)	56.7 (8.4)	61.9 (9.0)	62.6 (8.9)	64.4 (8.4)	63.9 (7.6)
Sex, Female (%)	685 (53.6%)	2077 (47.1%)	337 (42.4%)	899 (46.5%)	501 (42.7%)	251 (41.2%)
Race, African-American (%)	546 (42.8%)	1811 (41.1%)	179 (22.5%)	485 (25.1%)	247 (21%)	116 (19%)
Body-mass-index (kg/m^2)	31.9 (7.3)	28.9 (5.8)	27.0 (5.0)	28.7 (6.1)	28.1 (6.5)	25.5 (5.8)
Smoking Pack-years	42.7 (24.2)	37.1 (20.3)	44.9 (24.2)	50.7 (26.9)	54.8 (27.6)	56.5 (29.2)
Current Smokers (%)	807 (63.2%)	2626 (59.6%)	442 (55.7%)	957 (49.5%)	411 (35%)	142 (23.3%)
FEV_1 (L)	2.1 (0.5)	2.9(0.7)	2.7 (0.7)	1.9 (0.5)	1.1 (0.3)	0.6 (0.2)
FEV_1 % predicted	70.1 (8.5)	97.4(11.4)	90.7 (8.7)	65.0 (8.6)	40.3 (5.7)	22.6 (4.9)
FVC (L)	2.7 (0.7)	3.7 (0.9)	4.1 (1.0)	3.2 (0.9)	2.7 (0.8)	2.1 (0.7)
FVC % predicted	71.4 (9.3)	96.6 (11.8)	107.3 (12.0)	85.9 (12.6)	71.5(13.3)	55.8 (13.6)
FEV_1/FVC	0.77 (0.05)	0.79 (0.05)	0.65 (0.04)	0.58 (0.08)	0.44 (0.09)	0.32 (0.07)
PRM Emphysema (%)*	0.6 (2.6)	0.6 (1.3)	2.4 (3.6)	5.0 (7.3)	14.5 (12.5)	25.5 (14.8)
PRM fSAD (%)*	11.4 (9.3)	12.2(10.4)	20.4 (11.5)	25.4 (12.2)	36.4 (11.3)	40.5 (9.5)
CT airway wall area thickness (WA %)*	62.4 (3.0)	60.1 (2.8)	60.4 (2.6)	62.3 (2.9)	63.3 (2.9)	63.4 (2.8)
Pi10*	3.73 (0.13)	3.65 (0.11)	3.62 (0.11)	3.69 (0.13)	3.75 (0.14)	3.76 (0.14)

All values expressed as mean (standard deviation) unless specified otherwise. PRISm = Preserved Ratio Impaired Spirometry. COPD = Chronic Obstructive Pulmonary Disease. GOLD = Global Initiative for Chronic Obstructive Lung Disease. CT = Computed tomography. FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity. PRM = Parametric response mapping. fSAD = Functional small airway disease. WA% = Percent wall area of segmental bronchi. Pi10= Square root of the wall area of a theoretical airway with internal perimeter of 10 mm.

*CT data available in 9017 participants for WA%, 8963 for Pi10, and 7695 for PRM data.

Supplemental Table E2: Multivariable Associations* of Peak Index with Respiratory Outcomes with inclusion of PRISm subjects (n=9584)

Parameter	Regression Coefficient β (SE)	p value
St. George's Respiratory Questionnaire Score	0.78 (0.14)	< 0.001
Modified Medical Research Council Score	0.02 (0.001)	0.006
6-Minute Walk Distance (ft)	1.33 (2.53)	0.601
BODE Index¥	0.20 (0.01)	<0.001
FEV_1 change over 5 years (ml/year)‡	18.11 (1.24)	<0.001

*Adjusted for age, race, gender, body-mass-index, smoking status, pack years, FEV_1, and CT emphysema.
¥ Adjusted for age, race, gender, smoking status, pack years, and CT emphysema.
‡ Adjusted for age, race, gender, body-mass-index, smoking status, pack years, and baseline FEV_1. (n=5318)
FEV_1 = Forced expiratory volume in the first second. CT = Computed tomography. BODE = Body-mass-index, airflow Obstruction, Dyspnea and Exercise capacity.

Survival Analysis

We had mortality data on 8328 participants including those with PRISm. After adjustment for age, sex, race, BMI, current smoking status, pack-years of smoking, and FEV_1, the Peak Index was associated with all-cause mortality (adjusted HR = 1.05,95%CI = 1.02 to 1.09; p=0.006).

Peaks and Bronchodilator Response

We categorized participants by the ATS criteria for bronchodilator response (BDR). We also classified participants as FEV_1 responders if they had at least a 12% and 200 ml increase in FEV_1, and as FVC responders if they had at least a 12% and 200 ml increase in FVC. We found that participants with a positive bronchodilator response by any definition had a greater change in peaks and peak index with the administration of bronchodilator. These changes were greater in magnitude in FVC responders.

Supplemental Table E3: Change in Peaks and Peak Index by Bronchodilator Response

		Number of peaks			**Peak Index**		
		Pre-BD	Post-BD	Delta with BD	Pre-BD	Post-BD	Delta with BD
ATS-BDR*	No 6464 (78%)	7.5 (5.4)	7.1 (5.3)	-0.3 (3.6)	2.8 (1.9)	2.7 (1.9)	-0.1 (1.3)
	Yes 1841 (22%)	8.8 (5.5)	10.0 (6.0)	1.3 (4.5)	3.8 (2.1)	3.7 (2.0)	-0.01 (1.6)
FEV_1-BDR*	No 7336 (87%)	7.6 (5.4)	7.5 (5.5)	-0.03 (3.8)	2.9 (2.0)	2.8 (2.0)	-0.07 (1.4)
	Yes 1056 (13%)	9.3 (5.5)	9.6 (5.8)	0.4 (4.5)	3.7 (1.9)	3.4 (1.8)	-0.25 (1.6)
FVC-BDR*	No 6985 (82%)	7.6 (5.4)	7.3 (5.3)	-0.4 (3.7)	2.8 (1.9)	2.7 (1.9)	-0.1 (1.3)
	Yes 1407 (17%)	8.4 (5.3)	10.4 (6.2)	2.0 (4.2)	3.8 (2.2)	3.9 (2.1)	0.1 (1.6)

BD = Bronchodilator. BDR = Bronchodilator Response. ATS = American Thoracic Society. FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity.

*$p<0.05$ for all comparisons between positive and negative BD response in each BDR category.

References

1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J and Force AET. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-38.

2. Ferguson GT, Enright PL, Buist AS and Higgins MW. Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. *Chest*. 2000;117:1146-61.