The importance of appropriate reference values in patients suspected of having obstructive lung disease

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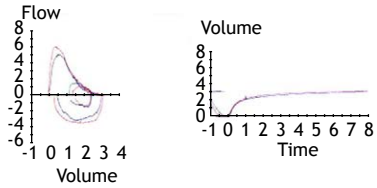
CLINICAL SCENARIO

A 69-year-old White female patient was suspected of having COPD and was therefore referred for functional evaluation. She reported a 4-year history of morning cough and sputum production, as well as dyspnea when hurrying on level ground or walking up a slight incline. She reported no wheezing attacks. The patient was a former

Spirometry		Pre	Ref		Ref	% Ref	Post	% Chg
FVC	Liters	3.02	2.78	(2.0 - 3.5)	109	3.11	112	3
FEV_1	Liters	2.08	2.16	(1.6 - 2.7)	96	2.19	101	6
FEV_1/FVC	%	69	78	(65.2 - 91.5)		71		
FEV_1/SVC	%	67				69		
$FEF_{25-75\%}$	L/sec	1.24	1.87	(0.9 - 2.9)	66	1.42	76	15
$FEF_{75-85\%}$	L/sec	0.25				0.34		33
$FEF_{50\%}$	L/sec	2.23				2.12		-5
$FEF_{75\%}$	L/sec	0.39	0.46	(0.2- 0.8)	85	0.54	117	38
PEF	L/sec	5.03				6.04		20
$FET_{25-75\%}$	Sec	1.22				1.11		-9
Vol Extrap	Liters	0.10				0.03		-70

Spirometry		Pre	Ref		Ref	% Ref	Post	% Chg
FVC	Liters	3.02	2.90	(2.3 - 3.5)	104	3.11	107	3
FEV_1	Liters	2.08	2.27	(1.7 - 2.9)	91	2.19	97	6
FEV_1/FVC	%	69	78	(69.7 - 86.7)		71		
FEV_1/SVC	%	67				69		
$FEF_{25-75\%}$	L/sec	1.24	2.06	(1.2 - 2.9)	60	1.42	69	15
$FEF_{75-85\%}$	L/sec	0.25	0.42	(0.2 - 0.6)	61	0.34	80	33
$FEF_{50\%}$	L/sec	2.23	2.79	(1.6 - 4.0)	80	2.12	76	-5
$FEF_{75\%}$	L/sec	0.39	0.68	(0.4 - 1.0)	57	0.54	79	38
PEF	L/sec	5.03	6.86	(5.1 - 8.6)	73	6.04	88	20
$FET_{25-75\%}$	Sec	1.22	0.81	(0.5 - 1.1)	150	1.11	136	-9
Vol Extrap	Liters	0.10				0.03		-70



Lung Volumes		Pre	Ref		Ref	% Ref	Post	% Chg
TLC	Liters	6.06	4.92	(4.2 - 5.7)	123	5.93	121	-2
VC	Liters	3.12	2.90	(2.3 - 3.5)	107	3.19	110	2
IC	Liters	2.97	2.31		103	2.54	110	7
FRC PL	Liters	3.69	2.55	(1.8 - 3.3)	145	3.39	133	-8
ERV	Liters	0.47	0.74		64	0.46	61	-4
RV	Liters	2.95	1.93	(1.3 - 2.6)	152	2.75	142	-7
RV/TLC	%	49	39	(29.5 - 49.3)		46		
Vtg	Liters	4.22				3.78		-10
Resistance								
sRaw	$cmH_2O/L/s/L$	10.57	5.95	(3.9 - 8.0)	178	7.04	118	-33
sGaw	$L/s/cmH_2O/L$	0.095	0.168	(0.1 - 0.2)	56	0.142	85	50

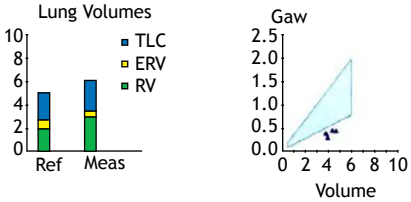


Figure 1. Functional values in patients suspected of having COPD, in comparison with the predicted values suggested by the Global Lung Function Initiative (in A)[1] and the predicted values for spirometry and lung volumes in the Brazilian population (in B and C).[2]

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smoker (with a smoking history of 35 pack-years), and her body mass index was 27.3 kg/m^2.

FUNCTIONAL ASSESSMENT

The patient underwent spirometry, which was performed in accordance with acceptability and reproducibility criteria. Spirometry results and lung volumes were determined on the basis of reference values suggested by the Global Lung Function Initiative (GLI) in 2012[1] and reference values for the Brazilian population,[2] and are shown in Figure 1.

When the GLI reference values were used,[1] the FEV_1/FVC ratio, $FEF_{25-75\%}$, and $FEF_{75\%}$ were found to be within the predicted range. When the reference equations for the Brazilian population were used,[2] the FEV_1/FVC ratio and $FEF_{75\%}$ were found to be slightly reduced. The presence of airflow obstruction was confirmed by increased specific airway resistance, RV, and TLC. There were no significant changes in lung function parameters after administration of 400 µg of bronchodilator via a metered dose inhaler.

COMMENTARY

In order to interpret pulmonary function test results correctly, it is critical to use appropriate reference values. Because numerous predicted value equations are available in the literature, reference values vary widely.

The GLI equations[1] included a large number of individuals from many centers. The results obtained were influenced by several factors, including sample selection and the variety of measurement and quality control techniques, all of which made it difficult to aggregate the results across studies and increased the range of predicted values, with very low lower limits. For example, for a 65-year-old male who is 170 cm in height, the lower limit of normal is 0.70 when the reference values for the Brazilian population are used[2] and 0.65 when the GLI reference values are used.[1] For a 65-year-old female who is 165 cm in height, the lower limit of normal is 0.70 when the reference values for the Brazilian population are used[2] and 0.66 when the GLI reference values are used.[3] The Global Initiative for Chronic Obstructive Lung Disease maintains that airflow obstruction should be defined by an FEV_1/FVC ratio of < 0.70; not surprisingly, a recent study[4] found that an FEV_1/FVC ratio of < 0.70 had better predictive value for long-term COPD-related hospitalization and mortality than did the lower limit of normal as defined by the GLI reference equations (i.e., < 0.70 for middle-aged individuals and the elderly).

The same applies to the lower limits of normal for $FEF_{25-75\%}$ and $FEF_{75\%}$, mid- and end-expiratory flows being of no value in characterizing airflow limitation when the limits recommended by the GLI[1] are used.[5]

In the study conducted in Brazil,[2] a small number of certified technicians supervised by the principal investigator throughout the study performed all tests at eight selected centers. Extensive efforts were made to meet acceptability and reproducibility criteria. In that study,[2] in addition to FEV_1 and FVC < 0.15 L, at least three peak flow values lower than the highest value by < 10% were required for acceptability. These criteria had not been used in previous studies.

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