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Original Article

The Correlations Between Measurement of Lung Diffusing Capacity for Carbon Monoxide and the Severity Group of Asthma Patients in Persahabatan Hospital Jakarta

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Abstract

Introduction: *Airway remodeling in asthma involving small airway can affect the alveoli and cause abnormalities in lung parenchyma. This study aimed to find lung parenchymal abnormalities in patients with asthma by examining diffusion capacity using the single breath DLCO method.*

Methods: *This was a cross-sectional study which divided asthma based on the degree of severity into two major groups, namely mild asthma (intermittent and mild persistent) and severe asthma (moderate and severe persistent). The number of each group was 31 subjects and 29 subjects, which were taken consecutively from stable asthma patients without comorbidities who were treated at Persahabatan Hospital during December 2015 - May 2016.*

Results: *The mean DLCO/prediction value in mild asthma group was 92.74±15.70% and while in the severe asthma group was 77.45±16.78%. Several spirometry values showed significant positive correlation with DLCO/prediction value, namely: FVC/prediction, FEV_1 /prediction and FEF25-75%/prediction with P<0.05. Correlation analysis showed FVC/prediction could dramatically affect the diffusion capacity of asthmatic patients. There was a significant correlation between lung function abnormalities (P=0,004) and the severity of asthma (P=0.000) with a corresponding decrease in DLCO/prediction (DLCO/prediction ≤75 %).*

Conclusion: *The severity of asthma had a correlation with the diffusion capacity of the lungs; the increasing severity led to a decrease in diffusion capacity of asthmatic patients. Decreased diffusion capacity showed that abnormalities in asthma occurred not only in the respiratory tract but also in the lung parenchyma.* ***(J Respirol Indones 2022; 42(1): 58-66)***

Keywords: *Asthma, lung diffusion, DLCO, airway remodeling*

Hubungan Pengukuran Kapasitas Difusi Paru Karbon Monoksida dengan Kelompok Keparahan Penderita Asma di RS Persahabatan Jakarta

Abstrak

Latar belakang: *Remodeling saluran napas pada asma yang melibatkan saluran napas kecil dapat mempengaruhi alveolus dan menyebabkan kelainan pada parenkim paru. Penelitian ini bertujuan mengetahui kelainan parenkim paru pada pasien asma melalui pemeriksaan kapasitas difusi menggunakan DLCO metode napas tunggal.*

Metode: *Penelitian ini merupakan uji potong lintang yang membagi asma berdasarkan derajat keparahannya menjadi dua kelompok besar, yaitu asma ringan (intermiten dan persisten ringan) dan asma berat (persisten sedang dan berat). Jumlah masing-masing kelompok adalah 31 subjek dan 29 subjek yang diambil secara berurutan dari pasien asma stabil tanpa penyakit penyerta yang berobat di RS Persahabatan selama bulan Desember 2015 - Mei 2016.*

Hasil: *Rerata nilai DLCO/prediksi pada kelompok asma ringan adalah 92,74±15,70% dan pada kelompok asma berat adalah 77,45±16,78%. Beberapa nilai spirometri menunjukkan korelasi positif yang bermakna dengan nilai DLCO/prediksi, yaitu: FVC/prediksi, FEV_1/prediksi dan FEF25-75%/prediksi dengan P<0,05. Analisis korelasi menunjukkan FVC/prediksi secara dramatis dapat mempengaruhi kapasitas difusi pasien asma. Terdapat hubungan bermakna antara kelainan fungsi paru (P=0,004) dengan beratnya asma (P=0,000) dengan penurunan DLCO/prediksi (DLCO/prediksi 75 %).*

Kesimpulan: *Derajat keparahan asma memiliki hubungan dengan kapasitas difusi paru; peningkatan keparahan menyebabkan penurunan kapasitas difusi pasien asma. Penurunan kapasitas difusi menunjukkan bahwa kelainan pada asma tidak hanya terjadi pada saluran pernapasan tetapi juga pada parenkim paru.* ***(J Respirol Indones 2022; 42(1): 58-66)***

Kata kunci: *Asma, difusi paru, DLCO, remodeling saluran napas*

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INTRODUCTION

Asthma is characterized by increased airway reactivity. Patients with asthma have a recurrent or persistent airflow obstruction, either reversible or spontaneous.[1] However, the description of restriction can also be found in some patients. Decreased FVC due to air trapping results in pseudo-restriction on spirometry.[2] Several studies have also explored the possibility of impaired diffusion capacity in asthma by examining the carbon monoxide diffuse lung (DLCO).[3,4] Miller et al reported 32 (8%) patients of 413 patients with asthma experienced a restriction and impairment of DLCO, so it was concluded that restriction disorders could also occur in asthmatic patients.[2]

A study from Khan et al., observed a correlation between the length of asthma and decreased diffusion capacity.[5] Kharevich et al. also found a decrease in diffusion capacity in patients with severe asthma.[6] The theory of airway remodeling is considered to be responsible for persistent damage to the peripheral airways and plays ab indirect role in parenchymal damage in asthmatic patients.[7–9] This study attempted to identify the possible dysfunction of diffusion in asthmatic patients and the correlation to asthma severity.

METHODS

This was an analytic cross-sectional study conducted on asthmatic patients who were treated in Persahabatan Hospital from December 2015 to March 2016. The inclusion criteria were asthmatic patients based on medical records and willing to participate in the study. Exclusion criteria were pregnant women, patients with heart failure, patients with lung parenchymal damage (such as tuberculosis, bronchiectasis and interstitial lung diseases), deformities of the thoracic cavity and patients who refused to participate in the study.

Sampling was carried out by consecutive sampling on asthmatic patients in Persahabatan Hospital. Patient history was taken and physical examination was performed to determine whether the patients met the inclusion criteria. The patients were given information about the purpose of the study. If the patient was willing to participate in the study, the patients was asked to fill out a research consent letter.

Furthermore, the patients underwent spirometry and DLCO test. The latest chest X-ray was not required except for certain cases that obliged the latest radiographic confirmation based on the consideration of researchers. Adjustment of hemoglobin (Hb) for DLCO predictive values was not carried out so that the predictive value used the standard values according to the tools used. The data was then analyzed using the Statistical Package for Social Science (SPSS) 23.

RESULTS

The total subjects were 60 people, divided into two groups based on the severity of asthma, namely 31 subjects of mild asthma and 29 subjects of severe asthma.

Table 1. Characteristics of subjects

Variable	Asthma Group			
	Mild		Severe	
	n	%	n	%
Gender				
Male	3	9.7	6	20.7
Female	28	90.3	23	79.3
BMI				
Underweight	0	0	0	0
Normal	12	38.7	12	41.4
Overweight	3	9.7	7	24.1
Obese class I	10	32.1	9	31
Obese class II	6	19.4	1	3.4
Exacerbation history				
Yes	10	32.3	17	58.6
No	21	67.7	12	41.4
Degree of asthma control				
Uncontrolled	7	22.6	15	51.7
Partially controlled	13	41.9	14	48.3
Completely controlled	11	35.5	0	0
Duration of asthma				
<30 years	26	83.9	10	34.5
≥30 years	5	16.1	19	65.5
Steroid history				
Yes	22	71	29	100
No	9	29	0	0
Smoking habits				
Yes	1	3.2	1	3.4
No	30	96.8	28	96.6
Asthma control test				
1–20	10	32.3	15	51.7
21–24	10	32.3	14	48.3
25	11	35.5	0	0
Spirometry				
Normal	13	41.9	0	0
Obstruction	15	48.4	14	48.3
Restriction	3	9.7	0	0
Mixed	0	0	15	51.7

The mild asthma group consisted of intermittent asthma and mild persistent asthma, while the severe asthma group consisted of moderate and severe persistent asthma. In two groups, most of the subjects were female: 28 subjects (90.3%) in mild asthma group and 23 subjects (79.3%) in severe asthma group. The details can be seen in Table 1.

Table 2. The mean value of age, spirometry and DLCO test

Variable	Mild-Moderate Asthma	Severe Asthma
	Mean (SD)	Mean (SD)
Age (years)	39.58 (13.89)	49.00 (13.93)
FVC (milliliter)	2518 (692.15)	1892 (592.66)
FVC (%)	97.51 (15.01)	77.45 (16.78)
FEV_1 (milliliter)	1980.00 (644.03)	1142 (360.06)
FEV_1 (%)	90.12 (15.67)	56.82 (14.35)
FEV_1/FVC	77.26 (8.50)	60.58 (7.98)
$FEF_{25–75}$ (liter/second)	1.72 (0.57)	0.64 (0.32)
$FEF_{25–75}$ (%)	58.41 (14.82)	24.31 (9.20)
PEF (liter/second)	5.36 (1.38)	3.39 (1.24)
DLCO (ml/minute/mmHg)	21.92 (4.81)	17.85 (4.28)
DLCO (%)	92.74 (15.70)	78.41 (14.21)
AV (liter)	3.82 (0.72)	3.35 (1.02)
AV (%)	89.61 (13.73)	80.38 (15.79)
KCO (ml/minute/mmHg/L)	5.78 (0.92)	5.40 (0.81)
KCO (%)	104.90 (16.61)	99.27 (16.25)
KPT (liter)	4.02 (0.76)	3.50 (1.02)
KPT (%)	89.64 (13.45)	81.13 (15.11)

Note: Data presented as mean; FEV_1=forced expiratory volume in one second; %pred=%predicted; FVC=forced vital capacity; FEF=forced expiratory flow 25–75 second; PEF=peak expiratory flow; DLCO=diffuse lung carbon monoxide; AV=alveolar volume; KCO=carbon monoxide diffusion constant; TLC=total lung capacity.

The mean FVC/prediction in mild asthma group was 97.51±15.01%, indicating a normal value (FVC/prediction >80%) while in the severe asthma group it was lower (77.45±16.78%). The mean FEV_1/prediction in mild asthma group also showed a normal value of 90.12±15.67% and it was decreased in the severe asthma group with 56.82±14.35%.

The mean FEV_1/FVC showed normal value (FEV_1/FVC >75%) in mild asthma group of 77.26±8.50%. In the severe asthma group, the mean FEV_1/FVC indicated a description of obstruction with 60.58±7.98%. Diffusion capacity described by DLCO/prediction showed a normal value in mild asthma group of 97.24±15.70% and slightly lower in the severe asthma group of 78.41±14.21%.

Table 3. The correlation of subject characteristics with DLCO

Variable	DLCO/prediction		*P*
	Mean (%)	SD	
Gender			
Male	78.22	18.42	0.136
Female	87.16	16.00	
BMI			
Underweight	0	0	
Normal	80.54	15.11	
Overweight	85.00	18.09	0.051
Obese class I	87.42	17.86	
Obese class II	85.72	8.00	
Exacerbation history			
Yes	87.61	16.93	0.359
No	83.62	16.08	
Degree of asthma control			
Well controlled	94.63	14.99	
Partly controlled	83.70	16.75	0.147
Uncontrolled	84.00	16.25	
Duration of asthma			
<30 years	88.25	18.71	0.165
≥30 years	82.16	12.05	
Steroid history			
Yes	85.22	17.06	0.507
No	89.22	13.45	
Smoking habits			
Yes	82.00	4.24	0.743
No	85.95	16.79	
Asthma control test			
1–20	84.85	15.53	
21–24	82.59	17.59	0.131
25	94.64	14.99	

Several variables had a close significance with *P*<0.05 compared to other factors namely BMI (*P*=0.051), gender (*P*=0.136), the degree of asthma control (*P*=0.147) and ACT (*P*=0.131).

Table 4. The correlation between age and spirometry with DLCO/prediction

Variable	R	*P*
Ages	-0.055	0.678
FVC/prediction	0.505	0.0001
FEV_1/prediction	0.409	0.001
FEV_1/FVC	0.207	0.113
$FEF_{25–75}$/prediction	0.279	0.031

Based on the mean analysis, we found no significant correlation between age (*P*=0.678), FEV_1/FVC (*P*=0.113) and DLCO/prediction value. On the other hand, FVC/prediction, FEV_1/prediction and FEF25–75%/prediction showed significant positive correlation.

Table 5. The correlation between lung function with decreased diffusion capacity

Spirometry	DLCO value/prediction		Total	*P*
	Normal (>75%)	Decreased (≤75%)		
Normal	12 (20%)	1 (1.7%)	13	0.001
Obstruction	23 (38.3%)	6 (10%)	29	
Restriction	3 (5%)	0 (0%)	3	
Mixed	5 (8.3%)	10 (16.7%)	15	
Total	43 (71.7%)	17 (28.3%)	60	

Lung function becomes one of the basis for determining the severity of asthma. We observed43 subjects (71.7%) with normal diffusion capacity and the remaining 17 subjects (28.3%) with decreased diffusion capacity in our study. We obtained a significant correlation between lung function and decreased diffusion capacity.

On the association between asthma severity and a decline in DLCO/prediction, we found that the mild asthma group had 28 subjects (93.3%) with normal diffusion capacity and 2 subjects (6.7%) with decreased diffusion capacity, while severe asthma group had each 15 subjects (50%) with normal and reduced diffusion capacity.

The results of this study indicated that there was a significant relationship between the severity of asthma and decrease in DLCO/prediction with *P*=0,0001.

Table 6. Correlation between severity of asthma and decline of DLCO/prediction

Asthma Group	DLCO value/prediction		Total	*P*
	Normal (>75%)	Decreased (≤75%)		
Mild-moderate asthma	29 (96.7%)	2 (3.3%)	31	0.0001
Severe asthma	14 (46.7%)	15 (53.3%)	29	

DISCUSSION

This study aimed to determine the factors that influenced the diffusion capacity in asthma through DLCO test. We found that gender had no significant correlation with *P*=0.136. This could be due to the small number of male subjects in both groups of asthma, namely 3 subjects (9.7 %) in the mild asthma group and 6 subjects (20.7%) in the severe asthma group. Neder et al. stated similar result with no significant correlation between the genders, although the mean DLCO was higher in men than women.[4] Marco et al concluded that the high incidence of asthma in women might be caused by hormonal changes during pubertal phase.[10] Other studies mentioned that pregnancy, use of oral contraceptives and hormonal therapy have shown that hormonal factors played a role in the severity of exacerbations and asthma.[11–13]

Body mass index also had no significant correlation with the value of DLCO/prediction (*P*=0.051) in asthmatic patients, although more than half of the subjects with normal body weight were exceeded. This may be due to the absence of evenly distributed number of subjects between each BMI category. Neder et al. pointed out that weight gain was positively associated with DLCO value but could not be a predictor that individually affected DLCO when added with age and height.[4]

Khan et al. conducted a study on subjects who had been diagnosed with asthma for 30 years and found that 89% of the subjects were obese.[5] Obese subjects with asthma had a large frequency in many studies with risk of developing asthma increasing by 50%.[14–16] Obesity in asthma lowers the response to asthma medications including corticosteroids. Other mechanisms related to the effects of obesity on the mechanical motion of the chest wall and the airway, noneosinofilic airway inflammation, extrapulmonary inflammation involving systemic components and adipose tissues of asthmatic patients.[17]

Past exacerbation history, degree of asthma control and ACT also had no significant correlation with the diffusion capacity. These three variables are able to give a description of how severe the asthma of the patient is. Intermittent asthma and mild persistent asthma may reflect normal lung function beyond an asthma attack, in contrast to severe persistent asthma. However, inhomogeneous severity of asthma might play a role in the results of the analysis of these three variables.

More than half of the patients had used inhaled corticosteroids (ICS) as a controller, especially in the severe asthma group, but we obtained mean FEV_1/prediction of 56.82±14.35%, mean FEV_1/FVC of 60.58±7.98% and decreased diffusing capacity in 15 subjects. This indicated a

persistent decline in lung function despite the ICS use. Khan et al. observed similar results and suggested that airway remodeling persisted despite taking steroids as a controller.[5] Nevertheless, this study did not find a statistically significant correlation between the ICS use and DLCO/prediction value. It could be due to the absence of data regarding the duration of steroids use and the steroids doses, as well as the inhomogeneity of asthma severity in the subjects.

This study obtained a mean value of DLCO/prediction in subjects who had been diagnosed with asthma less than 30 years of 88.25% and a slight decrease in subjects diagnosed with asthma over 30 years of 82.16%. Both still had a normal mean DLCO/prediction, in line with the results of this study which stated that there were no significant correlation between the length of time diagnosed with asthma and the DLCO/prediction value (*P*=0.165). The inhomogeneous severity of asthma might possibly be the cause of these results. A person may have long been diagnosed as having intermittent or mild persistent asthma in good control, so that they do not have irreversible pulmonary function abnormalities. Khan et al. examined asthmatic patients who had been diagnosed with asthma for more than 30 years and found only 6% of subjects with increased diffusion capacity, 57% with decreased diffusion capacity and the rest were within normal limits, however, they did not look for the correlation between duration of asthma and DLCO/prediction value.[5]

Smoking had no significant correlation with the value of DLCO/prediction (*P*=0.743). This could be due to our study only earned1 subject (3.3%) of mild asthma group and 1 subject (3.3%) of severe asthma group who had a history of smoking with mild Brinkman index. Longitudinal studies regarding reduction in diffusion capacity have failed to show a significant correlation between the DLCO test result with smoking status, but indicates that active smokers have a low value of DLCO/prediction.[18,19] Matheson et al. also found similar results that only the still smokers were linked to reduced diffusion capacity with or without resistance in the airways.[20] Smoke inhalation in animals and humans showed an increment in pulmonary artery pressure and it was considered as a result of pulmonary capillary vasoconstriction due to nicotine, thus contributing to the decline in pulmonary diffusion capacity.[21–23] Diffusion capacity alteration due to changes of membrane diffusion or blood volume in the capillaries and a variety of conditions will reduce the surface area of membrane diffusion, such as alveolar structural damage that occurs in emphysema.[24]

This study showed that there was a significant correlation between some spirometry values and lung diffusion capacity while Collard et al. obtained a dissimilar result.[25] The FVC/prediction value had a significant positive relationship with the value of DLCO/prediction (*P*=0.0001), although predictions had a weak strength (r<0.5). The mean FVC/prediction especially in the severe asthma group of this study described restriction in patients with asthma. Description of restriction also reported by Colp et al. which was seen as a reversible closure of the airway.[24] Miller et al. found one third of study subjects (33 of 100 subjects) had restrictions with a decrease in diffusion capacity but without clinical symptoms and radiographic evidence of disease or vascular/interstitial disease. Miller et al. also emphasized that obesity might be one of the factors which influenced restrictions in asthma.[2] Most study had a high prevalence of obesity in asthma.

In the severe asthma group impairment in FEV_1/prediction was observed with 56.82±14.35% and resulted in positive correlation that was weak but significant with value of DLCO/prediction. The more severe obstruction will further lower diffusion capacity. It was slightly different from the FEV_1/FVC value which showed a positive but not significant correlation (*P*=0.09) with the value of DLCO/prediction. Khan et al found no significant correlation between worsening or increasing FEV_1 with DLCO/predictionvalue.[5] This was caused by FEV_1 abnormalities which were more representative for the impairment in the large airways (conduction zone) than small airways such as the respiratory

bronchioles which was part of the respiratory zone of the lung.

The value of FEF25-75%/prediction also indicated a significant positive correlation with the value of DLCO/prediction (*P*=0.026). Kenneth et al. conducted study in asthmatic patients and found irreversible decline in FEF25-75%/prediction, which was a marker of small airway damage.[26] Sobonya et al. analyzed lung tissue biopsy specimens from six non-smoking severe asthma patients with a history of allergic asthma and who died not of status asthmaticus. They found that two of these patients had small airways inflammation and fibrosis in the trachea wall.[27]

This study achieved a significant correlation between lung function abnormalities and decreased diffusion capacity (*P*=0.001). Decreased diffusion capacity was found in 17 subjects (28.3%) with a description of normal lung function in 1 subject (1.7%), obstruction in 6 subjects (10%) and the remaining 10 subjects (16.7%) had mixed abnormal lung function (obstruction and restriction). Restriction abnormalities in asthma according to Keddissi et al. were caused by rapidly reversible airway closure resulting in air trapping and low FVC.[28]

Miller et al proved that there was restriction in 33% of subjects (33 of 100) with asthma accompanied by decreased diffusion capacity without evidence of pulmonary vascular and tissue abnormalities.[2] The more severe decline in lung function got along with a decrease in DLCO. Khan et al. obtained a reduction in diffusion capacity in 37 of 65 subjects (57%) weight loss occurred in 6 subjects but did not find an association between FEV1 with DLCO values.[5] Kharevich et al. concluded from their study on the diffusion capacity in asthma that persistent airflow limitation, air trapping and decreased diffusion capacity could occur in patients with severe asthma. This might be due to airway remodeling and structural changes in the lung parenchyma, thickening of the diffusion membrane and diminution of outer lung surface.[6]

This study found that two of 31 subjects (3.3%) in the mild asthma group experienced a decline in DLCO/prediction, whereas in the severe asthma group the decline was observed in 15 of 29 subjects (53,3%). The data showed that two subjects had decreased diffusion capacity in the mild asthma group, namely mild persistent asthma. One subject had obesity and mild restriction while the other subject had normal BMI and mild obstruction. The main limitation of this study was that the researchers did not perform further evaluation with chest X-ray or CT scan which could help finding the cause of decreased diffusion capacity in mild asthma group.

This study obtained a significant positive correlation between asthma severity and decreased diffusion capacity. The more severe the asthma severity, the more likely it was to experience DLCO/prediction impairment with a *P*-value of 0.000 (*P* <0.5). This result was in contrast to the study from Ohman et al. who pointed out normal or increased diffusion capacity in asthmatic patients.[29] They believed that the escalation in diffusion capacity was not caused by an elevation in pulmonary capillary flow (Vc). The increased diffusion capacity in asthma might be due to an increment in surface area and a decline in the thickness of pulmonary alveolar-capillary membrane due to hyperinflation, but this was not the only reason. The limitation of study from Ohman et al. was the number of subjects that was less than 10 stable asthmatic patients and there were no information regarding the severity of asthma in the subject which might explain the absence of impairment in diffusion capacity.[29]

Kharevich et al. who divided the study subjects into mild and severe asthma groups based on WHO criteria for severe asthma also gained impaired diffusion capacity in severe asthma group with *P*=0.008. They then concluded that there have been structural changes in airway remodeling and lung parenchyma in patients with severe asthma.[6] Similar to Miller et al., 8% of the subjects who reported asthma of varying severity and duration of diagnosed asthma had lower DLCO/prediction values even after removing all confounding factors.[2] This was on the contrary to Girodet et al. who

investigated the basement membrane remodeling of the respiratory tract in mild asthma patients and found an increase in the number of mitochondria even in patients with mild asthma. In some patients, elevated mitochondrial biogenesis is the key to augmented cell proliferation and basement membrane remodeling.[30]

Various studies of asthma in recent years have uncovered that the inflammatory process extends from the large airways to the peripheral airways and lung parenchyma. These studies indicated that severe inflammation and structural changes also occur in the small airways and lung parenchyma.[31–33] This was observed from specimens of asthmatic patients taken through resection of lung tissue, lung autopsy specimens and transbronchial biopsies.[34–36] Peripheral airways including lung tissue were recognized as the dominant areas of airway obstruction in asthmatic patients.[37–39]

Wagner et al. stated that mild asthmatic patients with normal spirometry had an approximately sevenfold increase in peripheral airway resistance compared with controls and this was associated with the response to methacholine.[40] Carrol et al. investigated the distribution of inflammatory cells along the bronchial tree in both fatal and non-fatal asthma cases.[41] They noticed a uniform increment in eosinophils in the large and small airways among mild and severe asthma compared with controls. Comparison of large and small airways exhibited an escalation in the number of eosinophils in airway diameter of less than 2 mm which proved that the inflammatory process also occured in small airways.

CONCLUSION

In summary, this study identified that there was a significant correlation between severity of asthma and decreased diffusion capacity of asthmatic patients. However, this study needs to do further research with a larger number of samples and representing each degree of asthma in the same amount. Diffusion capacity examination should be done regularly, especially in patients with severe asthma.

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