Pulmonary Function and Bronchial Hyper - Responsiveness Profile of Indonesian Patients with Asthma - Chronic Obstructive Pulmonary Disease Overlap Syndrome

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RI FN conceived idea, FN FY drafted the study, FY TD collected data, FN RI did statistical analysis and interpretation of data, FI TD FN critical review manuscript, All approved final version to be published.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Abstract

Background: Asthma - chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is characterized by a persistent airway obstruction that has several features of asthma and several features of COPD. ACOS was reported to have lower pulmonary function values compared to patients who had only asthma or COPD. Bronchial hyper-responsiveness profile in ACOS has also not been clearly determined.

Objective: The current study was conducted with the aimed to determine the pulmonary function and bronchial hyper-responsiveness profile of ACOS.

Methodology: This study was a cross sectional study conducted at Asthma-COPD Outpatient Clinic of national referral hospital for respiratory diseases, the Persahabatan Hospital, Jakarta, Indonesia. ACOS diagnosis was made using the modified 2017 Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Patients are diagnosed with ACOS if they have at least three clinical features that support asthma and COPD.

Results: The study involved 60 subjects. After bronchodilator (BD) test, the mean or median forced vital capacity (FVC)% predicted, forced expiratory volume within 1 second (FEV1)% predicted, FEV1/FVC ratio, FEV1 and the percentage of FEV1 were increased of 853%, 76.4%, 67.8%, 158.3 mL, and 101% respectively. Positive methacholine challenge test was found in 97.1% of ACOS patients. ACOS patients had mean post-BD FEV1/FVC of 67.7%, median percentage of FEV1 increase of 10.1% and most of them had positive methacholine challenge test.

Conclusion: The ACOS group had mean or median pre-BD VC% predicted, FVC% predicted, FEV1% predicted and FEV1/FVC of 82.2%, 77.4%, 66% and 65.9%, respectively. After BD administration, ACOS group had mean or median FVC% predicted, FEV1% predicted, FEV1/FVC, FEV1 increase and percentage of FEV1 increase of 85.3%, 76.4%, 67.8%, 158.3 mL, and 10.1%, respectively. Positive bronchial provocation test was found in 97.1% of ACOS patients.

Keywords: Asthma-COPD overlap syndrome; Pulmonary Function; Bronchial hyper-responsiveness; Methacholine challenge test

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Introduction

Asthma-COPD Overlap Syndrome is characterized by persistent airway obstruction that has several features of asthma and several features of chronic obstructive pulmonary disease. ACOS patients were reported to have greater morbidity, mortality and comorbidity than patients who had asthma or COPD only.[2-13] ACOS were reported to have lower pulmonary function values compared to patients who had only asthma or COPD but this result did not always consistent.[3-6,14,15] Bronchial challenge test profile in ACOS has also not

been clearly determined.

Methodology:

This was a cross-sectional descriptive study. This study has been granted an ethical approval from the Institutional Review Board (IRB) of the Faculty of Medicine Universitas Indonesia (Number 869/UN2. F1/ETIK/2017). All subjects gave their written consent prior to the study. This study was conducted in March 2018-August 2018 to determine the pulmonary function and methacholine challenge test profile in Asthma-COPD Clinic of national referral hospital for respiratory diseases, the Persahabatan Hospital, Jakarta, Indonesia. The inclusion criteria were patients who had been diagnosed with asthma or COPD, had no exacerbation within 4 weeks, ≥40 years of age and agreed to participate in the study. The exclusion criteria were patients who have chest x-ray consistent with tuberculosis (TB), patients who cannot perform spirometry and patients who have contraindication to perform methacholine challenge test. subjects were recruited through consecutive sampling. Final diagnosis of ACOS was diagnosed using modified 2017 GINA/GOLD criteria (Table 1). ACOS diagnosis was made if a patient has minimum 3 features for both asthma and COPD. Final diagnosis of asthma and COPD was diagnosed if a patient has 3 or more features for either asthma or COPD.

Results

There were 60 patients who fulfilled inclusion and exclusion criteria. All study subjects underwent spirometry test and methacholine challenge test. Study subjects consist of 35 patients diagnosed with ACOS, 17 patients diagnosed with asthma and 8 patients diagnosed with COPD. Of the 35 patients

Table 1. Diagnostic criteria for ACOS, modified GINA/GOLD 2017 criteria

Feature	Asthma	COPD
Age of onset	■ Onset before age 20 years	■ Onset after age 40 years
	■ Variation in symptoms over minutes, hours or days ■ Symptoms worse during the night or early morning ■ Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	■ Persistence of symptoms despite treatment ■ Good and bad days but always daily symptoms and exertional dyspnea ■ Chronic cough and sputum preceded onset of dyspnea unrelated to triggers
Pattern of symptoms	■ Lung function normal between symptoms	■ Lung functions abnormal between symptoms
Past history or family history	■ Previous doctor diagnosis of asthma ■ Family history of asthma and other allergic conditions (allergic rhinitis or eczema)	■ Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ■ Heavy exposure to a risk factor: tobacco smoke, biomass fuels
Time course	■ No worsening of symptoms over time. Symptoms varyeither seasonally or from year to year ■ May improve spontaneously or have an immediate response to bronchodilator (BD) or inhaled corticosteroid (ICS) over weeks	■ Symptoms slowly worsening over time (progressive course over years) ■ Rapid-acting bronchodilator treatment provides only limited relief
Spirometry	■ Post BD FEV1/FVC > 0.7 ■ Post BD FEV1 ≥ 80% predicted ■ Post BD increase in FEV1 ≥12% and 200 mL	■ Post BD FEV1/FVC <0.7 ■ Post BD FEV1 <80% predicted ■ Post BD increase in FEV1 <12% and 200 mL
Bronchial challenge test	■ PC20 ≤ 8 mg/mL	■ PC20 >16 mg/mL
Chest x-ray	■ Normal	■ Severe hyperinflation

Abbreviations: ACOS, asthma-COPD overlap syndrome; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive lung disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PC20, methacoline provocative concentration causing 20% drop in FEV1.

diagnosed with ACOS, 27 patients had initial diagnosis of asthma and 8 patients had initial diagnosis of COPD. The demographic characteristics of study subjects can be seen in Table 2.

First we determined the pulmonary function profile of the ACOS patients. As seen in Table 3, ACOS patients

Table 2. Characteristics of study subjects

Characteristics	Final Diagnosis				
	Asthma	COPD	ACOS (all)	ACOS (initially diagnosed as asthma)	ACOS (initially diagnosed as COPD)
	n (%) Mean±SB Median (minimum-maximum)				
Sex					
Male	4 (23.5)	6 (75.0)	17 (48.6)	12 (44.4)	5 (62.5)
Female	13 (76.5)	2 (25.0)	18 (51.4)	15 (55.6)	3 (37.5)
Age	56.3±10.9	67±7.2	61.5±10.2	62.2±10.4	58.9±9.0
Employment					
Employed	3 (17.6)	6 (75.0)	12 (34.3)	9 (33.3)	3(37.5)
Unemployed	14 (82.4)	2 (25.0)	23 (65.7)	18 (66.7)	5 (62.5)
Education					
Lower	3 (17.6)	4 (50.0)	12 (34.3)	8 (29.6)	4 (50.0)
Higher	14 (82.4)	4(50.0)	23 (65.7)	19 (70.4)	4 (50.0)
BMI	26.5±5.8	22.4±3.7	24.9±3.8	25.1±3.8	24.3±3.9
Smoking history					
Smoker	4 (23.5.0)	6 (75.0)	19 (54.3)	13 (48.1)	6 (75.0)
Non smoker	13 (76.5.0)	2 (25.0)	16 (45.7)	14 (51.9)	2 (25.0)
Brinkman index	0 (0-120)	738±665	0.5 (0-1536)	0 (0-1536)	78 (0-1152)
Initial diagnosis					
Intermitten asthma	5 (29.4)	0 (0.0)	3 (8.6)	3 (11.1)	0 (0.0)
Mild persistent asthma	1 (5.9)	0 (0.0)	8 (22.9)	8 (29.6)	0 (0.0)
Moderate persistent asthma	11 (64.7)	0 (0.0)	14 (40.0)	14 (51.9)	0 (0.0)
Severe persistent asthma	0 (0.0)	0 (0.0)	2 (5.7.0)	2 (7.4)	0 (0.0)
COPD, group A	0 (0.0)	4 (50.0)	3 (8,6.0)	0 (0.0)	3 (37.5)
COPD, group B	0 (0.0)	3 (37.5)	1 (2,9.0)	0 (0.0)	1 (12.5)
COPD, group C	0 (0.0)	1 (12.5)	2 (5,7.0)	0 (0.0)	2 (25.0)
COPD, group D	0 (0.0)	0 (0.0)	2 (5,7.0)	0 (0.0)	2 (25.0)
Medication history					
None	4 (23.5)	1 (12.5)	3 (9.1)	3 (12.0)	0 (0.0)
ICS	2 (11.8)	0 (0.0)	7 (21.2)	7 (28.0)	0 (0.0)
ICS+LABA/LAMA	11 (64.7)	1 (12.5)	13 (39.4)	11 (44.0)	2 (25.0)
ICS+LABA+LAMA	0 (0.0)	2 (25.0)	8 (24.2)	4 (16.0)	4 (50.0)
LABA/LAMA	0 (0.0)	3 (37.5)	1 (3.0)	0 (0.0)	1 (12.5)
LABA+LAMA	0 (0.0)	1 (12.5)	1 (3.0)	0 (0.0)	1 (12.5)
Duration of initial diagnosis (asthma or COPD)	25.9±15.8	4.6±3.5	7 (1-55)	14 (1-55)	1 (1-16)

Abbreviations: COPD, chronic obstructive lung disease; ACOS, asthma-COPD overlap syndrome; BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting -2 agonist; LAMA, long-acting muscarinic antagonist.

had mean or median vital capacity (VC)% predicted, forced expiratory volume in 1 second (FEV1)% predicted and pre-BD FEV1/forced vital capacity (FVC) 82.2%, 66% and 65.9% respectively. These values are almost the same compare to asthma and COPD groups. The mean FVC% predicted of the ACOS group in this study was 77.4%. ACOS subjects who had initial diagnosis of COPD had a higher FVC% predicted than subjects who had initial diagnosis of asthma. The mean FEV% predicted and FEV1/FVC of the ACOS group increased after BD administration but did not reach normal values. The mean increase in FEV1 and the percentage increase in FEV1 of the ACOS group were 158.3 mL and 10.1%, respectively.

Next we performed the methacholine challenge testing to all study subjects. There were 97.1% of ACOS patients in this study who had positive methacholine challenge test (table 4). All of ACOS subjects who had initial diagnosis of asthma had positive methacholine challenge test and 87.5% of ACOS subjects who had initial diagnosis of COPD had positive methacholine challenge test.

Discussion

Our study obtained spirometry values of the ACOS group are lower than the asthma group but higher compare to the COPD. Our results similar to study conducted by Kauppi et al. Kauppi et al. concluded that the ACOS group had pulmonary physiological values (FEV1% predicted, FVC% predicted and FEV1/FVC) between the asthma and COPD groups. The results of this study are different from those of Chung et al. Menezes et al. and Milanese et al. which reported that pulmonary function (VEP1% predicted, FVC% predicted and FEV1/FVC) of the ACOS group

Table 2. Characteristics of study subjects

Pulmonary Function Parameter	Final Diagnosis				
	Asthma	COPD	ACOS (all)	ACOS (initially diagnosed as asthma)	ACOS (initially diagnosed as COPD)
	Mean±SB Median (Minimum-Maximum)				
Pre-BD					
VC*	2024±673	1904±621	2153±731	2091±724	2363±762
VC% predicted**	91.1±18.5	73.3±152	82.2±14.7	80.8±138	86,8±177
FVC*	1931±633	1759±466	2026±708	1953±689	2275±761
FVC% predicted**	86.8±17.3	68.1±10.1	77.4±14.5	75,7±13.5	83.1±16.9
FEV1*	1414±462	1045±255	1172±417	1289±407	1403±464
FEV1% predicted**	81.7±19.2	53.5 (50.2-82)	66 (50-106)	68.5±16.0	69±15.2
FEV1/FVC**	73.1±7.9	59.7±6.3	65.9±7.3	66.9±7.1	64 (51-69.8)
Post-BD					
FVC*	2093±634	1844±578	2223±782	2150±771	2470±819
FVC% predicted**	93.9±14.6	71±13.9	85.4±14.9	84.1±14.9	89.9±15.3
FEV1*	1601±448	1071±279	1470±439	1449±425	1540±507
FEV1% predicted**	92.6±15.8	60.3±13.1	76.4±15.5	76.7±16.2	75.3±13.9
FEV1/FVC**	76.9±7.8	58.9±5.5	67.7±8.3	69.1±8.3	65.5 (51.8-69.1)
FEV1increase*	189.4±126	45±47.5	158.3±97.2	164±95	140±109
Percentage of FEV1 increase**	11.6 (0-43.7)	4.4±4.9	10.1 (0-39.7)	10.3 (0-39.7)	10±6.1

Values stated in mL* and %**. Abbreviations: COPD, chronic obstructive lung disease; ACOS, asthma-COPD overlap syndrome; BD, bronchodilator; VC, vital capacity; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

Table 4. Metacholine challenge test result of study subjects

Variables	Final Diagnosis				
Methacoline challenge test	**Asthma** n (%)	**COPD** n (%)	**ACOS (all)** n (%)	**ACOS (initially diagnosed as** asthma) n (%)	**ACOS (initially diagnosed** as COPD) n (%)
Positive	17 (100.0)	4 (50.0)	33 (97.1)	27 (100.0)	7 (87.5)
Negative	0 (0.0)	4 (50.0)	1 (2.9)	0 (0.0)	1 (12.5)

Abbreviations: COPD, chronic obstructive lung disease; ACOS, asthma-COPD overlap syndrome.

were lower than the asthma and COPD group. Our study also obtained that ACOS patients who had initial diagnosis of asthma have post-BD FEV1/FVC less than 70%. This result is similar to the study by Wang et al. who studied ACOS patients from the asthma population and obtained median post-BD FEV1/FVC of 54%.

The FEV1 increase and the percentage of FEV1 increase in the ACOS group (158 mL and 10.1%) was similar to the asthma group (189 mL and 11.6%) but higher than the COPD group (45 mL and 4.4%). This result is similar to that obtained by Guerriero et al., who stated that the FEV1 increase and the percentage of FEV1 increase in the ACOS group (346 mL and 18.7%) was similar to the asthma group (411 mL and 21.2%) but higher than the COPD group (121 mL and 4.9%). Our study obtained median percentage of FEV1 increase in the STAP group 2.5 times greater than COPD group. Kawamatawong et al. had different results and stated that the ACOS group had the highest FEV1 increase and the highest percentage of FEV1 increase compared to asthma and COPD groups, with the values of 149.8 mL, 115.8 mL, 63.6 mL ($p = 0.009$) and 12.5%, 8% and 4.8% ($p = 0.009$), respectively. Different diagnosis criteria and age of subjects in each study can cause differences in pulmonary function profile in our study compared to other studies.

The asthma group in this study had normal FVC% predicted, FEV1% predicted and post-BD FEV1/FVC but the mean or median FEV1 increase and the percentage of FEV1 increase was not in accordance with the diagnosis requirements for asthma according to GINA 2017. Evidence of airway obstruction and airway reversibility is difficult to find in asthmatic patients who have normal pulmonary function. One of our inclusion criteria is patients who have stable disease so it is possible that our subjects has reach their maximum pulmonary function values so that administration of bronchodilator did not have much effect on FEV1 increase. The 2017 GINA guideline also stated that the diagnosis of asthma can be made from other examinations such as peak flow rate (PFR) variability within 2 weeks, significant improvement in pulmonary function after 4 weeks of anti-inflammatory administration or positive bronchial provocation test, and pulmonary function variability between visits so that the reversibility of FEV1 itself cannot be used as the only modality for diagnosing asthma.

The COPD group and ACOS group who had initial diagnosis of asthma in our study had mean FVC% predicted in below 80% which indicates restriction abnormalities. This can be happened because 25% of subjects in the COPD group had cardiomegaly and 37.5% of subjects are overweight or obese. The same thing can explain restriction abnormalities of ACOS patients who had initial diagnosis of asthma. 33.3% subjects of the group had cardiomegaly and 59.2% of subjects were overweight or obese. Our study found 97.1% of ACOS patients had positive methacholine challenge test. These results are similar to those of de Marco et al. who stated that 92.1% of ACOS patients in their study had positive bronchial provocation test. However, de Marco et al. used methacholine concentration cut off of ≤1 mg / mL to determined positive result, lower than that used in this study.

Our study found that 100% patients with asthma and ACOS patients who had initial diagnosis of asthma, had positive metacholine challenge test. This result is not surprising. The bronchial provocation test in this study used methacholine so that it was a direct provocation test. The main use of the direct provocation test is to exclude asthma. The direct provocation test stimulates the airway smooth muscle directly and has high negative predictive value for the diagnosis of asthma (almost all asthma patients will have a positive test result). Sensitivity and negative predictive value of direct provocation test with histamine reaches 100% at the cut off of 8 mg/mL or 16 mg/mL.

The presence of airway hyper-responsiveness is associated with the diagnosis of ACOS in COPD patients because most asthma patients have airway hyper-responsiveness. Airway hyperresponsiveness in COPD can also predict the patient's response to

steroid therapy. Mechanism for airway hyper-responsiveness of COPD patients include airway smooth muscle function disorders, loss of bronchodilator effects from deep breathing, inflammation, allergies and smoking status effects. The number of mechanisms that influence airway hyper-responsiveness in COPD causes difficult interpretation of bronchial provocation tests. This study found that 50% of COPD patients had positive bronchial provocation test. In the ACOS group who had initial diagnosis of COPD, there were 87.5% of patients who had a positive bronchial provocation test. This is in accordance with the theory, that ACOS patients have characteristics of both COPD and asthma. One characteristic of asthma is airway hyper-responsiveness, so that COPD patients who finally diagnosed as ACOS have greater airway hyper-responsiveness. Even so, the occurrence of airway hyper-responsiveness in COPD was not only occurs due to allergies so that bronchial provocation test can also be positive in COPD patients who did not have ACOS.

Our study revealed there was one subject in the ACOS group who had negative metacholine challenge test. These patients were ACOS patients who had initial diagnosis of COPD. Negative result on bronchial provocation tests must be interpreted carefully. Patients with negative bronchial provocation test results are usually patients who have normal pulmonary function. Methacholine sensitivity can also be affected by taking deep breaths, such as by the forced expiration volume examination technique carried out in this study. Subjects that are tested negative for bronchial provocation with metacholine may not necessarily have negative results if tested by indirect bronchial provocation tests, such as exercise challenge test, eucapnic voluntary hyperpnea and mannitol challenge test. Furthermore, technical and procedural factors such as the metacholine dissolution technique, nebulizer performance, inspiration flow and patient inspiratory volume as well as breathing measures can affect metacholine deposition and give false negative results to patients.

Conclusion

The ACOS group had mean or median pre-BD VC% predicted, FVC% predicted, FEV1% predicted and FEV1/FVC of 82.2%, 77.4%, 66% and 65.9%, respectively. After BD administration, ACOS group had mean or median FVC% predicted, FEV1% predicted, FEV1/FVC, FEV1 increase and percentage of FEV1 increase of 85.3%, 76.4%, 67.8%, 158.3 mL, and 10.1%, respectively. Positive bronchial provocation test was found in 97.1% of ACOS patients.

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