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Low DLCO Can Provide Insights into Treatment Response in PAH Patients Irrespectively of the Reason of Its Decrease

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Abstract

Group of PAH patients encompasses patients with a diverse underlying aetiological condition, having histological modifications that can affect gas exchange across the alveolar-capillary membrane as it is reflected by decreased DLCO. DLCO values did not identify the exact reason of its decrease, but can provide insights into the underlying pathobiology and prognosis of PAH patients. Our aim was to explore if PAH patients with low DLCO constitute a different subpopulation and describe their characteristics and response to treatment. 69 PAH patients were studied retrospectively and divided into *group1*: DLCO≥45% and *group2*: DLCO<45%. IPAH and PAH-CTD constituted mainly our population. The proportion of IPAH and PAH-CTD was almost the same. Patients in *group 2* were older (66.83± 11.61 vs 59.27±111.90, p=0.035), more often male (47.5% vs 11.5% p=0.008) and ever smokers (59% vs 22%, p=0.049). They had mainly WHO-FC III ((68%) vs 32%) and have received more advanced therapy (40% on triple combination therapy vs 16%). The two groups had the same mean PAP (*group1*=32 (22.00-38.00) vs *group2*=35 (28.50-48.50) mmHg) and PVR was higher in *group 2* (6.49(4.10-9.52) vs 3.61 (2.95-5.22) WU). In *group 2* neither IPAH nor PAH-CTD patients did improve WHO-FC, 6MWD, or NT-proBNP after treatment. In our centre PAH patients with low DLCO have some distinct clinical characteristics. poor prognosis and treatment response in vasodilatory therapy. Understanding the role of DLCO in phenotyping PAH patient and in treatment response would be useful in guide therapeutic approaches, especially now that new therapeutic targets are involved in the PAH treatment.

Keywords: PAH; DLCO; phenotype; clinical characteristics; treatment

1. Introduction

Pulmonary Arterial Hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance, leading to right heart failure and significant morbidity. The Group of PAH patients encompasses patients with a diverse underlying aetiological condition, having distinguished histological modifications [1,2] such as augmented contractility of pulmonary arterioles, endothelial dysfunction, disrupted signaling pathways and changes in endothelial and smooth muscle cells [3]. Despite their different etiology, guidelines suggest a similar therapeutic approach, based on data showing that these patients can have a beneficial treatment effect regarding

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the reduction of risk of morbidity/mortality or time to clinical worsening. Idiopathic (IPAH) and connective tissue disorders (CTD) are the most common etiologies of PAH patients.

The **Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO)**, reflects the efficiency of gas exchange across the alveolar-capillary membrane and pulmonary microvascular integrity and seems to be a parameter reflecting the degree of the pulmonary vascular bed alternations [4–6] where the main pathological changes in PAH occur. DLCO can provide insights into the underlying pathobiology [7–11], as well as prognosis of PAH patients irrespectively of the PAH etiology [12–16].

Recently a registry analysis in patients with idiopathic PAH (IPAH) indicate that patients with reduced DLCO (<45%) constitute a different phenotype, the lung phenotype of IPAH patients. These patients have worse survival outcomes despite being treating with PAH specific drugs [17]. Data in the literature regarding the response to current, thus far, PAH therapies (PDE5i, ERA, prostanoids) are limited and findings suggest that **these patients can still experience hemodynamic and cardiac function improvements** following treatment [18].

Our purpose was to explore if PAH patients in general and not just those with IPAH with low DLCO in our center constitute a different subpopulation and describe their clinical and hemodynamic characteristics as well as their response to treatment. In other words, our purpose was to explore if low DLCO irrespective of the reason of its decrease, can recognize patients with specific characteristic and response to treatment. Understanding the role of DLCO in PAH phenotyping can guide personalized therapeutic approaches.

2. Methods

We retrospectively studied PAH patients seen at the Evangelismos Hospital PH center (Athens, Greece) between September 2022 and November 2024.

PAH diagnosis was made by our center physicians and included a multidisciplinary team assessment.

Diagnosis was based on right heart catheterization. PAH were diagnosed in patients with a mean pulmonary arterial pressure (PAP) ≥20 mmHg, pulmonary arterial–wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance >2 Wood Units (WU), not explained by an underlying parenchymal lung disease or chronic obstructive pulmonary disease (COPD) or chronic thromboembolic disease (CTEPH) or multiple/unclear mechanisms (1) .

The patients were also evaluated clinically and by echocardiography; additionally chest CT (HRCT or CTPA), perfusion lung scanning, pulmonary function testing, were performed and 6 minutes walking distance (6MWD) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were measured.

All patients were adults. Patients categorized as PAH due to congenital heart diseases were excluded.

Patients' response to treatment was assessed by WHO functional class (WHO-FC), 6MWD and NT-proBNP values, as suggested by current ESC/ERS guidelines follow-up assessment.

The study was approved by the Evangelismos Hospital Research Ethics Committee (4783/22-2-2022) and conducted in compliance with the Helsinki Declaration.

Statistical Analysis

Data were presented as *mean ± standard deviation* for continuous variables with normal distribution, and as median and interquartile range for non-normally distributed variables. Categorical variables were presented as frequencies and percentages (%). Continuous variables were compared using the *t*-test for independent samples or the Mann-Whitney U test, while the chi-square test or the Fisher exact test was used to assess categorical variables. Statistical tests were pairwise when appropriate.

A p-value < 0.05 was considered statistically significant in this study. Data were analyzed using the SPSS version 25.0. (IBM SPSS Statistics for Windows, Version 25.0.)

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3. Results

69 PAH patients have been followed and treated in our center over 26 months. 42% have been diagnosed as IPAH, 55% as PAH due to CTD mostly systemic sclerosis (76%), and 3% due to portal hypertension and HIV. In our study population no patient has been categorized as suffering from PAH due to pulmonary veno-occlusive disease (PVOD); patients with congenital heart disease were excluded, due to the known effect of this clinical condition on DLCO and their different clinical course.

PAH patients were divided into 2 groups according to their DLCO (*group1* = DLCO≥ 45%, *group2* = DLCO<45%). The cut off value of 45% of predicted for DLCO was based on previous studies in order for our results to be comparable [17,19,34]. DLCO measurement was performed during patient's initial evaluation and before treatment initiation, using the single-breath method. We have used the predicted DLCO values corrected to hemoglobin. The main clinical characteristics are seen in Table 1 revealing the following results.

Table 1. Patients' main characteristics and received treatment.

	***group 1* (n=33)**	***group 2* (n=36)**	**p**
IPAH%/PAH-CTD%	32/63	39/61	
Age	59.27±111.90	66.83± 11.61	0.035
Male %	11.5	47.5	0.008
BMI kgr/m²	28.32 (26.14-34.01)	25.81 (23.55-30.68)	0.128
WHO-FC			0.016
WHO-FCII %	68	30	
WHO-FCIII %	32	61	
WHO-FCIV %	0	9	
Ever smokers %	22	59	0,049
Comorbitities %	32	43.5	0.632
FEV_1	90 (74.2-105.8)	81.6 (59.3-92.0)	0.073
FVC	99 (79.3-103.6)	92 (60.6-100.0)	0.189
FEV1/FVC	79.8(75-84)	74 (65-82.6)	0.044
6MWD	417.88±77,61	285.45±125.54	0.001
NT-proBNP	939.00±1565.54	1126.22±1491.42	0,452
Treatment			0.208
Monotherapy	21%	8 %	
Double oral combination	63%	52%	
Triple combination therapy	16%	40%	

WHO-FC: WHO functional class, FEV_1: Forced Expiratory Volume in 1 sec, FVC: Forced Vital Capacity, 6MWD: 6 minutes walking distance, NT-proBNP: N-terminal prohormone of brain natriuretic peptide. .

IPAH and PAH due to CTD constitute the majority of PAH patients in our group. The proportion of IPAH and PAH-CTD is almost the same in our groups. Patients in *group 2* were older (66.83± 11.61 vs 59.27±111.90, p=0.035), more often male (47.5% vs 11.5% p=0.008) and ever smokers (59% vs 22%, p=0.049). *Group 2* suffered more often by comorbidities, such as arterial hypertension, diabetes mellitus and coronary disease, however the difference between the groups did not reach statistical significance. *Group 1* patients has had mainly WHO-FC II (68%), whereas *group2* III (61%). The 63% of *group 1* and 52% of *group 2* received oral combination therapy, whereas 40% of *group 2* received triple combination therapy including parental prostanoids versus 16% of *group 1*.

The main hemodynamic and echocardiographic differences of the two groups are seen in Table 2. There was no statistically significant difference in mean pulmonary artery pressure (mean PAP) between the two groups (*group1*=32 (22.00-38.00) mmHg vs *group2*=35 (28.50-48.50) mmHg, p=0.063) and similarly in pulmonary arterial wedge pressure (PAWP) (*group1*= 11.00±0.98mmHg vs *group2*=9.90±2.67mmHg, p=0.317) and cardiac index (CI) (*group1*=2.58 ±0.79 L/min/m2 vs

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group2=2.30±0.58 L/min/m2, p=0.077). Statistically significant different were pulmonary vascular resistance (PVR) (*group1*=3.61 (2.95-5.22)WU vs *group2*=6.49(4.10-9.52)WU, p=0.006), and stroke volume index (SVI) (*group1*=40.28±13.24ml/m2 vs *group2*=30.88±7.33ml/m2, p=0.028).

Table 2. Hemodymanic and echocardiographic characteristics.

	group 1	*group 2*	p
RAP mmHg	7.05±0.75	6.18±0.74	0.405
Mean PAP mmHg	32 (22.00-38.00)	35 (28.50-48.50)	0.063
PAWP mmHg	11.00±0.98	9.90±2.67	0.317
PVR WU	3.61 (2.95-5.22)	6.49 (4.10-9.52)	0.006
CI L/min/m²	2.58±0.79	2.30±0.58	0.077
SVI ml/m²	40.28±13.24	30.88±7.33	0.028
TAPSE mm	22 (20.5-24)	18 (16.5-20)	0.003
RVSP mmHg	50.26±20.96	62.55±18.10	0.059
TAPSE/RVSP mm/mmHg	0.48± 0.17	0.32±0.14	0.004
TRVmax m/sec	3.23±0.64	3.64±0.55	0.039
RA cm²	19.18 ±6.81	19.35±5.27	0.939
Pad mm	24.76±5.37	28.22±3.37	0.032

RAP: Right Atrium Pressure, PAP: Pulmonary Artery Pressure, PAWP: Pulmonary Arterial Wedge Pressure, PVR: Pulmonary Vascular Resistance, CI: Cardiac Index SVI: Stroke Volume Index, TAPSE: Tricuspid Annular Plane Systolic Excursion, RVSP: Right Ventricular Systolic Pressure, TRVmax: Tricuspid valve maximal Velocity, Pad: Pulmonary artery diameter.

Echocardiographic parameters that were statistically significant different were tricuspid annular plane systolic excursion (TAPSE) (*group1*=22 (20.5-24)mm vs *group2*=18 (16.5-20)mm, p=0.003), tricuspid annular plane systolic excursion/ right ventricular systolic pressure (TAPSE/RVSP) (*group1*=0.48± .17mm/mmHg vs *group2*=0.32±0.14mm/mmHg, p=0.004) , tricuspid valve maximal velocity (TRVmax)(*group1*=3.23±0.64m/sec vs *group2*=3.64±0.55m/sec, p=0.039), pulmonary artery diameter (Pad) (*group1*=24.76±5.37mm vs *group2*=28.22±3.37mm, p=0.032).

Our patients have been treated according to their physician as seen in Table 1. In the follow up WHO-FC, 6MWT, NT-proBNP were reassessed. The results are seen in Table 3, 4, 5 and are pairwise. *Group 1* patients improved WHO-FC, 6MWT and NT-proBNP, whereas *group 2* did not have significant improvement. In *group 2* neither IPAH nor PAH-CTD patients did improve clinical status, 6MWD, NT-proBNP.

Table 3. WHO-FC assessment before and after treatment in two groups.

WHO-FC	**Before treatment**	**After treatment**	**P**
group 1			0.023
WHO-FCII	68%	76%	
WHO-FC III	32%	24%	
WHO-FC IV	0%	0%	
group 2			
WHO-FC II	30%	30%	0.19
WHO-FCIII	61%	62%	
WHO-FC IV	9%	8%	

Table 4. 6MWD before and after treatment in two groups.

6MWDm	**Before treatment**	**After treatment**	**p**

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group 1	417.88±77,61	457.77±56.17	0.023
group 2	285.45±125.54	294.63±132.18	0.834
group 2 IPAH	215.75±167.24	198.75±123.31	0.899

6MWD: 6min Walking Distance, IPAH: Idiopathic Pulmonary Arterial Hypertension.

Table 5. NT-proBNP before and after treatment in two groups.

NT-proBNP pg/ml	Before treatment	After treatment	P
group 1	**558.70.±647.73**	358.48±204.83	0.045
group 2	1126.22±1491.42	1476.13±2117.22	0.210
group2 IPAH	1232±1077.96	1465±949.51	0.155

NT-proBNP**:** N-terminal prohormone of brain natriuretic peptide, IPAH: Idiopathic Pulmonary Arterial Hypertension. .

4. Discussion

In our center PAH patients with DLCO<45% tend to be older, men, and smokers or ex-smokers. They have worse functional status, parameters and indices that carry worse prognosis and respond worse to treatment. They have also normal pulmonary function that does not differ in comparison with patients with DLCO≥45%. We did not evaluate chest computed tomography (CT) scans for underlying ephysema and fibrosis, based on the above mentioned normal spirometric values. Having known that spirometry does not correlate to HRCT findings we cannot exclude that our patients, especially those with a smoking history and connective tissue disease, may also have some degree of parenchymal lung disease that would not exclude them from the PAH Group. Furthermore the median PVR value of *group 2* (>5WU) suggests a certain pulmonary arterial component.

In our study the two patients' groups have the same hemodynamic impairment in terms of mean PAP. Mean PAP in *group 2* although has been higher, did not reach statistically significant difference when compared to *group 1*. However PVR were statistically different between the two groups implying more severe disease in *group 2*. A larger sample of patient may be needed to clarify it.

Based on the marginal no statistically significant hemodynamic difference between our two groups, PH severity could be an obvious explanation for our results. Nevertheless, from our findings emerge some interesting points.

In our study PAH patients with low DLCO have clinical characteristics similar to IPAH patients with low DLCO, meaning that they tend to be older, male and with a smoking history. First Trip et al studied IPAH patients with severe pre-capillary PH and DLCO<45%. Most of these patients were men and had a smoking history but relatively well-preserved lung function, and 32% had normal findings on CT [19]. Similarly, analysis from COMPERA and ASPIRE patients showed that IPAH patients with 'lung phenotype' had normal or near normal spirometry, a severe reduction in DLCO, they were older and they had lower proportion of female patients than those with classical IPAH, and also were all ever smokers [17]. In our population approximately 60% of patients are PAH-CTD, meaning that both IPAH and PAH-CTD patients with reduced DLCO <45% are sharing similar clinical characteristics.

Data in the literature have shown loss of functional capillary surface area in vivo in both IPAH and PAH-CTD patients [20–23] with a correlation to DLCO levels only in PAH-CTD patients and a more severe pulmonary capillary endothelial metabolic dysfunction in patients with PAH-CTD compared to IPAH patients (24). Our data may indicate that despite the different pathogenity of endothelial function between the two types of PAH, some common factors may influence further the endothelial dysfunction leading to PAH patients with severely decreased DLCO.

Age and smoking habit are known factors that decrease DLCO and can also independently affect PH, as well as male sex. Furthermore, Trip et al found in their study that on multivariate regression analysis age and the number of pack years were independently associated with a severely reduced DLCO [19]. Smoking-related vasculopathy is a relatively recent theory [25], where smoking is

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thought to be a cause of reducing DLCO in PAH patients, even in the absence of any obvious emphysema or interstitial lung disease upon chest imaging [26]. In murine experimental models, animals which were exposed to tobacco smoke had pulmonary vascular damage with loss of capillaries that preceded the development of emphysema [26]. Although male sex has not been correlated to decreased DLCO, male gender is correlate to worse survival, even more to worse right ventricle (RV) adaptability as compared to female PAH patients [27–29].

Another finding of our study is that *group 2* has a worse response to PAH therapy, although these patients receive more frequently triple combination PAH specific therapy including parental prostanoids; this undrlies in part their poor prognosis. In our study, *group 2* patients have parameters that carry worse prognosis namely WHO-FC, 6MWT, NT-proBNP, TAPSE/RSVP, SVI. Once again, PH severity may be an explanation and one can hypothesize that the poor response to treatment of our *group 2* is due to known worse prognosis of PAH-CTD compared to IPAH [15,30,31], since our PAH population is mainly PAH-CTD patients. Until now, studies indicating poor response to treatment in PAH-CTD did not have any information regarding DLCO [32,33]. Data on PAH-specific therapy response regarding DLCO are referred to comparison of PAH-CTD patients and CTD patients with PH due to lung disease and are scarce (35). Moreover, in our population the same poor response was detected in IPAH patients of *group 2*, who did not have more severe hemodynamics compared to IPAH patients of *group 1* (not seen in the results). Previous studies have demonstrated the same response in IPAH patients with low DLCO and/or mild lung parenchyma lung disease, resembling PH patients with lung disease (group 3) [17,34]. Our results need further investigation and confirmation from other studies.

The presence of even mild parenchymal lung disease affects both IPAH and PAH-CTD patients' outcome [34,35].The possibility that mild lung parenchyma abnormalities are the reason for the poor response of our *group 2* patients cannot be answered by our study. However, our purpose was to explore the meaning of low DLCO in PAH patients in term of clinical characteristic, hemodynamic severity and response to treatment, irrespective of the reason of the DLCO decrease. If chest CT can aid to understand further, phenotype and treat PAH patients need more investigation.

Our study is a retrospective, single center study and has some limitations. The small number of patient at each group has the risk of not recognizing differences and correlations between groups, due to underlying beta error. Small number and missing values did not allow us to proceed to further statistical analysis to determine the characteristics that were independently associated with a severely reduced DLCO and poor response to therapy. Furthermore, we did not evaluate CT scans because they were performed in various different centers leading to great heterogeneity of the quality of CT scans. Finally we did not analyze hemodynamic or echocardiographic post treatment data and we preferred to be based on more clinical meaningful parameters and ease, widely available tests.

Taken together our results suggest that PAH patients with low DLCO, irrespective of the reason of the DLCO decrease, have some distinct clinical characteristics. They are older, males, smokers with reduced functional class, poor prognosis and treatment response in vasodilatory therapy. Although risk stratification, functional class, as well as PH severity constitute major parameters that determine the therapeutics decisions; the worse response to vasodilatory treatment of patients with low DLCO may generate the question of an alternative therapeutic approach in this patient group. Certainly, further studies are needed to determine if DLCO except of being a prognostic factor for PAH, can also phenotype PAH patient according to their response on vasodilatory treatment. It would be of interest to explore further if PAH patients with low DLCO, mainly patients with IPAH and CTD have worse response to therapy, especially now that new therapeutic targets are involved in the treatment of PAH patients.

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