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Low DLCO in idiopathic pulmonary arterial hypertension — clinical correlates and prognostic significance

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Abstract

Introduction: Decreased diffusing capacity of the lung for carbon monoxide (DLCO) is observed in some idiopathic pulmonary arterial hypertension (IPAH) patients, but its clinical significance is uncertain. We aimed to assess clinical correlates and prognostic significance of low DLCO in IPAH patients.

Material and methods: In the group of 65 IPAH patients the cut off value for low DLCO was set up based on histogram as < 55% of predicted value. Demographic data, exercise capacity, lung function tests, hemodynamic parameters and survival of the patients were compared depending on DLCO value.

Results: Low DLCO was found in 18% of the patients, and it was associated with male sex, older age, worse functional status and exercise capacity, and higher prevalence of coronary artery disease. Low DLCO carried a 4-fold increase of death risk in 5-year perspective.

Conclusions: Low DLCO was a marker of worse functional capacity and increased risk of death in studied IPAH patients.

Key words: diffusing capacity for carbon monoxide, pulmonary hypertension, prognostic factor

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Introduction

The risk stratification in idiopathic pulmonary arterial hypertension (IPAH) patients is currently based on hemodynamic [1–4] and functional parameters such as: functional class [1, 4], distance of six-minute walking test [2, 3, 5], peak exercise oxygen consumption [6, 7]. The other factors predictive of survival are biomarkers of myocardial injury (troponin) [8] and myocardial strain (BNP/NT-proBNP) [9]. Mild to moderate disturbances in blood gases and lung function tests, such as hypoxemia, hypocapnia, impaired maximal midexpiratory airflow were found in IPAH patients, but their clinical significance was not well defined [5, 10, 11]. Diffusing capacity of the lung for carbon monoxide (DLCO) impairment has been already described in pulmonary arterial hypertension (PAH), mainly in connective tissue disease with both interstitial and vascular lung pathology [12–14]. The prevalence and clinical significance of DLCO impairment in IPAH is less obvious [15, 16]. Thus the aim of the present study was to assess clinical correlates and prognostic significance of low DLCO in IPAH patients.

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Material and methods

Study population

The study population consisted of 65 IPAH patients, 49 women and 16 men, median age 43 years (17–74 years), who were diagnosed in the pulmonary hypertension reference center (Department of Chest Medicine at the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland) in the period of 1998–2006. The study was approved by the Human Ethics Committee of the National Institute of Tuberculosis and Lung Diseases. Written informed consent was obtained from every patient.

Chronic thromboembolic pulmonary hypertension was excluded based on the results of chest computed tomography (CT) angiography and lung scintigraphy in all of the patients. High resolution chest CT scans (HRCT) were also analyzed to exclude interstitial lung disease.

Right heart catheterization (RHC) was performed in all of the patients (in 9 patients the first RHC was performed outside of our centre). The diagnosis of pulmonary arterial hypertension (PAH) was based on finding of mean rest pulmonary artery pressure (mPAP) higher than 25 mm Hg measured directly, in absence of elevated pulmonary artery wedge pressure (PAWP ≤ 15 mm Hg), and with pulmonary vascular resistance higher than 3 Wood units. Vasoreactivity testing was performed with nitric oxide or with inhaled iloprost. In the patients who were receiving calcium channel blockers (CCB) upon referral (28 cases), the drug was stopped for 12–24 hours before RHC and vasoreactivity testing. Positive response was defined as the decrease of mPAP of at least 10 mm Hg and to the value lower than 40 mm Hg, with no change or with the increase of cardiac output (CO). In responders, CCB were continued in maximal tolerated doses, in non-responders the CCB were stopped.

IPAH was recognized after the exclusion of all secondary causes of PAH. Connective tissue disease was excluded based on lack of the signs and symptoms of systemic disease and absence of specific antinuclear antibodies. PAH associated with portal hypertension was excluded based on negative medical history, absence of signs of portal hypertension or liver disease on abdomen ultrasonography, and normal serum hepatic enzymes.

In all patients pulmonary function testing (PFT) was performed as a part of a differential diagnosis of PH.

The mean time span between PFT and RHC was 19,25 (± 33.08) days. Comparison of PFT and RHC results was performed only in those 50 patients in whom both procedures were performed within the short time span (30 days).

Exercise capacity was measured with 6-minute walking test (6MWT), performed on a corridor in accordance with the ATS guidelines [17]. Oxygen saturation (SaO_2) was measured before (SaO_2 pre-test) and in the 6^{th} minute of the test (SaO_2 6 min). The results were expressed as the distance covered during the test, and SaO_2 6 min.

In 9 patients with RHC performed in other centre, PAH-specific therapy was introduced before referral to our department. Nevertheless, further treatment and its subsequent modifications were performed at our centre. In the remaining patients the treatment was started by our team. The first drug introduced was endothelin receptor antagonist (in 38 patients), or prostacycline analog (in 18 patients), or sildenafil (in 8 patients). Regular face to face control visits were performed. The adherence to treatment was very good. The subsequent decisions to add the medication of different class were made in cases of significant clinical worsening, after assessment of 6MWT, NT-proBNP, echocardiography and RHC results. At the end of the study 44 patients were receiving monotherapy with PAH specific drug, 20 patients — combined PAH-specific treatment (2–3 drugs belonging to different classes).

The patients were followed up for at least 60 months from PFT. During that period of time 34 (52%) patients died due to end-stage right heart insufficiency, 3 underwent lung transplantation (observations censored at the time of the operation), 2 were lost to follow-up (both after 10 months), 26 patients stayed alive.

Pulmonary Function Testing

PFT was performed with use of MasterLab v.3.26 equipment (until January 2002) and Master Screen Body Plethysmograph (after January 2002), both Jaeger (Germany), with accordance to ERS guidelines [18–22]. Spirometry, whole body plethysmography, and single-breath diffusing capacity for carbon monoxide measurements were performed. DLCO results were corrected for hemoglobin levels.

Predicted values for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were taken from Falaschetti et al. [23], and from ERS, for all other parameters [19]. Values corresponding to 5^{th} and 95^{th} percentile were used to define lower and upper limits of normal (LLN and ULN, respectively) [24]. An obstructive ventilatory defect was defined as FEV_1/VC_{max} (maximum vital capacity) below LLN. Its severity was based

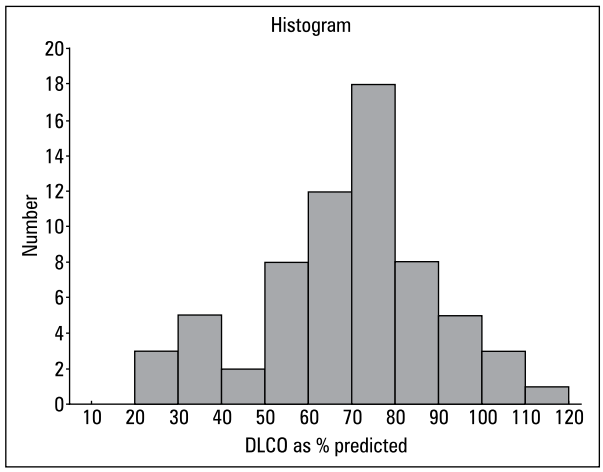

Figure 1. Histogram of DLCO%pred.

on the FEV_1 as follows: $FEV_1 \geq 70\%$ pred. — mild, and FEV_1 60-69 % pred. — moderate obstruction. A restrictive ventilatory defect was diagnosed in patients with TLC < LLN, and was recognized as mild if TLC was ≥ 70% pred., or moderate if TLC was 60–69% pred. [24]. Hyperinflation was defined as RV (residual capacity)/TLC > ULN [24].

Statistical analysis

All analyses were performed using STATISTICA 6.0 (Statsoft) computer software. The results were expressed as the median values (range), unless otherwise stated. Arbitrary used cut off value for low DLCO was calculated from the histogram. Fisher's chi-square test was used for comparison of categorical variables and U Mann-Whitney test for continuous variables. Survival analysis was performed with Kaplan-Meier method. Survivals in groups were compared with F-Cox test. The prognostic value of selected variables was tested by univariate Cox proportional hazard regression analysis, and expressed as hazard ratios (HR) with 95% confidence intervals (95% CIs). $P \leq 0.05$ was considered statistically significant.

Results

RHC revealed the following hemodynamic indices (mean ± SD): pulmonary artery pressure systolic/diastolic/mean −83.4 (± 19.1)/39.3 (± 10.4)/55.9 (± 12.7) mm Hg, pulmonary artery wedge pressure — 9.6 (± 1.9) mm Hg, right atrial pressure — 8.5 (± 4.8) mm Hg, stroke volume −57.3 (± 17.0) ml, cardiac output −4.4 (± 1.1) l/min, cardiac index –2.6 (± 0.7) l/min*m^2, pulmonary vascular resistance index — 6.9 (± 2.9) jW*m^2, total pulmonary vascular resistance index –8.0 (± 3.2) jW*m^2, mixed venous blood saturation (SaO_{2mv}) –56.8 (± 8.0)%. 17 out of 65 (26%) patients were responders in acute vasoreactivity testing.

WHO functional class (FC) was: I — in one patient, II — in 40 patients (61%), III — in 21 (32%) and IV — in 2 patients (3%), status of 1 patient was not established.

Mean resting partial oxygen (PaO_2) and partial carbon dioxide ($PaCO_2$) pressures in arterialized capillary blood were 65.9 (± 14.7) mm Hg and 31.4 (± 4.17) mm Hg, respectively. Mean 6MWT distance was 377.5 (± 110) m, desaturation exceeding 5% was observed in 23 (35%) of the patients.

Serum NT-proBNP (N-terminal pro-brain natriuretic peptide) was measured in 32 patients,

Mean concentration was 2186.7 (± 2235.2) pg/ml.

Median DLCO value for the whole group of IPAH patients was 72.0 (22.7–117.9) % pred., mean value was 69.1 (± 20.0) % pred. The DLCO % pred. histogram showed a double-peak contour (Fig. 1). Based on it, the patients were divided in two groups: a group with DLCO < 55% pred. consisting of 12 (18%) patients, and a group with DLCO ≥ 55% pred. comprising remaining 53 (82%) patients.

The comparison of demographic data, comorbidities and type of PH-specific treatment is presented in Table 1. The patients with low DLCO were significantly older, and with significantly higher prevalence of coronary artery disease than the patients with DLCO ≥ 55% pred. There were more males, smokers, and patients with higher BMI in the group with low DLCO compared to the other, but the differences were not significant.

HRCT results were similar in both groups and revealed the presence of: ill-defined centrilobular nodules (8% and 12% respectively), focal ground glass opacities (16% and 25% respectively), centrilobular emphysema (16% and 8% respectively), post-tuberculous scaring (8% and 16% respectively). In the remaining patients no parenchymal lesions were described on chest HRCT. No expiratory air-trapping was found in the patients with centrilobular nodules or with focal ground glass opacifications.

The comparison of pulmonary function tests and blood gases between the two groups of patients is presented in Table 2. Airway obstruction was found in 5 patients with DLCO < 55% pred. (42%) and 9 patients with DLCO ≥ 55% pred. (17%), difference was not significant. Isolated MMEF < LLN was found in 2 patients with DLCO < 55% pred. (17%) and 12 patients with DLCO ≥ 55% pred. (22%). Hyperinflation was found in 6% of patients with DLCO ≥ 55% pred. and none in the group with DLCO < 55% pred.

Table 1. Comparison of demographic characteristics, comorbidities and PH-specific treatment in IPAH patients with DLCO < 55% pred. and DLCO ≥ 55% pred.

Characteristic	DLCO < 55% pred.		DLCO ≥ 55% pred.		p*
	n	Median (IQR)	n	Median (IQR)	
Gender: Male:Female	12	1:1	53	1:4	0.059
Smokers (past and present), n (%)	12	7 (58%)	53	15 (28%)	NS
Age, years	12	58 (48–68)	53	41 (29–45)	0.0008
Arterial hypertension, n (%)	12	3 (25%)	53	5 (10%)	NS
Coronary artery disease, n (%)	12	5 (42%)	53	0 (0%)	0.0002
Astma,well controlled, n (%)	12	0 (0%)	53	3 (5%)	NS
COPD Gold stage 2, n (%)	12	2 (17%)	53	0 (0%)	0.07
BMI kg/m^2	12	27.5(19–40.7)	53	24(18.6–44.5)	0.06
Prostanoids, n (%)	12	5 (42%)	53	21 (40%)	NS
Endothelin-1 antagonists, n (%)	12	8 (67%)	53	25 (47%)	NS
Phosphodiesterase-5 inhibitors n (%)	12	4 (33%)	53	23 (43%)	NS
Riociguat, n (%)	12	0 (0%)	53	2 (4%)	NS

BMI — body mass index; COPD — chronic obstructive pulmonary disease

Table 2. The results of pulmonary function tests, arterialized blood gases analysis in 65 IPAH patients depending on DLCO % predicted value

Characteristic	DLCO < 55% pred.		DLCO ≥ 55% pred.		p*
	n	Median (IQR)	n	Median (IQR)	
FEV_1, %pred.	12	109.1 (95.6–122.0)	53	107.3 (98.9–122.6)	0.07
VC, % pred.	12	88.8 (80.1–102.2)	53	99.5 (83.2–109.0)	NS
bronchial obstruction n (%)	12	5 (42%)	53	9 (17%)	NS
Isolated MMEF < LLN n (%)	12	2 (17%)	53	12 (22%)	NS
TLC, % pred.	12	111.7 (93.4–117.1)	53	110.6 (99.8–116.4)	NS
TLC < LLN n (%)	12	1 (8%)	53	1 (2%)	NS
RV/TLC, % pred.	12	107 (84.5–125.5)	53	105 (57.7 137.5)	NS
RV/TLC > ULN n (%)	12	0 (0%)	53	3(6%)	NS
PaO_2, mm Hg	12	51.5 (46.4–56.2)	53	71.7 (60.8–80.8)	0.00003
$PaCO_2$, mm Hg	12	29.1 (26.7–31.3)	53	31.8 (29.8–34.2)	0.065
SaO_2, %	12	89.1 (86.3–91)	53	95.3 (92.3–96.5)	0.00003

DLCO — diffusion capacity for carbon monoxide; FEV_1 — forced expiratory volume in 1 second; IQR — interquartile range; K_{co} — carbon monoxide transfer coefficient; MMEF — maximum midexpiratory flow; ns — not significant; ULN — upper limit of normal; LLN — lower limit of normal; $PaCO_2$ — partial carbon dioxide pressure; PaO_2 — partial oxygen pressure; pred. — predicted; RV — residual volume; SaO_2 — oxyhemoglobin saturation, TLC — total lung capacity; VC — maximum vital capacity

Both PaO_2 and hemoglobin oxygen saturation (SaO_2) were significantly lower in the group with low DLCO compared to the other.

The comparison of 6MWT, functional class, NT-proBNP, and right heart catheterization parameters in both groups is presented in Table 3. In the patients with low DLCO, significantly shorter 6MWT distance, lower SaO_2 at the end of 6MWT, and higher percentage of class III and IV patients, were observed compared to the other patients.

Median NT-pro BNP concentration was significantly higher in the group with low DLCO than

Table 3. The results of 6MWT, functional class, NT-proBNP, and hemodynamic parameters in 65 IPAH patients depending on DLCO % predicted value

Characteristic	DLCO < 55% pred.		DLCO ≥ 55% pred.		p*
	n	Median (IQR)	n	Median (IQR)	
6MWT distance, m	12	284 (190–388)	52	395.5 (366–459)	0.01
6MWT SaO_2 pre-test, %	10	91 (87–93)	51	97 (95–98)	0.0001
6MWT SaO_2 6 min, %	10	82 (75–87)	48	94 (90–97.5)	0.0006
Functional class III and IV n (%)	12	9 (75%)	52	14 (27%)	0.005
NT-proBNP, pg/ml	10	3005 (1929–5093)	22	1202 (166.9–2031)	0.016
RAPm, mm Hg	10	9 (7–12)	40	8 (4–11)	NS
PAPm, mm Hg	10	52.5 (48–55)	40	56.5 (46.5–64.5)	NS
PAWP, mm Hg	10	10 (5–14)	40	10 (6–14)	NS
CO, l/min	10	4.47 (3.56–5.09)	40	4.19 (3.61–5.11)	NS
CI, l/min/m^2	10	2.32 (2.13–2.57)	40	2.53 (2.09–2.86)	NS
PVRI, jW*m^2	10	10.36 (7.87–12.54)	40	10.31 (8.44–15.48)	NS
SaO_{2mv}, %	10	57 (43–59)	40	57 (51.5–64)	NS
Responders n (%)	10	2 (20%)	40	10 (25%)	NS

CI — cardiac index; CO — cardiac output; DLCO — diffusion capacity for carbon monoxide; IQR — interquartile range, ns-not significant; NT-proBNP — N-terminal pro-brain natriuretic peptide; PAPm — mean pulmonary artery pressure; pred. — predicted; PAWP — pulmonary artery wedge pressure; PVRI — pulmonary vascular resistance index; SaO_2-oxyhemoglobin saturation; SaO_{2mv} — mixed venous oxygen saturation; 6MWT — six-minute walk test; RAPm — mean right atrial pressure.

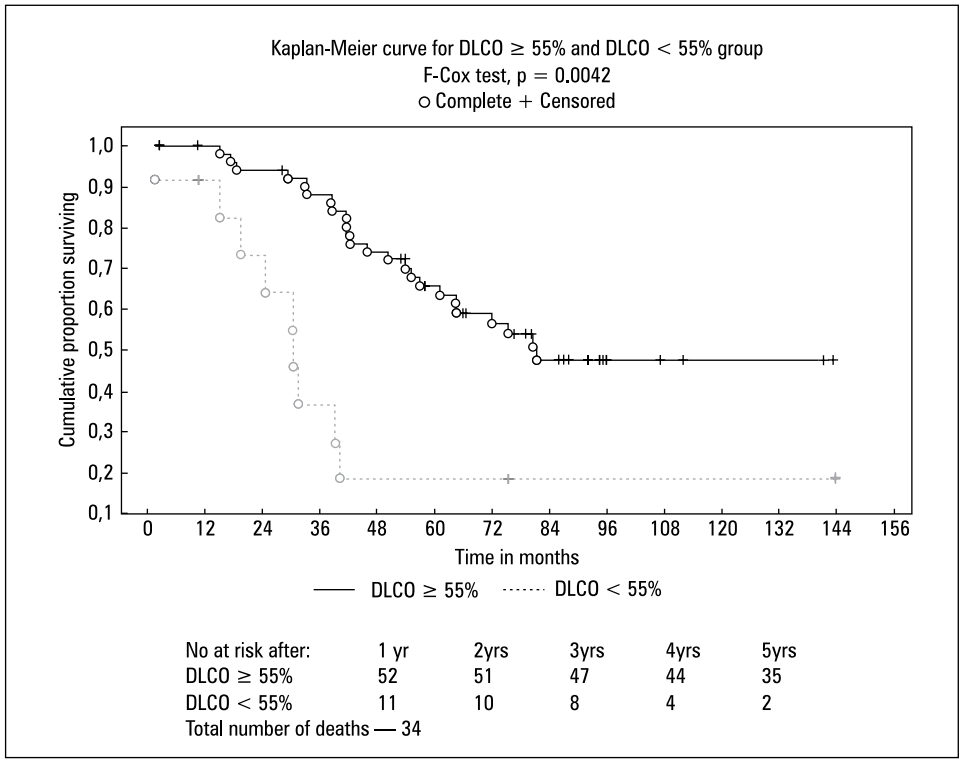

Figure 2. Comparison of survival rates between patients with DLCO < 55%pred. and with DLCO ≥ 55%pred.

in the other (3005 vs. 1202 pg/ml, p = 0.016). There were, however, no significant differences between the two groups concerning hemodynamic indices and the percentage of responders to acute vasoreactivity test (Table 3).

Mean survival time for the whole group was 56 (± 33) months. The cumulative survival rates were: 1 year — 97%, 2 years — 88%, 3 years — 77%, 4 years — 63%, 5 years — 57%. Survival curves of IPAH patients depending on DLCO %

Table 4. Univariate survival analysis in 65 IPAH patients

Parameter	n	HR	−95%CI	+95%CI	p
Age, years	65	1.01	0.99	1.04	NS
Male gender	65	2.34	1.18	4.63	0.015
SaO_2%	65	0.81	0.76	0.87	0.0000002
SaO_2 < 90%	65	5.44	2.62	11.29	0.000005
PaO_2, mm Hg	65	0.94	0.92	0.97	0.00002
PaO_2 < 60 mm Hg	65	2.71	1.40	5.22	0.003
$PaCO_2$ mm Hg	65	0.93	0.86	1.02	NS
DLCO < 55%pred	65	3.92	1.79	8.60	0.0006
FEV_1/VC_{max}, %pred.	65	1.00	0.96	1.03	NS
6MWT distance, per 10 m	65	0.96	0.93	1.00	0.03
NT-proBNP, per 100 pg/ml	34	1.03	1.01	1.05	0.001
RAPm, mm Hg	50	1.04	0.97	1.11	NS
PAPm, mm Hg	50	1.00	0.98	1.03	NS
CO, l/min	50	0.93	0.69	1.27	NS
PVRI, jW*m^2	50	1.01	0.90	1.14	NS
SaO_2mv < 63 mm Hg	50	4.63	1.39	15.39	0.01

CI — confidence interval; CO — cardiac output; DLCO — diffusion capacity for carbon monoxide; FEV_1 — forced expiratory volume in 1 second; HR — hazard ratio; MMEF — maximum midexpiratory flow; ns — not significant; NT-proBNP — N-terminal pro-brain natriuretic peptide; $PaCO_2$ — partial carbon dioxide pressure; PAPm — mean pulmonary artery pressure; pred. — predicted; PaO_2 — partial oxygen pressure; pred. — predicted; PVRI — pulmonary vascular resistance index; SaO_2 — oxyhemoglobin saturation; SaO_{2mv} — mixed venous oxygen saturation; 6MWT — six-minute walk test

pred. are presented in Figure 2. The prognosis was significantly worse for patients with DLCO < 55 % pred. compared to those with DLCO ≥ 55% pred., median survival time was 30.5 months vs 66.4 months, respectively, p = 0.004.

Univariate Cox proportional hazard regression revealed significant influence of male gender, PaO_2, SaO_2, DLCO < 55% pred., 6MWT distance, NT-pro BNP serum concentration, and SaO_{2mv} < 63% pred., on survival (Table 4). DLCO, SaO_2, and SaO_{2mv} were the strongest prognostic indicators. The risk of death was increased 4 times if DLCO was less than 55% pred., 5 times if SaO_2 was less than 90%, and more than 4 times if SaO_{2mv} was less than 63%. We failed to demonstrate the independent prognostic significance of DLCO, probably due to small number of patients with low DLCO and the strong correlation between DLCO% pred. and SaO_2 (r = 0,43, p = 0,0003).

Discussion

Low DLCO (< 55% pred.) was diagnosed in 18% of IPAH patients in our study. These patients were significantly older, and the percentage of males and prevalence of coronary artery disease were higher among them in comparison to the others. Other authors also found the association between low DLCO and older age and male gender [10, 25, 26]. Such characteristics could suggest the influence of left heart disease and/or cigarette smoking on DLCO. The influence of chronic left heart failure on PFT was reported recently by Minasian et al., who found DLCO impairment and airway obstruction in 44-58% of patients [27]. Nevertheless, in none of our patients pulmonary artery wedge pressure exceeded 15 mm Hg, thus significant left heart disease was excluded. Moreover, PAWP in the patients with DLCO < 55% pred. was comparable with those from the group with DLCO ≥ 55% pred. The influence of cigarette smoking cannot be completely ruled out, even if statistically there was no significant difference in share of smokers between two groups distinguished on the base of DLCO in our study.

A well-known cause of severe DLCO decrease in PAH patients is pulmonary veno-occlusive disease (PVOD) [28]. Inhomogeneous lung attenuation in form of ill-defined centrilobular nodules and focal ground glass opacifications seen on HRCT scans in some of our patients could suggest the presence of this condition. However, no other radiological signs of PVOD such as thickened interlobular septa, enlarged mediastinal lymph nodes and pleural effusion were found. What's more, inhomogeneous lung attenuation was observed with similar frequency in the patients with low DLCO and

the remaining ones. The presence of various lung attenuation disturbances on HRCT was described by other authors in 5–10% of IPAH patients [28] and was also reported by our group previously [29].

Lung diseases coexisting with IPAH should be always taken into account as the cause of low DLCO. In the recommendations published as a result of the Fifth World Symposium on Pulmonary Hypertension, the proposed criteria to exclude significant lung disease were as follows [30]:

TLC ≥ 70%pred., FVC ≥ 70%pred., and FEV_1 ≥ 60% pred.

No significant fibrosis and/or emphysema on chest HRCT.

All of the patients from our group meet these criteria.

Nevertheless, bronchial obstruction was diagnosed in 14 of our 65 IPAH patients (22%). The non-significant tendency to more frequent bronchial obstruction was noticed in the patients with low DLCO compared to the others (42% and 17%, respectively). The obstructive lung diseases were diagnosed in 5 patients only (2 patients with COPD in the group with DLCO < 55% pred, and 3 patients with asthma in the group with DLCO ≥ 55%pred.). In the remaining patients the cause of bronchial obstruction remained unclear. Bronchial pathology in the course of IPAH has to be taken into account.

The decrease of peripheral airflow and decrease of DLCO were previously reported in IPAH patients without coexisting lung diseases, suggesting the influence of vascular pathology on ventilation parameters or the coexisting changes in small bronchi in the course of IPAH [10, 11]. Nevertheless, in our group of patients, the percentage of those with isolated MMEF < LLN was the same in the group with low and with higher DLCO.

Noteworthy is also the fact that the degree of DLCO impairment didn't reflect the extent of vascular lesions in our study group of IPAH patients. The comparison of pulmonary vascular resistance as well as the remaining hemodynamic parameters between the group with low DLCO and the other group didn't reveal any differences. The percentage of responders in the acute hemodynamic test was also comparable between the groups. Our results are in line with data of Sun et al. [10] and Chandra et al. [13], who found no relationship between DLCO and hemodynamic variables, either.

Despite being not correlated with hemodynamic profile, low DLCO was clearly associated with worse functional status: higher percentage of WHO III and IV class patients, shorter 6MWT distance, and greater desaturation on exertion. Moreover, significantly higher median NT-proBNP values were found in the patients with low DLCO comparing to the others. Therefore, it was not surprising that DLCO < 55% pred. was a significant negative prognostic indicator for survival in our group and carried a 4-fold increase of death risk in 5-year perspective. We reported similar finding on negative prognostic value of low DLCO in IPAH patients in three years follow-up, previously [31]. In study of Chandra et al. [13], DLCO < 43% pred. was associated with 2.7-fold increase of risk of death. Low DLCO also appeared as a negative prognostic factor in larger groups of patients in national PAH registries. Benza et al. [1] reported that DLCO ≤ 32% pred. was one of the negative prognostic factors in the patients enrolled to REVEAL Registry. Lee et al. [3] found relationship between DLCO and survival in the UK Registry.

The patients were enrolled into the present study between 1998 and 2006. Therefore the limitation might be related to suboptimal treatment due to unavailability of some PAH specific drugs at that period of time. Nevertheless, the survival reported in the present study was slightly better than the results reported by Humbert et al. based on French Registry (PAH patients enrolled in 2002–2003) [2] and better that the survival in USA registry (PAH patients enrolled in 1982–2006) [14]. Moreover, there were no significant differences between the type of treatment in the patients with low DLCO compared to the remaining ones. Thus we suppose that the treatment type didn't influence survival in the present study.

Summary

In the present study, low DLCO value (< 55% pred.) was found in 18% of IPAH patients, and it was significantly associated with older age, higher prevalence of coronary artery disease, worse functional status and worse exercise capacity. Patients with low DLCO had 4-fold increase of death-risk as compared to the patients with higher DLCO values.

Conflict of interest

The authors declare no conflict of interest.

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