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Title: The effect of Pulmonary Rehabilitation on the value of inspiratory capacity-to-total lung capacity (IC/TLC) ratio in patients with COPD

Short title: The effect of Pulmonary Rehabilitation on the value of IC/TLC

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Abstract

OBJECTIVE: In patients with COPD, IC/TLC has been found to be correlated with mortality and reduced exercise capacity. Pulmonary rehabilitation (PR) is known to improve exercise capacity and respiratory functions of COPD patients. Our study aims to examine the impact of PR on IC/TLC ratio in patients with COPD.

MATERIALS AND METHODS: We included a total of 122 patients with COPD, who received PR therapy twice a week over a period of 8 weeks in an outpatient clinic.

RESULTS: Patients' mean age was 62.5 (±8.2), 15 patients (12.3%) were female. Post-PR FEV1, TLCO, and pO2 values, and 6mWD, dyspnea, and quality of life scores indicated a statistically significant improvement ($p<0.05$ for all). Patients were grouped as follows: IC/TLC>0.25 as Group 1 and IC/TLC≤0.25 as Group 2. Both groups exhibited a significantly increased post-PR 6mWT distance (375-420, 336-400 m) with no difference between the groups. We observed significantly increased FEV1% in both groups after the PR ($p=0.007$, 0.004). Again, quality of life questionnaires and mMRC scores significantly improved for both groups ($p<0.001$). Although no post-PR IC/TLC improvement was detected in patients with good prognosis, we identified an IC/TLC improvement in the poor prognosis group (Group 2) ($p=0.002$).

CONCLUSION: COPD patients with IC/TLC≤0.25 benefit from the PR just as those COPD patients with IC/TLC>0.25.

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Key words: COPD, IC/TLC, pulmonary rehabilitation, dyspnea

INTRODUCTION

COPD is a treatable and preventable disease which represents an important public health problem [1]. Today, COPD is known to be the fourth leading cause of death worldwide [2]. In the future, by 2020, estimations suggest it to become the third leading cause of death [2]. Inspiratory capacity to total lung capacity (IC/TLC) ratio, demonstrated to be in strong association with exercise tolerance and exercise-associated dynamic hyperinflation, is used as an indicator of static lung hyperinflation in several studies [3-4]. Moreover, publications showed a powerful association between resting IC and functional exercise limitation in patients with COPD [5]. Casanova et al. evaluating a cohort of 689 subjects (95% male) suggested that an IC/TLC ratio of ≤25% provided the best combined sensitivity and specificity to predict all-cause mortality in COPD patients in comparison with FEV_1 and the BODE index [6].

The pulmonary rehabilitation (PR) is among the most effective non-pharmacological therapies of patients with COPD [7]. Exercise performance is limited with static pulmonary hyperinflation in COPD patients therefore for an effective PR program; exercise training should be an important component of it [8]. In clinically stable patients with COPD, IC/TLC is a predictor of exercise capacity decline however the change of IC/TLC after a PR program is unknown [2]. Therefore, we aimed to study the effect that pulmonary rehabilitation exerts on the value of IC/TLC ratio in patients with COPD.

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MATERIAL AND METHODS

We performed a retrospective cohort study to find out, by comparison, the effectiveness of PR on the value of IC/TLC ratio in patients with COPD. The study's Ethics Committee Approval was provided by the local institutional review board. Subjects included in the present study completed an informed written consent form.

Subject Selection

We recruited stable (for at least 4 weeks, no increase in the use of rescue medication, no worsening of respiratory symptoms, and no unscheduled visits because of COPD worsening) patients with COPD, who were diagnosed based on the Global initiative for Chronic Obstructive Lung Disease (GOLD) definition. All patients had reduced exercise tolerance and were suffering from dyspnea, also have limitations in daily living activities. The recruitment criteria included; a ratio of FEV-1-to-FVC of 0.7 or less following bronchodilator administration, a history of 10 or more pack-years of smoking history, and a minimum age of 40 years old [9]. GOLD grading system is used for the patient's COPD severity [10]. At the beginning of the study, respiratory symptoms self-reported by patients, medication usage, smoking history, and coexisting medical conditions were documented. We excluded patients presenting a history of other pulmonary diseases, (coexisting pneumoconiosis, interstitial lung disease, pulmonary tuberculosis etc.); and any impairment (neurologic, orthopedic, or cardiovascular) that might prevent the subject from completing the exercise training and also those patients with acute COPD exacerbation. In addition, subjects with poor compliance; who did not attend the program more than two times, and subjects with poor motivation or transportation difficulties were excluded. We grouped patients as follows: patients with an IC/TLC >0.25 as Group 1 and patients with an IC/TLC ≤0.25 as Group 2 [11].

Measurement of Pulmonary Parameters and Questionnaires

All patients had blood gas analysis and chest X-rays before and after PR as well as cardiac and respiratory system examinations. We assessed the pulmonary function by measuring carbon monoxide diffusing capacity (Zan 300, Germany) and body plethysmography (Zan 500, Germany). IC/TLC is calculated from body plethysmography results. The Modified Medical Research Council (MMRC) dyspnea scale was used for assessing dyspnea and modified BORG scales was used before and after PR [10]. The assessment for quality of life was performed with the disease-specific St. George Respiratory Questionnaire and SF-36 health-related quality of life questionnaire [12, 13]. The Hospital Anxiety and Depression Questionnaires were used for assessing psychological symptoms [14,15]. A six-minute walking test (6 mWT) was used in line with the standards published by the American Thoracic Society (ATS) [16]. Including the blood gas analysis, all measurements were assessed at admission and at the end of the PR.

Pulmonary Rehabilitation Parameters

In our hospital's Pulmonary Rehabilitation Unit, patients underwent an 8-week hospital-based outpatient pulmonary rehabilitation program twice a week. Pulmonary rehabilitation was totally tailored to conform to a subject's needs. The PR program consisted of supervised exercise training, education, psychological counseling, and nutritional intervention. We chose exercises for each patient based on their disease severity and exercise toleration capacity. Exercises included the following: cycle training (at least 15 minutes), breathing exercises, treadmill (min. 15 minutes), peripheral muscle training, and stretching. In addition, the trainers gave the patients advice on bronchial hygiene techniques, medication, relaxation techniques to reduce dyspnea, energy conservation, and home exercises [17]. Upper and lower extremity stretching and strengthening exercises were performed after respiratory physiotherapy education. The strengthening exercises were initiated with no weight. According to the BORG scale a half-kilogram weight was added after every four cycles of exercises [7-8]. The bicycle/arm ergometer and treadmill were used for aerobic exercises. We calculated workloads for cycling and walking speed for treadmill from 6 MWT results [18]. Treadmill walking speed is calculated as 80% of the average 6 MWT speed using the following formula: (6 mWT distance x 10) ÷ 1000 km/hr). Cycling workload was calculated with the formula (Watt= 103.217 + (30.500 x Sex) + (-1.613 x age) + [(0.002 x distance x weight)] sex; male=1 female=0). Patients were trained at 60-90% of the maximum heart rate. We used BORG dyspnea scores to regulate exercise duration and loads [10, 17]. Exercise intensity was observed to increase with patient progress. We used pulse oximetry to supervise patients during the exercise, and supplementation was provided if the SpO_2 decreased below 90% oxygen. Pre-PR and post-PR arterial blood gas analyses were taken.

Statistical Analysis

For numeric variables normality distribution were tested by Kolmogorov Smirnov Test. Continuous variables with normal distribution were presented with means and standard deviations, whereas categorical variables were described by frequencies and percentages. Numeric variables without normal distribution were presented by medians and interquartile ranges. For defining relationship between two categorical variables Chi-square test (or Fisher's exact test) was utilized. We compared two independent means by Student t-test, and compared two independent medians by Mann-

Whitney U-Test, and two dependent medians were compared by Wilcoxon test. A p-value less than 0.05 was considered to indicate a statistically significant difference between parameters examined.

RESULTS

The majority of included patients were male (87.7%). Patients had a mean age of 62.5 years (±8.2) and a mean forced expiratory volume in 1 second in % of predicted of 40.5% (±27.5%). Patient characteristics are presented in Table 1. Apart from BMI and COPD stages classification, all baseline variables were well balanced between two groups (Table 2). The median IC/TLC ratio (IQR) was 0.29 (0.19) for all participants and did not significantly changed after PR (p=0.291). For all participants after PR there is an increase in FEV1% predicted, TLCO, pO2 levels and an improvement in QoL and dyspnea scores ($p<0.05$ for all). Patients with IC/TLC>0.25 classified as Group 1 ve IC/TLC≤0.25 as group 2. The differences after PR for both groups are shown in Table 3. 6mWD improved in both groups after PR (375-420, 336-400 meter, respectively) but the difference in between groups were not significant. In both groups the pO2 levels significantly increased after PR ($p<0.001$), but the difference between groups were not significant ($p>0.05$). Also after PR there is a significant increase in FEV1% predicted level in both groups (p=0.007, 0.004). Both QoL scores and mMRC scores improved significantly after PR in two groups ($p<0.001$). In group 1 (IC/TLC>0.25) there was a statistically significant decrease in this ratio after PR (p=0.001). In group 2 (IC/TLC<0.25) there is a statistically but not clinically significant improvement in IC/TLC score after PR (p=0.002), this improvement was not observed in group 1. When we compare the difference of IC/TLC (ΔIC/TLC) before and after PR there was a statistical significance between two groups ($p<0.001$).

DISCUSSION

IC/TLC ratio is an important predictor of mortality in emphysematous patients with COPD. Moreover, IC/TLC ≤25% is associated with a higher risk of death [6]. In our study we showed that in COPD patients with IC/TLC<0.25; a significant improvement in FEV1, QoL parameters and exercise capacity was observed, and also there was a statistically significant but not clinically insignificant improvement in IC/TLC after PR.

PR is an evidence-based non-pharmacological treatment in managing patients with COPD. PR is shown to mitigate symptoms of dyspnea, improve exercise capacity, and increase health-related QoL [20]. Respiratory function tests present differing results following the PR. No significant change in FEV1, FVC and FEV1/ FVC values was observed in most of them [21,22]. However, the findings seem to be controversial. In a study by Cecily et al. 100 patients with COPD had showed significant improvement in FEV1 and FVC as well as the value of peak expiratory flow rate (PEFR) [23]. Shebl et al. showed that after a supervised two-month home based exercise program FEV1 increased exclusively in severe COPD, while FVC and FEV1/FVC ratio was increased in the medium and severe COPD. However, such increases were insignificant [24]. In a study comparing the differences of improvement by gender; FEV1 and FVC increased in both gender however a greater improvement was obtained in man after PR program [25]. In another study assessing 225 patients based on the severity of COPD after PR program; FEV1 increased significantly in stage 3 and 4, vital capacity rose to a significant extent to 2, 3 and 4, TLC was reduced significantly in stage 3 only, and residual volumes were significantly lower in stage 3 and 4 [26]. In our study we found a significant increase in FEV1% predicted level in both groups. We believe that after breathing exercises and techniques COPD patients are able to perform better pulmonary functions test results.

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Our knowledge of the process concerning the COPD disease has been increasing continuously. Despite the initial studies' promotion of FEV_1 to be one of the best predictors of COPD-associated mortality [19], more recent publications have shown that other factors prove more accurate predictors of mortality than FEV_1 [4-6]. It is capable of showing that the IC/TLC ratio was in correlation with the risk of death in patients with an emphysematous phenotype of COPD, using an IC/TLC ratio of ≤25%, which is a representation of static lung hyperinflation. For those patients with an IC/TLC ≤25%, French et al. showed that patients with an IC/TLC ratio ≤25% had a median survival of 4.3 years versus 11.9 years. In our study patients with a good prognosis had a decrease in IC/TLC ratio after PR reversely the bad prognosis group had an increase in this ratio after PR. It is not well defined if these alterations have a clinically significant importance. More data is needed to confirm these results. But we believe that this is the one of the few studies showing the COPD patients with a high risk of mortality, benefit from a pulmonary rehabilitation program.

Cebollero et al studied 35 men presenting moderate to severe COPD, the patients were categorized into those with IC/TLC≤25% (n=16) and >25% (n=19). They concluded that IC/TLC≤25% was associated with lower maximal strength and peak power output of the lower extremities. IC/TLC≤25% may have an important clinical relevance as an index to determine peripheral muscle dysfunction [27]. In a study by Ramon et al., it was demonstrated by a bivariate analysis that patients with lower levels of IC/TLC presented higher 6MWD decline (-27.4 ± 42.5, -24.9 ± 36.5 and -13.4 ± 39.9 m/year in the first, second and third tertile of IC/TLC, respectively; P-for-trend = 0.018)[28]. We believe that with the new studies investigating IC/TLC ratio; this index will not only be a prognostic marker but also a severity index and a follow up marker.

In our daily practice, PR is known to be a standard method that is effective in increasing exercise capacity, reducing perceived dyspnea, and improving the quality of life in patients with COPD [17-20]. As part of the present study, all COPD patients who completed the PR program showed reduced perceived dyspnea, increased exercise capacity, and improved quality of life. Our PR program which has multi-component interventions included in supervised physical exercise training, theoretical training, psychological counseling and nutritional intervention. We believe that the improvement in COPD patients after PR may be due to multi-component interventions. Coventry et al. showed that, after receiving training and psycho-social support in the PR program, patients with COPD reported lower levels of anxiety and depression [29]. Yet this study found that anxiety scores decreased significantly in both groups, but the depression scores only significantly decreased in group 1.

Our results must be considered in the context of the limitations of our study. First of all, our pulmonary function test laboratory is not a research but a clinical laboratory. IC/TLC is calculated from body plethysmography results therefore like any clinical test, the body plethysmography results must be interpreted carefully. Secondly COPD is a heterogeneous disease and prediction of mortality depends on various factors. Only a pulmonary function test ratio may not reflect the whole diseases process.

CONCLUSION

IC/TLC ratio is a significant predictor of mortality in patients with COPD. As a conclusion our study showed that COPD patients with IC/TLC≤25% had a significant improvement in FEV1, QoL parameters and exercise capacity also there was a statistically but not clinically significant improvement in IC/TLC after PR program. We believe that to benefit most from PR program; further studies should be performed to provide an opportunity for COPD patients, IC/TLC≤25% in particular.

Declaration of Interest

The authors declared that they have no conflict of interest.

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Table 1: Baseline demographic and clinical features of patients

Age (Mean, SD)	62,5	8,2
Sex (n, %)		
Female	15	12,3
Male	107	87,7
BMI kg/m2 (Median, IQR)	26	8
Comorbidity (n, %)		
Absent	55	45,1
Present	67	54,9
Biomass exposure (n, %)	6	4,9
Smoking history (n, %)	116	95,1
Smoking pack x years (Median, IQR)	60	40
FEV1 (%) mean ±SD	40.5	27.5
IC/TLC Median IQR	0.29	0.19
Stage (n, %)		
I	4	3,3
II	35	28,7
III	53	43,4
IV	30	24,6

Table 2: The comparison of the demographic differences between two groups

	IC/TLC>0.25	IC/TLC≤0.25	p
Age (Mean, SD)	61.9±7.2	63.1±9.3	0,406
Sex (n, %)			
Female	9 (12.5)	6 (12.2)	0,967
Male	63 (87.5)	43 (87.8)	
BMI (Median, IQR)	27 (7)	25 (8)	0,015
Comorbidity (n, %)			
Absent	31 (43.1)	23 (46.9)	0,673
Present	41 (56.9)	26 (53.1)	
Biomass exposure (n, %)			
Smoking	68 (94.4)	47 (95.9)	>0.999
Others	4 (5.6)	2 (4.1)	
Smoking (Median, IQR)	50 (43.75)	60 (30)	0,330
Stage (n, %)			
I	4 (5.6)	0 (0)	0,003
II	26 (36.1)	8 (16.3)	
III	31 (43.1)	22 (44.9)	
IV	11 (15.3)	19 (38.8)	

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Table 3: The comparison of two groups before and after Pulmonary rehabilitation in terms of pulmonary function tests, blood gas analysis, exercise capacity and quality of life parameters

	IC/TLC>0.25			IC/TLC≤0.25	
	Before Median (IQR)	After Median (IQR)	p	Before Median (IQR)	After Median (IQR)
FEV1	47 (27.8)	49 (26.5)	0,007	33 (14.5)	35 (16.5)
FEV1/FVC	61 (19.5)	62 (21)	0,552	51 (21)	51 (23.5)
IC	70.5 (34.5)	67.5 (38)	0,061	41 (22.5)	46 (32.5)
TLC	92 (32)	95.5 (33)	0,832	103 (26.5)	114 (33.5)
IC/TLC	0.37 (0.19)	0.31 (0.17)	0,001	0.19 (0.1)	0.22 (0.16)
TLCO	42 (27)	43.5 (28)	0,026	34 (27)	34 (21)

	IC/TLC>0.25			IC/TLC≤0.25	
	Before Median (IQR)	After Median (IQR)	p	Before Median (IQR)	After Median (IQR)
pO2	74 (16)	79.5 (15.8)	<0.001	67 (11.4)	73.7 (13)
pCO2	40.4 (7.2)	40 (7.8)	0,022	40.3 (9)	41 (7.7)
Saturation	95 (2)	96 (2.5)	<0.001	93.6 (4.6)	95 (3)
pH	7.4 (0.04)	7.4 (0.04)	0,923	7.4 (0.04)	7.4 (0.04)

	IC/TLC>0.25			IC/TLC≤0.25	
	Before Median (IQR)	After Median (IQR)	p	Before Median (IQR)	After Median (IQR)
Distance	375 (140)	420 (117.5)	<0.001	336 (130)	400 (130)
BORG difference	1.5 (1)	1 (0.5)	<0.001	2 (2)	2 (1.8)
Saturation difference	2 (2.8)	1 (3.8)	0,436	2 (5)	3 (5.5)

	IC/TLC>0.25			IC/TLC≤0.25	
	Before Median (IQR)	After Median (IQR)	p	Before Median (IQR)	After Median (IQR)
SGRQ Symptoms	48.4 (31)	39.2 (27.6)	0,001	67.4 (36)	50.7 (27.9)
SGRQ Activity	60.5 (31.7)	48.05 (30.5)	<0.001	72.3 (32.9)	60.4 (38.3)
SGRQ Impact	42.3 (31.4)	27.8 (26.6)	<0.001	50.7 (31.7)	35.6 (34.3)
SGRQ Total	52.7 (32.5)	37.4 (25.7)	<0.001	61.3 (31)	46.5 (33.6)

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Physical functioning	57.5 (40)	70 (35)	0,002	45 (45)	60 (35)
Social functioning	75 (37.5)	87.5 (31.3)	0,001	50 (50)	75 (50)
Role limitations due to physical health	25 (75)	75 (75)	<0.001	0 (25)	25 (100)
Role limitations due to emotional problems	33.3 (100)	66.7 (66.7)	0,024	5 (66.7)	66.7 (100)
General health	45 (36.3)	62 (35)	<0.001	30 (36.3)	40 (47)
Emotional well being	70 (24)	76 (22)	0,033	60 (36)	68 (36)
Pain	67 (45.3)	84 (34)	0,001	42 (52)	74 (48)
Energy/fatigue after	55 (35)	70 (27.5)	0,002	40 (35)	60 (30)
HADA	7 (6)	5 (5.5)	<0.001	8 (8)	7 (5)
HADD	5 (6)	4 (6)	0,005	7 (5)	7 (6)