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ORIGINAL PAPER

Pulmonary Diffusion Capacity for Carbon Monoxide (DLCO) in Indonesian Patients with End-stage Renal Disease

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ABSTRACT

Objectives: *End-stage renal disease affects all systems in human including the respiratory system. This study aimed to discover the lung diffusion capacity of carbon monoxide (D_{LCO}) in chronic hemodialysis patients and to establish its relation to several demographic and clinical factors as well as spirometry parameters.*

Materials and Methods: *This was a cross-sectional study among chronic hemodialysis patients aged ≥18 years, clinically stable in the last four weeks, without prior history of lung and cardiac disorder. Spirometry and D_{LCO} examination were performed in the span of 24 hours after hemodialysis.*

Outcomes: *There were 40 subjects analyzed. Majority of them were males (67.5%), non-smokers (55%), with a median age of 51 years, a mean body mass index of 22.6±3.9 kg/m², a hemoglobin level of 9.5±1.3 g/dL, a median dialysis adequacy of 1.62 and a hemodialysis duration of 31.5 months. Hypertension was the most common underlying disease. About 20% of subjects had varying degrees of dyspnea. Prevalence of D_{LCO} reduction was 52.5% with mild to moderate degree. Restrictive spirometry pattern was evident in 47.5% of subjects and obstructive pattern in 5%. There was a significant relation between D_{LCO} reduction with smoking history (OR 4.52 [95% CI 1.04–19.6]) and also with restrictive disorder [OR 5.5 (95% CI 1.29–23.8)]. We suspected a lung parenchymal disorder as the cause of lung restriction and diffusion inhibition.*

Conclusion: *Reduction of lung diffusion capacity in chronic dialysis patients is common, although not accompanied by dyspnea. Risk factors for D_{LCO} reduction are smoking history and restrictive disorder in spirometry.*

Keywords: pulmonary diffusion capacity, end-stage renal disease, hemodialysis

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INTRODUCTION

Chronic kidney disease (CKD) is one of the major health problems in the world. An estimated 10% of the global population has CKD. About two million people are currently undergoing dialysis or kidney transplant to survive. Data from the Indonesian Nephrology Society (PERNEFRI) showed that in 2011 there were about 15,000 new patients and nearly 7,000 active patients who underwent hemodialysis. According to data from the Basic Health Research of the Ministry of Health, in 2013 there was 0.2% of population who reported to have been diagnosed with CKD (1-4).

Chronic kidney disease affects the entire system in the body. However, there have not been many studies that revealed the impact of renal failure on the respiratory system. Respiratory complaints are often not detected properly, even though respiratory disorder contributes to lower quality of life among CKD patients (5, 6). Indonesia does not have data on the prevalence and severity of dyspnea in CKD patients, especially in those with end-stage renal disease (ESRD). Similarly, there are no data on the lung diffusing capacity of patients with ESRD in Indonesia.

This study aimed to elucidate the pulmonary diffusion capacity by D_{LCO} test in ESRD patients undergoing hemodialysis and the factors that influence it. ❑

METHOD

This was a cross-sectional study conducted in September-October 2016 at the Indonesian national reference for respiratory diseases, Persahabatan Hospital, Jakarta. The present study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No. 516/UN2.F1/ETIK/2016). The inclusion criteria were patients with ESRD undergoing chronic hemodialysis, aged ≥18 years, clinically stable in the last four weeks, and willing to participate in the study by signing an informed consent. Exclusion criteria were prior respiratory and cardiac disease (confirmed by interview, physical examination, chest X-ray and ECG), and inability to hold breath at least 10 seconds and to complete spirometry and D_{LCO} tests.

Subjects recruited through consecutive sampling were interviewed and underwent physical examination, spirometry and D_{LCO} tests. Breathlessness assessment was done by the modified Medical Research Council (mMRC) scale. Spirometry and D_{LCO} examinations were performed within 24 hours after the last hemodialysis. Lung function test was performed by SPIROBANK II (Medical International Research, Rome, Italy) and pulmonary diffusing capacity was measured by single breath method with Easyone™ Pro Lab (NDD Med, Andover, MA, USA). Briefly, patients were first instructed to breathe (inspire and expire) normally. They were then requested to expire maximally, followed by maximal inspiration. The gas valve was opened to allow the gas enter the lungs. Afterwards, patients hold their breath for 10 seconds. Lastly, without hesitating, patients were asked to exhale maximally. Inspections were carried out minimally twice. The time between procedures was at least four minutes. We considered two test results with the value of the difference of 2 mL/min/mm Hg as acceptable results.

Statistical analysis

The data were statistically analyzed using Statistical Package for Social Science (SPSS) version 21 (IBM Corp, Armonk, NY, USA). Continuous variables were analyzed for normality using Kolmogorov–Smirnov statistics at level of significance of 0.05. Normally distributed data was presented as mean + standard deviation (SD), while abnormal distribution data was presented as median + range. Differences between means of continuous variables were analyzed using Student's t-test or Mann-Whitney test; and relationship between categorical variables was analyzed using Chi-square test or Mann-Whitney test, accordingly, and described as odds ratio (OR) and 95% confidence interval (CI). A *P* value bellow 0.05 was considered to be statistically significant.

RESULTS

There were 42 subjects who met the inclusion criteria, but two of them had to be excluded because they were unable to complete spirometry maneuvers. All 40 subjects enrolled in this study underwent chronic hemodialysis twice a week.

Characteristics of subjects

Majority of the subjects were males, with a median age of 51 and non-smoking status. The

body mass index (BMI) was calculated by a body weigh measured after the last hemodialysis session. Subjects' general information and characteristics were highlighted in Table 1.

Characteristic	Description	N	%
Gender			
Male		27	67.5
Female		13	32.5
Age (years)	51 (26-72)		
Smoking history			
Smoker		3	7.5
Ex-smoker		15	37.5
Non-smoker		22	55
Brinkman Index			
Low		13	32.5
Moderate		3	7.5
High		2	5.0
BMI (kg/m^2)	22,6 ± 3,9		
Underweight		4	10
Normal		20	50
Overweight		12	30
Obese		4	10
Hemoglobin (g/dL)	9.5 ± 1.3		
Dialysis adequacy	1.62 (1.16-2.60)		
< 1,9		27	67.5
≥ 1,9		13	32.5
HD duration (months)	31.5 (2-195)		
< 5 years		34	85
≥ 5 years		6	15
Underlying disease			
Hypertension		25	62.5
Diabetes mellitus		11	27.5
Unknown mMRC score		4	10
0		32	80
≥1		8	20

TABLE 1. Characteristics of subjects

Spirometry results

Of all subjects, 47.5% had restrictive lung and 5% obstructive airway by spirometry (Table 2).

Characteristic	Description	N	%
FVC (mL)	2574±738		
FVC/prediction (%)	84.25±17.93		
Normal		21	52.5
Mild restriction		15	37.5
Moderate restriction		4	10
Severe restriction		0	0
FEV_1 (mL)	2064±568		
FEV_1/prediction	84.87±17.51		
Normal		38	9.5
Mild obstruction		1	2.5
Moderate obstruction		1	2.5
Severe obstruction		0	0
FEV_1/FVC (%)	80.27 ± 7.14		

TABLE 2. Spirometry results

D_{LCO} results

As described in Table 3, the mean D_{LCO} value was 16.42 ± 4.49 mL/min/mm Hg. During the study, subjects presented anemia all along, and therefore, the prediction value of D_{LCO} had to be adjusted according to their hemoglobin levels; afterwards, it was compared with the prediction values, which showed that 21 subjects (52.5%) had reduced D_{LCO}.

Characteristic	Description	N	%
DLCO (mL/min/mm Hg)	16.42±4.49		
DLCO/prediction (adjusted to Hb)	72.06±16.21		
Normal			47.5
Reduced		21	52.5
Mild reduction		13	61.9
Moderate reduction		7	33.3
Severe reduction		1	4.8
VA (L)	3.81±1.17		
VA/prediction (%)	75±18		
KCO (ml/min/mm Hg/L)	4.38 (2.11-10.85)		
KCO/prediction (%)	82 (35-206)		

TABLE 3. D_{LCO} results

Relationship between subjects' characteristics and D_{LCO}

Table 4 shows the relationship between subjects' characteristics and D_{LCO} reduction. There was a significant ($P = 0.024$) relationship between smooking history and reduced pulmonary diffusion capacity, with an OR of 4.55 (95% CI 1.18–17.53).

Characteristic	DLCO		OR (95% CI)	*p*
	Reduced	Normal		
Smoking history				
Yes	13	5	4.55	0.024*
No	8	14	(1.18-17.53)	
BMI				
Obese	3	1	0.33	0.445**
Non-obese	18	18	(0,03-3.51)	
Dialysis adequacy				
< 1.9	16	11	2.33	0.217*
≥ 1.9	5	1	(0.60-9.03)	
Duration				
< 5 years	2	4	0.40	0.404**
≥ 5 years	19	15	(0.06-2.45)	
Underlying disease				
DM	4	7	0.40	0.208*
Non DM	17	12	(0.09-1.69)	
mMRC scale				
0	17	15	0.88	0.908**
≥ 1	4	4	(0.19-4.16)	

*Chi Square test ** Mann-Whitney. mMRC: modified Medical Research Council. mMRC scale 0: I only get breathless with strenuous exercise. mMRC scale 1: I get short of breath when hurrying on level ground or walking up a slight hill. mMRC scale 2: On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level. mMRC scale 3: I stop for breath after walking about 100 yards or after a few minutes on level ground. mMRC scale 4: I am too breathless to leave the house or I am breathless when dressing.

TABLE 4. Relationship between subjects' characteristics and a D_{LCO} reduction

The relationship between subject the age of the subject and the D_{LCO} value/prediction that has been corrected in accordance to the hemoglobin levels was analyzed with the Spearman test, which found no significant relationship ($P = 0.612$).

Characteristic	Description
Gender	
Male	5
Female	3
Smoking history	
Smoker	0
Ex-smoker	3
Non-smoker	5
Age (years)	50.38 ± 6.37
BMI (kg/m2)	21.33 ± 4.86
Hemoglobin (g/dL)	9.61 ± 1.47
Dialysis adequacy	1.68 ± 0.36
Hemodialysis duration (months)	33.88 ± 30.02
Underlying disease	
DM type 2	2 (25%)
Hypertension	4 (50%)
Unknown mMRC score	2 (25%)
FCV (mL)	1 (1-3)
FVC/prediction (%)	2218.75 ± 717.07
FEV1 (ml)	72.69 ± 16.20
FEV1/prediction (%)	1820.00 ± 617.23
FEV1/FVC (%)	74.81 ± 17.08
DLCO (ml/min/mm Hg)	81.98 ± 5.06
DLCO/prediction (%)	15.32 ± 4.43
VA (L)	67.82 ± 17.68
VA/prediction (%)	3.44 ± 0.82
KCO (ml/min/mm Hg/L)	66.87 ± 11.05
KCO/prediction (%)	4.43 ± 0.66
	83.25 ± 11.73

TABLE 5. Characteristics of subjects with dyspnea

Obese subjects were more often prone to have reduced D_{LCO} than non-obese participants to the study (75% *vs.* 50%), but the difference was not significant. Reduction of D_{LCO} occurred more frequently in subjects who had dialysis adequacy values of <1.9 [16/27 (59.3%)] than in those with dialysis adequacy values of ≥ 1.9, although this difference was also not significant. There was no relationship between hemodialysis period, underlying disease and dyspnea (mMRC scale) with a reduction in D_{LCO}.

Eight subjects had dyspnea at the time the study was conducted (mMRC score ≥1) and their characteristics have been shown in Table 5.

After it was discovered that a reduction in D_{LCO} was not related to the clinical aspects of hemodialysis, we tried to find the relationship between the aspect of hemodialysis and each component in the lung diffusing capacity. Table 6 shows that both the alveolar volume (VA) and the carbon monoxide transfer coefficient (KCO) were not related to the duration of hemodialysis and to dialysis adequacy.

	VA/prediction		KCO/prediction	
	Mean	*p**	Mean	*p**
Hemodialysis duration				
< 5 years	74.71	0.815	84.88	0.782
≥ 5 years	76.67		80.50	
Dialysis adequacy				
< 1.9	75.41	0.844	82.30	0.177
≥1.9	74.15	18	88.23	
*t-test ** Mann-Whitney test				

TABLE 6. Relationship between clinical aspects of hemodialysis with VA and KCO

Relationship between spirometry value and D_{LCO} reduction

Subjects with restrictive disorder had more often a reduced D_{LCO} (73.7%) than those without restriction (33.3%). This difference was statistically significant ($P = 0.011$). Obstruction was not associated with a decrease in D_{LCO} (Table 7).

	D_{LCO}		OR (95% CI)	*p**
	Reduced	Normal		
Restriction				
Yes	14	5	5.60 (1.43-21.95)	0.011*
No	7	14	0.90 (0.05-15.47)	
Obstruction				
Yes	1	1		0.974**
No	20	18		
*Chi Square test ** Mann-Whitney test				

TABLE 7. Relationship between spirometry results and D_{LCO} reduction

Multivariate analysis

Smoking history, dialysis adequacy and restriction variables were eligible for multivariate analysis. Finally, there were only two statistically significant variables that influenced D_{LCO} reduction: smoking history and restriction (see Table 8).

Variable	OR	OR (95% CI)	*p*
Smoking history	4.52	1.04 - 19.6	0.044
Restriction	5.58	1.29 - 23.8	0.021

TABLE 8. Multivariate analysis

DISCUSSION

The present study has elucidated the prevalence and factors associated with declined lung diffusion capacity among patient with CKD who were under hemodialysis in the Persahabatan Hospital, an Indonesian National Reference Hospital for Respiratory Diseases.

Our study showed a mean of D_{LCO}/prediction after adjustment for hemoglobin of 72.06 ± 16.21%, which was lower than reported in other several studies. According to Herrero *et al* (7), in hemodialysis subjects, D_{LCO} value was 110.1 ± 13.9 in <one year and 86.2 ± 14.0% in >five years, similarly to Bush and Gabriel *et al* (8), who reported 87.5% (95% CI 80-96%), but much higher than reported by Moinard and Guenard *et al* (9), who found only 17% – such a low D_{LCO} reported by the latter authors was explained by the difference in timing of examination conducted before hemodialysis, the interval between the examination and the last hemodialysis being 2.3 ± 0.5 days. Bush and Gabriel *et al* (8) and our study conducted D_{LCO} examination within 24 hours after hemodialysis, while Herrero *et al* (7) did not mention it clearly.

The prevalence of D_{LCO} reduction in our study was 52.5%, comprising 61.9% mild reduction, 33.3% moderate reduction and 4.8% severe reduction. These findings are lower than those previously reported by Bush and Gabriel *et al* (8), who showed a reduction of D_{LCO} in 70% of subjects, while Herrero *et al* (7) obtained a D_{LCO} reduction in 10% of <one year hemodialysis subjects and in 75% of >five years hemodialysis subjects.

Patients with CKD who had a smoking history had more often a D_{LCO} reduction than those who had never smoked. Bush and Gabriel *et al* (8) did not find a correlation between D_{LCO} reduction and smoking history, while Herrero *et al* (7) stated that most of their subjects had a smoking history, although they have not analyzed that association. In one study involving COPD patients, Ismail *et al*

(10) demonstrated that smoking history and Brinkman Index did not have a significant association with D_{LCO} reduction.

There was no firm conclusion about the relationship between dialysis duration and D_{LCO}. Bush and Gabriel (8) also found no relationship between the two variables, while Herrero (7) showed a significant difference between subjects undergoing hemodialysis <one year (110.1±13.9 mL/min/mm Hg) and >five years (86.2±14.0 mL/min/mm Hg). Reduction of D_{LCO} in subjects with dialysis adequacy <1.9 increased 2.33 times, although it was not statistically significant. We predict that statistical significance will be likely to appear when the number of study subjects is enlarged. This study suggested that dialysis adequacy was important to assess complications of ESRD and hemodialysis to the respiratory system.

Hemoglobin level would certainly affect the D_{LCO} value in accordance with the theory stated by Roughton and Forster *et al* (11). Our findings were consistent with the above-mentioned concept. There was a fairly strong correlation between the level of hemoglobin and D_{LCO} value, with r = 0.5 and $P = 0.001$.

Lung diffusion capacity is the result of measurement of two different parameters, each of them varying independently, *i.e.*, the rate constant for carbon-monoxide (CO) clearance from alveolar gas (also known as permeability factor, KCO) and the alveolar volume (VA). Restriction will reduce the value of VA, so that D_{LCO} will also decrease (12). In normal circumstances, with lower VA, KCO (D_{LCO}/VA) will increase as a compensation (13). In reality, diseases that cause restriction are often accompanied by abnormalities in the parenchyma, so that KCO does not increase as expected. Different patterns will occur when restriction is caused by extra-pulmonary factors such as neuromuscular disorder. In such circumstances, KCO can increase even though VA is low, so that the end result of decreased D_{LCO} is not as severe as in intrapulmonary disorder.

This study showed that the mean of D_{LCO}/prediction in subjects with restriction was amounted to 63.60%, lower than the mean of all subjects. The mean of KCO/prediction of subjects with restriction was also lower than the overall value (79.11% *vs.* 84.22%), and the value of VA/prediction was also decreased (65.21% *vs.* 75%). A decline in VA (restriction) was confirmed as the cause of D_{LCO} reduction. However, the decrease in VA was not compensated by the increase in KCO. Therefore, it can be concluded that the decrease in D_{LCO} was caused by disorder in the parenchyma, which resulted in restriction and inhibited CO diffusion (Figure 1).

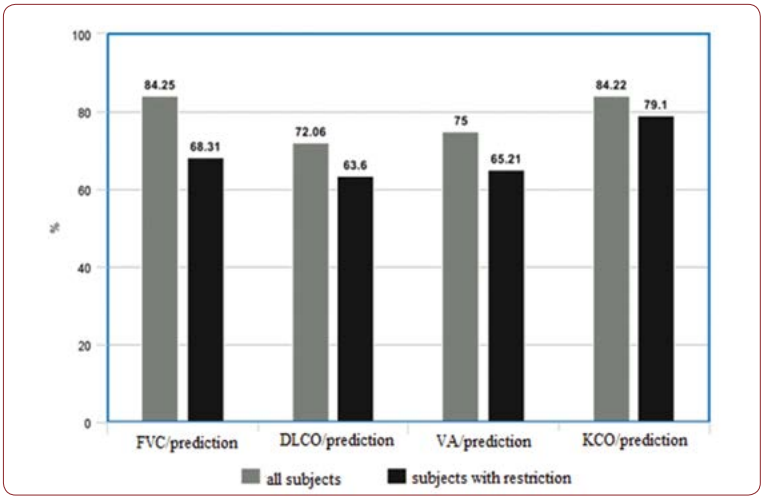

FIGURE 1. The difference in DLCO between all subjects and patients with restriction

This study had several limitations. It involved small sample numbers, so that further studies would require much more subjects to obtain more representative data. Other limitation was that there was no prediction value of D_{LCO} for the Indonesian population; therefore, the international prediction value may not correspond well to local population. ❑

CONCLUSION

About half of patients under routine hemodialysis had a D_{LCO} reduction, mostly a mild one. Factors that were associated with the increased risk of declined pulmonary diffusion capacity were restrictive findings by spirometry, smoking, and hemoglobin. Further studies should be conducted involving healthy population as a control group to accurately describe the magnitude of lung diffusion capacity reduction in hemodialysis patients, because there is no prediction value of D_{LCO} in Indonesian population. ❑

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