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Research Article

Airway Clearance Index, Gas Exchange and Pulmonary Functions in Obstructed and Restricted Pulmonary Diseases Patients

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Abstract

Background: The lungs clearance index (LCI) is used to assess the efficiency of ventilation distribution homogeneity among the bronchial tree.

Purpose: The purpose of this study was to compare LCI with the standard pulmonary functions tests (PFT) as well as some selected gas exchange measures in three groups; healthy individuals, chronic obstructive pulmonary (COPD) and chronic restrictive pulmonary diseases (CRPD).

Methods: LCI was determined from the slope of phase-III of the nitrogen washout curve during single breath (SBN2W). PFT and gas exchange measures were determined using metabolic cart, Vmax29.

Results: One Way analysis (ANOVA) showed significant ($p<0.05$) main effects of group membership (Healthy vs. COPD Vs. RLD) on LCI and PFT forced breathing measures (FEV1, FVC, FEV1/FVC ratio). In addition, there was a significant main effect of group membership on gas exchange (VO2(max)). Bonferroni multiple comparisons showed that significantly ($p<0.05$) higher mean differences for LCI among groups, being highest for COPD, as compared with healthy and RLD. Multiple regression analysis showed significant ($p<0.05$) coefficients of determinations (r2) and regression coefficient (b) of LCI on FEV1 and FEV1/FVC ratio.

Conclusion: LCI, as determined by SBN2W, is a valid test to differentiate between COPD and RLD.

Keywords: Lung clearance index; LCI; FEV1; COPD; RLD

Introduction

Obstructive lung diseases (COPD) such as chronic bronchitis, bronchiectasis and bronchiolitis; are clinical conditions that are characterized by irreversible obstruction in the small airways Hogg [1]; Pellegrino et al. [2] Verbank et al. [3] and Verbanck et al. [4] and that elevates residual volume, anatomic VD/VT ratio and the subsequently hyperventilation of the lungs. On the other hands, however, restricted lung diseases (RLD) such as pneumonia, adult respiratory distress syndrome (ARDS), tuberculosis, sarcoidosis, pulmonary fibrosis and pleural effusion; are characterized by irreversible reduced total lung capacity, residual volume plus vital capacity Aron et al. [5]; Barreiro et al. [6]; Miller et al.,[7] and that increases the physiologic VD/VT ratio and the subsequent mismatch of ventilation to perfusion (VA/Q) and gas mixing in the lungs Hansen et al. [8]; ATS Guideline [9]; Swanney et al. [10]; GOLD Guideline [11]; Vesbo et al. [12].

Although FEV1 and FEV1/FVC ratio had been standardized to differentiate between COPD and RLD, however FEV1 is relatively insensitive to monitor progression of treatment follow up Beydon, et al. [13], diagnose early stages of COPD and CRD and difficult to perform on some elderly and children patients Verank et al. [3];

Swanney et al. [10]; Amin et al. [14]; keen et al. [15]. Furthermore, FEV1 may not directly assess neither the homogeneity of gases in the bronchial tree nor the insufficiency of the lungs' parenchyma in gas mixing. Besides its easiness to perform lungs clearance index (LCI) test is specific to assess efficacy of ventilation distribution homogeneity among the bronchial tree. Until now, there exist no differential data regarding the assessment of LCI of COPD, as compared with, RLD. Thus, there is a need to know whether LCI correlates with already well proven clinical outcome parameters in terms of FEV1 and FEV1/FVC ratio, for COPD as compared with RLD patients.

Furthermore, oxygen consumption (VO2) is a gas exchange measure that relies on the homogeneity of gases in the bronchial tree and gas mixing in the lungs' parenchyma. Until now, there exist no data to correlate gas exchange measure, maximal oxygen consumption (VO2) and LCI with already well proven clinical outcome (FEV1 FEV1/FVC ratio) to discriminate between COPD and CRD elderly patients. The aim of the present study was to investigate whether LCI and VO2max measurements are suitable tests to differentiate between COPD and RLD clinical conditions. The secondary aim was to validate the LCI finding with the already well proven and standardized clinical outcomes, FEV1 and FEV1/FVC ratio.

Methods

Study Design and Subjects

A retrospective study design was undertaken for the study. Thirty patient's records, 15 chronic pulmonary obstructed disease (COPD) and 15 restricted pulmonary lungs diseased (CRPD) were, selected and reviewed from patients' pool who visited Pulmonary clinics at LAC+USC Medical Center, LA, CA, USA. The criteria for selection were BMI 25+ 3, absence of comorbidity of cardiovascular diseases and absence of respiratory infection and the need of oxygen. A matched with BMI control group no smoker and never smoked individuals were chosen to serve as control match group. All patients signed an informed consent that was approved by Institutional Review Board (IRB) of LAC+USC Medical Center.

Pulmonary Function and Single Breath Test tests (SNB)

Pulmonary function tests (PFT) consisted of three repeated tests were performed, 15 min a part, to assess short-term repeatability between tests. All PFT test were conducted using Vmax-29 (Senor Medics, Yorba Linda, CA USA) that generated an automated full PFT report, with reference values of all lungs' mechanics and gas exchange measures in accordance to the American Thoracic Society (ATS) guideline. For single breath N2 washout was performed on flowmeter (Valadine Engineer, Huston USA) which measured molar mass and tidal flow. N2 measured directly using mass spectrometer (Perkin Elma-11. Dallas, USA). The slope of Phase-III (S-III) analysis was conducted by the same technician in order to minimize intraindividual errors. Tidal SBW tests were selected if tidal volumes were sufficiently large, i.e. phase-III of the washout curves reflected at least 50% of expired tidal volume Husemann et al. [16]. The slope of phase-III (S-III) was calculated automatically by linear fit program, between 65 and 95% of expired volume from tidal tests as described previously Horsley et al. [17,18], and between 25 and 75% of expired volume from the vital capacity N2-SBW Singer [19]; Houltz et al. [20,21] S-III was normalized with tidal volume to account for physiological differences in breaths within and between subjects Fuch et al. [22]; Robinson et. al. [23,24].

Statistical Analysis

Mean group differences for the dependent variables were evaluated using Univariate ANOVA to reveal the main effect of each group on the dependent variables. Bonferroni pairwise multiple comparisons were used to compare differences between each means pairs. Multiple linear regression (MLR) was utilized to validate the regression models of LCI on FEV1 and FEV1/FVC ratio. All statistical analysis was conducted using SPSS program (Ver. 16).

Results

Part I: Descriptive Findings

a) Gas Exchange Measures and Lungs Clearance Index:

The mean of oxygen uptake at rest (VO2rest), during symptom limited maximal exercise (VO2max) and lung clearance Index (LCI) of the normal healthy control (C), chronic obstructive pulmonary diseases (COPD) and chronic restrictive pulmonary diseases (RLD) were presented in Table 1A. The mean of oxygen uptake at maximal symptom limited exercise (VO2max) of normal healthy was higher than the clinical groups (COPD & RLD). The corresponding observed mean of lungs' clearance index (LCI) of obstructive pulmonary diseases (COPD) was higher than the mean of restrictive pulmonary diseases (RLD) and the normal healthy control (C), respectively (Table 1A).

Table 1A: Gas Exchange Variables ($VO2_{rest}$ & $VO2_{max}$) and Lungs Clearance Index (LCI).

Variable	Condition	N	Mean	Std. Error	Minimum	Maximum
$VO2_{rest}$	Normal Healthy	15	0.276	0.01899	0.13	0.38
	Obstructive	15	0.4013	0.03301	0.2	0.61
	Restrictive	15	0.4507	0.06282	0.14	0.79
$VO2_{max}$	Normal Healthy	15	3.046	0.08908	2.57	3.5
	Obstructive	15	1.0373	0.07894	0.72	1.71
	Restrictive	15	0.778	0.04377	0.49	1.01

LCI	Normal Healthy	15	7.3227	0.52358	4.07	10.13
	Obstructive	15	12.6193	0.57967	9.05	16.99
	Restrictive	15	10.534	0.6069	7.89	14.3

b) Lungs' Mechanics Measures (PFT), Spirometry:

The descriptive measures of the forced expiratory vital capacity at one second (FEV1), forced vital capacity (FVC), and the ratio of FEVC1 to FVC (FEVC1/FVC ratio) of the normal healthy control (C), chronic obstructive pulmonary diseases (COPD) and chronic restrictive pulmonary diseases (RLD) were presented in Table 1B. It was noted that the means of the lungs' mechanic measures (LCI) of the normal heathy control group were higher, as compared to, the clinical groups (COPD & RLD). However, there was no noticeable difference in the ratio of FEVC1 to FVC (FEVC1/FVC) of restrictive pulmonary diseases (RLD), as compared to, normal healthy control (C).

Table 1B: Means (+) SE of the Lungs' Mechanic Measures.

Measure	Condition	N	Mean	Std. Error	Minimum	Maximum
FEV1	Normal Healthy	15	3.1513	0.09149	2.69	3.88
	Obstructive	15	1.586	0.08179	0.94	1.9
	Restrictive	15	2.4627	0.0739	2.09	2.83
FVC	Normal Healthy	15	3.7147	0.09259	3.04	4.42
	Obstructive	15	3.3787	0.18915	1.96	4.12
	Restrictive	15	2.9413	0.14851	2	3.47
FEV1FVC Ratio	Normal Healthy	15	84.8667	0.7676	80	90
	Obstructive	15	47.1333	0.70283	42	51
	Restrictive	15	85.5333	2.74966	71	106

Part-II: Inferential Findings

Gas Exchange Measures and Lungs Clearance Index

The results of One-Way Analysis of Variance ANOVA (Table 2.1A) showed significant ($p<0.05$) F ratio ($p<0.05$) for gas exchange measures (VO2rest and VO2max) and lung clearance index (LCI) which means that the differences in the obtained means and the overall potential observations are significantly ($p<0.05$) different. That is the main effects of the clinical conditions (COPD and RLD) on VO2max, VO2rest and LCI, caused poor ventilation distribution among the bronchial tree and the lungs' parenchyma, hence negatively impacted gas exchange measures, VO2max, VO2rest. and further impacted N2 mixing, hence elevated LCI.

Table 2.1A: One-Way Analysis of Variance ANOVA for $VO2_{rest}$, $VO2_{max}$ and LCI.

Measure	Source of Variations	Sum of Squares	df	Mean Square	F	Sig.
VO2rest	Between Groups	0.243	2	0.122	4.508	0.017
	Within Groups	1.133	42	0.027		
VO2max	Between Groups	46.229	2	23.115	287.435	0
	Within Groups	3.377	42	0.08		
LCI	Between Groups	213.58	2	106.79	21.828	0
	Within Groups	205.482	42	4.892		

*The mean difference is significant at the 0.05 level.

Table 2.2A: Bonferroni Multiple Comparisons.

Dependent Variable	(I) Group	(J) Membership	Mean Difference (I-J)	Std. Error	Sig.
VO2rest	Normal Healthy	Obstructive	-0.12533	0.05998	0.128
		Restrictive	-.17467*	0.05998	0.017
	Obstructive	Normal Healthy	0.12533	0.05998	0.128
		Restrictive	-0.04933	0.05998	1
VO2max	Normal Healthy	Obstructive	2.00867*	0.10355	0
		Restrictive	2.26800*	0.10355	0
	Obstructive	Normal Healthy	-2.00867*	0.10355	0
		Restrictive	.25933*	0.10355	0.049

LCI	Normal Healthy	Obstructive	-5.29667*	0.80767	0
		Restrictive	-3.21133*	0.80767	0.001
	Obstructive	Normal Healthy	5.29667*	0.80767	0
		Restrictive	2.08533*	0.80767	0.04

*The mean difference is significant at the 0.05 level.

Bonferroni pairwise multiple comparisons (Table 2.2A) showed that the means of LCI in the clinical groups (COPD & RLD) were significantly ($p<0.05$) higher than the control group (C) and also the difference between the two clinical groups were significant ($p<0.05$), being higher in the COPD, as compared with, RLD group. On the contrary, the means of VO2max in the clinical groups (COPD and RLD) were significantly ($p<0.05$) lower than the control group (C) and also the difference between the two clinical groups were significant ($p<0.05$), being higher in the COPD, as compared with RLD group. These findings justify that VO2 and LCI are appropriate indices that can be used to differentiate among COPD and CRPD clinical conditions.

Lungs' Mechanics Measures (PFT), Spirometry

The results of One-Way Analysis of Variance ANOVA (Table 2.1B) showed significant ($p<0.05$) F ratio ($p<0.05$) for the lungs mechanics measures (FEV1, FVC & FEV1/FVC) which means that the differences in the obtained means of lungs mechanics measurers and the overall potential observations are significantly ($p<0.05$) different. Thus, there was significant ($p<0.05$) main effects of the clinical conditions (COPD and RLD) on FEV1, FVC and FEV1/FVC ratio, reflecting higher load of respiratory impedance, elevated anatomic VD/VT ratio, physiologic VD/VT ratio and ventilation to perfusion mismatch. Bonferroni pairwise means difference (Table 2.2B) showed that FVC was significantly ($p<0.05$) higher in the control, as compared with, COPD and RLD. Mean FEV1 of the control group was significantly ($p>0.05$) higher than the means of FEV1 of the two clinical groups (COPD and RLD). However pairwise means difference of the ratio of FEV1/FVC in the control and RLD was not significantly ($p>0.05$) different Table 2.2B).

Table 2.1B: One-Way Analysis of Variance ANOVA for the lungs Mechanics Measures.

Measure	Source of Variations	Sum of Squares	Df	Mean Square	F	Sig.
FEV1	Between Groups	18.465	2	9.233	89.978	0
	Within Groups	4.31	42	0.103		
	Total	22.775	44			
FVC	Between Groups	4.511	2	2.256	6.793	0.003
	Within Groups	13.945	42	0.332		
	Total	18.456	44			
FEV1/ FVC Ratio	Between Groups	14494.04	2	7247.022	167.681	0
	Within Groups	1815.2	42	43.219		
	Total	16309.24	44			

Table 2.2B: Bonferroni Multiple Comparisons.

Dependent Variable	(I) Group	(J) Membership	Mean Difference (I-J)	Std. Error	Sig.
VO2rest	Normal Healthy	Obstructive	-0.12533	0.05998	0.128
		Restrictive	-.17467*	0.05998	0.017
	Obstructive	Normal Healthy	0.12533	0.05998	0.128
		Restrictive	-0.04933	0.05998	1
VO2max	Normal Healthy	Obstructive	2.00867*	0.10355	0
		Restrictive	2.26800*	0.10355	0
	Obstructive	Normal Healthy	-2.00867*	0.10355	0
		Restrictive	.25933*	0.10355	0.049
LCI	Normal Healthy	Obstructive	-5.29667*	0.80767	0
		Restrictive	-3.21133*	0.80767	0.001
	Obstructive	Normal Healthy	5.29667*	0.80767	0
		Restrictive	2.08533*	0.80767	0.04

*The mean difference is significant at the 0.05 level.

PART-III Validation of LCI:

Two regression models were generated, using SPSS stepwise multiple linear regression subroutine, to validate LCI. The predictor for model-1 was FEV1 alone whereas, the predictors for model-2 were FEV1 and FEV1/FVC ratio (Table 3A). Although both models were significant ($p<0.05$), yet adding FEV1/FVC ratio in the model didn't improve the predictability, hence FEV1 alone is more powerful predictor for LCI. Clearly FVC reflect the lungs capacity and that somewhat had resulted in slim distortion of the second regression model. Figures 1a & 1b display the scatter plot of the linear associations of the two regression models, model-1 and model-2, respectively. The multicollinearity parameters of the predictor variables (FEV1 and FEV1/FVC ratio) were not significant ($p<0.05$), as evident by low variability of inflation factor (VIF below 5), significant ($p<.05$) zero order correlation (r-zero) and the small value of standard errors of beta (Table 3B).

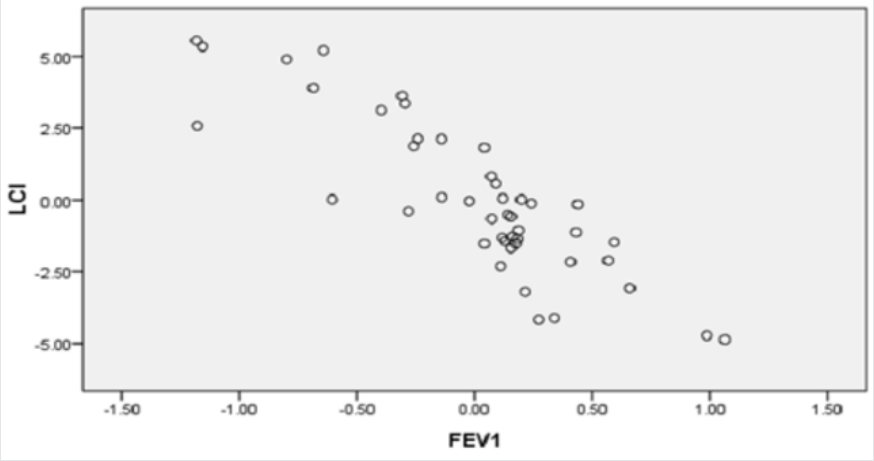

Figure 1a: Model-1: Linear regression of LCI on FEV1.

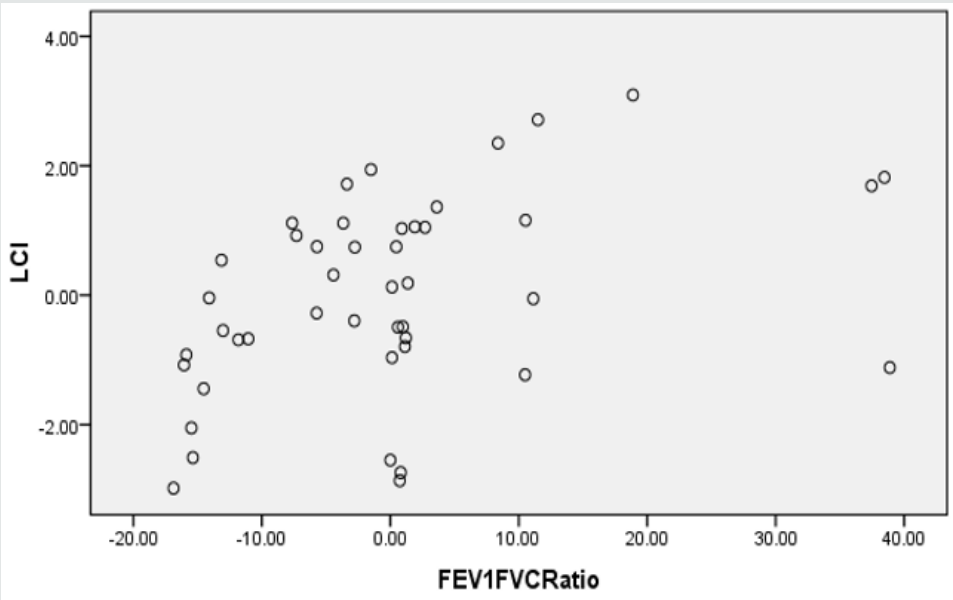

Figure 1b: Model-2: Linear Regression of LCI on FEV1 & FEV1/FVC Ratio.

Table 3A: Regression of LCI on FEV1 and FEV1/FVC Ratio.

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	319.438	1	319.438	137.878	.000a
	Residual	99.623	43	2.317		
	Total	419.062	44			

2	Regression	335.827	2	167.913	84.728	.000b
	Residual	83.235	42	1.982		
	Total	419.062	44			

a. Predictors: (Constant), FEV1;

b. Predictors: (Constant), FEV1, FEV1FVCRatio

c. Dependent Variable: LCI

Table 3B: Multicollinearity Among the Predictors Variables (FEV1 and FEV1/FVC Ratio).

Model		Unstandardized Coefficients		Correlations			Collinearity Statistics	
		B	Std. Error	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	19.147	0.798					
	FEV1	-3.745	0.319	-0.873	-0.873	-0.873	1	1
2	(Constant)	17.947	0.848					
	FEV1	-4.625	0.425	-0.873	-0.859	-0.748	0.482	2.076
	FEV1FVCRatio	0.046	0.016	-0.491	0.406	0.198	0.482	2.076

Discussion

The major findings of the present study showed that the means of LCI in the clinical groups (COPD & RLD) were significantly ($p<0.05$) higher than the control group (C) and also the difference between the two clinical groups were significant ($p<0.05$), being higher in the COPD, as compared with RLD group. Practically an obstructive defect is indicated by low FEV1/FVC, below 70 percent, based on GOLD criteria and/or below the fifth percentile of lower limit of normal (LLN) based on ATS criteria ATS guideline [25]; Beydon et al. [13]; Bhatt and Wood [26]. Remodeling of airways tree inducted by COPD diseases and related lungs' parenchymal changes inducted by RLD had influenced N2 homogeneity mixing. Compared to the classical tests, FEV1, we found that LCI test was easy for patients to perform, highly repeatable within trials and detected differences among the clinical groups, COPD and RLD, sensitive to differentiate COPD from RLD. Some of those findings were noted previously Kieninger et al. [19]; Subbaro et al. [27]. Because only tidal breathing is required without forced respiratory maneuver, LCI is suitable to use in children and elderly in whom respiratory effort related procedures are difficult to perform. The LCI test can therefore be successfully performed in all ages, hence is an exciting development in the field of the lungs' physiology assessments.

It was previously reported that LCI reflect slim improvement of ventilatory capacity after bronchodilator inhalation in children with advanced cystic fibrosis lung disease Lum et al. [10]; Amin et al. [28], Vesbo et al., [12]. Kramer and associates followed up 142 cohort children (age 6 – 18 years) with cystic in whom 4 subsequent annual evaluation of PFT, FRC and LCI (using N2 washout) were conducted. Their results demonstrated that LCI was the earliest measurement to deteriorate and was elevated in more than half of those with FEV1 within the normal range. In their previous investigation, the same authors reported that LCI continued to increase accompanied with the rise in pulmonary hyperinflation and trapped gas volume, beyond the age of 12 years, whereas FEV1 Z-scores was not changed Kramer et al. [29]. In their subsequent work, they reported elevated LCI in patients with allergic bronchopulmonary aspergillosis (ABPA), and that the slope of longitudinal progression of LCI was greatest in those chronically infected with P. aerugi- nosa Kramer et el. [30]. Interestingly, it was reported that LCI was the most sensitive differentiating factor between subgroups, based on chronic and intermittent P. aeruginosa colonization of the lower airway Kramer et el. [30].

The findings that higher VO2rest for the clinical groups can be explained by the increased work of breathing, mainly due to elevated O2 consumption by the respiratory muscles, also known as muscle wasting. Obviously, hyperinflation of COPD shortens the diaphragm, moving it to a biomechanical disadvantageous portion of its length-tension curve. Moreover, the zone of apposition is reduced, and this impairs the optimal inspiratory action of the muscle resulting in greater load, elevated work of breathing Miller et al. [31]; Keen et al. [32]; Jones et al. [12]. The findings of the present study showed that means of VO2max in the clinical groups (COPD and RLD) were significantly ($p<0.05$) lower than the control group (C) and also the difference between the two clinical groups were significant ($p<0.05$), being higher in the COPD, as compared with RLD group. These findings justify that VO2max and LCI are appropriate indices that can be used to differentiate among COPD and RLD clinical conditions. Clearly, bronchoconstriction elevates air flow resistance in the bronchial tree and decrease in the physiological dead space to tidal volume ratio (VD/VT).

Furthermore, bronchoconstriction results in increasing CO2 load on the lungs and lower respiratory drive. Both COPD and RLD patients increases their total minute ventilation (VE) via increasing breathing frequency, in attempt, to maintain efficient carbon dioxide output because of their reduced alveolar ventilation. The findings

that VO2max of the clinical groups were lower in the clinical groups, as compared with control, implying that both diseases severely impacted gas exchange reserve and reduced physical working capacity. Several physiological mechanisms that underlie reduced VO2max that includes, but not limited to; 1) increased the work of breathing, hence respiratory muscle fatigue, 2) impaired efficiency of pulmonary gas exchange and 3) Mismatching of ventilation to perfusion which inhibits cardiovascular and muscular systems to keep up with increasing exercise intensity. It was reported previously COPD and RLD patients their pulmonary artery wedge pressure rises sharply on exercise and their cardiac output fail to keep up with an adequate increase with increasing exercise load resulting in functional impairment of the pulmonary and cardiovascular systems Güder et al. [33,34].

In restrictive lung diseases (RLD), modulation of the lungs' parenchyma contributes to reduced gas transfer, which may be marked clinically by reduced VO2max and desaturation during maximal exercise. Corris and associates reported a fall of 18 – 40 percent in VO2max following lobectomy and pneumonectomy Corris et al. [35]. In addition, both COPD and RLD conditions are systemic diseases that impact other organs such as cardiovascular and muscular system, high proportion of glycolytic type II fibers, decreased muscle mass, decreased capillary density, and reduced number of aerobic enzymes. Clearly all these systemic factors induct negative changes on the maximal rate of oxygen uptake [36-39].

Conclusion

Based on the results of the present study and other studies [40, 41], it can be concluded that LCI, as determined by SBN2W, is a valid test to differentiate between normal healthy, COPD and RLD.

References

1. Hogg JC, Chu F, Utokaparch S (2004) The nature of small-airway obstruction in chronic obstructive pulmonary disease NEnglJ Med 350(26): 2645-2653.
2. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, et al. (2005) Interpretative strategies for lung function tests. Europium Respiration Journal 26(5): 948-968.
3. Verbanck S, Schuermans D, Vincken W (2007) Small airways ventilation heterogeneity and hyperinflation in COPD: response to tiotropium bromide. International journal of chronic obstructive pulmonary disease 2(4): 625-634.
4. Verbanck S, Thompson BR, Schuermans D, Kalsi H, Biddiscombe M, et al. (2012) Ventilation heterogeneity in the acinar and conductive zones of the normal ageing lung. Thorax 67(9): 789-795.
5. Aaron SD, Dales RE, Cardinal P (1999) How accurate is spirometry at predicting restrictive pulmonary impairment? Chest 115(3): 869-873.
6. Barreiro TJ, Perillo I (2004) An approach to interpreting spirometry. Am Fam Physician. 69(5): 1107-1114.
7. Miller MR, Hankinson J, Brusasco V, , Burgos F, Casaburi R , et al. (2005) Standardization of spirometry. European Respir Journal 26(2): 319-338.
8. Hansen JE, Sun XG, Wasserman K (2007) Spirometric criteria for airway obstruction: use percentage of FEV1/FVC ratio below the fifth percentile, not < 70%. Chest 131(2): 349-355.
9. (1991) American Thoracic Society Lung function testing: selection of reference values and interpretative strategies Am Rev Respir Dis 144(5): 1202-1218.
10. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, et al. (2008) Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruc- toon. Thorax 63(12): 1046-1051.
11. (2009) Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2008 Global strategy for diagnosis, management, and prevention of COPD.
12. Vesbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, et al. (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary dis- ease: GOLD executive summary. American Journal of Respiration Critical Care Med 187(4): 347-365.
13. Beydon N, Davis SD, Lombardi E (2007) An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med 175: 1304-1345.
14. Amin R, Subbarao P, Jabar A (2010) Hypertonic saline improves the LCI in pediatric patients with CF with normal lung function Thorax 65: 379-383.
15. Keen C, Olin AC, Wennergren G, Gustafsson P (2011) Small airway function, exhaled NO and airway hyper-responsiveness in paediatric asthma. Respir Med 105(10): 1476-1484.
16. Husemann K, Berg N, Engel J, Port J, Joppek C, et al. (2014) Double tracer gas single-breath washout: reproducibility in healthy subjects and COPD. Eur Respir Journal 44(5): 1210-1222.
17. Horsley AR, Macleod KA, Robson AG (2008) Effects of cystic fibrosis lung disease on gas mixing indices derived from alveolar slope analysis. Respiratory physiology & neurobiology 162(3): 197-203.
18. Horsley AR, Gustafsson PM, Macleod KA (2008) Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. Thorax 63(2): 135-140.
19. Kieninger E, Singer F, Fuchs O, Abbas C, Frey U, et al. (2011) Long-term course of lung clearance index between infancy and school-age in cystic fibrosis subjects. Journal Cyst Fibros 10(6): 487-490.
20. Singer F, Stern G, Thamrin C, Abbas C, Casaulta C, et al. (2013) A new double-tracer gas single-breath washout to assess early cystic fibrosis lung disease. Europium Respiration Journal 41(2): 339-345.
21. Singer F, Houltz B, Latzin P, Robinson P, Gustafsson P (2012) A realistic validation study of a new nitrogen multiple-breath washout system. PLoS One 7(4): e36083.
22. Fuchs SI, Buess C, Lum S, et al. (2006) Multiple breath washout with a sidestream ultrasonic flow sensor and mass spectrometry: a comparative study. Pediatr Pulmonol 41(12): 1218-1225.
23. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, et al. (2013) Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Europium Respiration Journal 41(3): 507-522.
24. Robinson PD, Goldman MD, Gustafsson PM (2009) Inert gas washout: theoretical background and clinical utility in respiratory disease. Respiration 78(3): 339-355.
25. Burgel PR (2011) The role of small airways in obstructive airway diseases European respiratory review: an official journal of the European Respiratory Society 20(119): 23-33.
26. Bhatt NY[1], Wood KL (2008) What defines abnormal lung function in older adults with chronic obstructive pulmonary disease? Drugs Aging 25(9): 717-728.

27. Subbarao P, Stanojevic S, Brown M, Jensen R, Rosenfeld M, et al. (2013) Lung clearance index as an outcome measure for clinical trials in young children with cystic fibrosis. A pilot study using inhaled hypertonic saline. American Journal Respiration Critical Care Med 188(4): 456-460.

28. Amin R, Subbarao P, Lou W (2011) The effect of dornase alfa on ventilation Inhomogeneity in patients with cystic fibrosis Eur Respir J 37 (1): 806-812.

29. Kraemer R, Blum A, Schibler A, Ammann RA, Gallati S (2005) Ventilation inhomogeneities in relation to standard lung function in patients with cystic fibrosis. American Journal Respiration Crit Care Med 171(4): 371-378.

30. Kraemer R, Delosea N, Ballinari P, Gallati S, Crameri R (2006) Effect of allergic bronchopulmonary aspergillosis on lung function in children with cystic fibrosis. American Journal Respiration Crit Care Med 174(11): 1211-1220.

31. Miller MR, Quanjer PH, Swanney MP, Ruppel R, Enright PL, et al. (2011) Interpreting lung function data using 80% predicted and fixed thresholds misclassifies more than 20% of patients. Chest 139(1): 52-59.

32. Jones P, Miravitlles M, Van Der Molen T (2012) Beyond FEV(1) in COPD: a review of patient-reported outcomes and their measurement. International journal of chronic obstructive pulmonary disease 7: 697-709.

33. G, Brenner S, Störk S, Hoes A, Rutten FH (2014) Chronic obstructive pulmonary disease in heart failure: accurate diagnosis and treatment Eur J Heart Fail 16(12): 1273-1282.

34. Güder G, Brenner S, Angermann CE (2012) GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study Respir Res 13(1): 13.

35. Corris PA, DA Ellis, T Hawkins, GJ Gibson (1987) Use of radionuclide scanning in the preoperative estimation ofpulmonary function after pneumonectomy Thorax 42(4): 285-291.

36. Horsley A (2009) Lung clearance index in the assessment of airways disease Respir Med 103(6): 793-799.

37. Horsley AR, Macleod KA, Robson AG (2008) Effects of cystic fibrosis lung disease on gas mixing indices derived from alveolar slope analysis. Respir Physiol Neurobiol 162(3): 197-203.

38. Houltz BG, K Lindblad, A Singer, F Nielsen, K Gustafsson et.al. N2 (2012) washout ventilation inhomogeineity indices in a reference population ages 7-70 years. European Respiratory Journal 40(56): 694s.

39. Lum S, Gustafsson P, Ljungberg H, Hulskamp G, Bush A, et al. (2007) Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. Thorax 62(4): 341-347.

40. Singer F, Kieninger E, Abbas C, Yammine S, Fuchs O, et al. (2012) Practicability of nitrogen multiplebreath washout measurements in a pediatric cystic fibrosis outpatient setting. Pediatr Pulmonol 2012 48(8): 739-746.

41. Stromberg NO, Gustafsson PM (2000) Ventilation inhomogeneity assessed by nitrogen washout and ventilation-perfusion mismatch by capnography in stable and induced airway obstruction. Pediatr Pulmonol 29(2): 94-102.

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