

Long-lasting dyspnoea in patients otherwise clinically and radiologically recovered from COVID pneumonia: a probe for checking persisting disorders in capillary lung volume as a cause

Roberto W. Dal Negro,¹ Paola Turco,² Massimiliano Povero³

¹National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology - CESFAR, Verona

²Research & Clinical Governance, Verona

³AdRes Health Economics and Outcome Research, Turin, Italy

ABSTRACT

Background: During SARS-CoV-2 infection, diffuse alveolar damage and pulmonary microvascular abnormalities are critical events that result in gas exchange disorders of varying severity and duration. The only measure of carbon monoxide (CO) diffusing capacity (DL_{CO}) is unable to distinguish the alveolar from the vascular side of present and residual diffusive abnormalities, and measure of nitric oxide (NO) diffusing capacity (DL_{NO}) is also recommended. Dyspnoea, despite being understudied, persists in a significant proportion of patients for several weeks after hospital discharge. The goal of this study was to look into the underlying cause of long-term dyspnoea in patients who were "clinically and radiologically recovered" from COVID pneumonia by assessing DL_{CO} and DL_{NO} at the same time.

Methods: Patients of both genders, aged ≥ 18 years, who had a CT scan showing complete resolution of COVID-related parenchymal lesions were recruited consecutively. Spirometrical volumes, blood haemoglobin, SpO_2 , DL_{CO} , DL_{NO} and capillary blood volume (V_c) were measured. Data from patients without dyspnoea (group A) and from patients still claiming dyspnoea after 12-16 weeks from their hospital discharge (group B) were statistically compared.

Results: Forty patients were recruited: 19 in group A and 21 in group B. Groups were comparable for their general characteristics and spirometrical volumes, that were in the normal range. Mean values for DL_{CO} , DL_{NO} and V_c were significantly and substantially lower than predicted only in patients of group B ($p < 0.011$; $p < 0.0036$; $p < 0.02$; $p < 0.001$, respectively). The DL_{NO}/DL_{CO} ratio was higher in group B ($p < 0.001$) and inversely correlated to V_c values (-0.3636).

Conclusions: The single-breath, simultaneous measurement of DL_{CO} , DL_{NO} , and V_c demonstrated that problems with blood gas exchange can persist even after parenchymal lesions have healed completely. Regardless of the normality of spirometric volumes, there was a significant reduction in lung capillary blood volume. In these patients, the cause of long-term dyspnoea may be related to hidden abnormalities in the vascular side of diffusive function. In the near future, novel therapeutic approaches against residual and symptomatic signs of long-COVID are possible.

Key words: COVID-19; vascular effects; lung perfusion, capillary blood volume (V_c); carbon monoxide diffusing capacity (DL_{CO}); nitric oxide diffusing capacity (DL_{NO}).

Correspondence: Roberto W. Dal Negro, National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology, Via G. Rossetti 4, 37124 Verona, Italy. E-mail: robertodalnegro@gmail.com

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Introduction

COVID-19 caused by SARS-CoV-2 infection has an extremely variable natural history, ranging from asymptomatic or mild clinical picture involving only the upper airways to diffuse interstitial pneumonia with hypoxemic respiratory failure (and/or fatal multiorgan failure), especially in fragile or predisposed individuals [1-7].

The effects of two major biologic cascades dominate the field: the diffuse damage at alveolar level (including injury to the alveolar epithelial cells, hyaline membrane formation, fibrin deposition, hyperplasia of type II pneumocytes) [8], and pulmonary congestion, with microvascular thrombosis and occlusion [9]. The local high concentration of cytokines and chemokines that contribute to the recruitment of inflammatory cells, combined with the production of IgM-mediated immunocomplexes, can contribute to platelets and tissue factors activation, further leading to coagulation and micro-thrombosis, as seen in COVID-19 patients with acute respiratory failure (RF) [2]. All of these structural changes can essentially support the occurrence of a significant disruption in alveolar-blood gas exchange [10].

Though understudied in clinical practice, long-term dyspnoea of varying extent and duration is claimed by a not insignificant proportion of patients who were incorrectly defined as “clinically recovered” from COVID-19 pneumonia several weeks before [11].

In terms of lung function abnormalities, in addition to a variable restrictive pattern of lung volumes, a mild reduction in diffusing capacity for carbon monoxide (DL_{CO}) was the only lung function limitation reported as occurring in approximately 30% of patients for several weeks after hospital discharge [12-15].

Unfortunately, due to the slow binding of CO with intracapillary haemoglobin (Hb), the current assessment of DL_{CO} is insufficient to distinguish abnormalities in the alveolar membrane diffusing conductance (DM) from those involving the vascular side of diffusion, such as capillary blood volume in the lung (Vc). For these reasons, DL_{NO} evaluation is also recommended [16-18]. Furthermore, it has recently been demonstrated that changes in gas transport can be observed even in subjects who have mild COVID-19 pneumonia with no or minimal persisting CT abnormalities [19].

A non-invasive, single-breath technology that allows rapid differentiation between DM and Vc disorders is now available for clinical use [20-21], providing an excellent opportunity to investigate deeper into the unexplained cause of persistent dyspnoea in long-COVID patients.

The purpose of this study was to look into the cause of dyspnoea that lasted several weeks in patients who were otherwise considered “clinically and radiologically recovered” from COVID pneumonia.

Methods

Patients of both genders aged ≥ 18 years who had been previously regarded as “clinically recovered” for 12-16 weeks after discharge for COVID pneumonia (hospital admission over the previous six months) and provided with a recent (i.e., within the last two weeks before recruitment) CT scan showing a complete resolution of any COVID-related parenchymal lesions were recruited consecutively between September 1, 2021 and March 15, 2022, after their informed consent.

Exclusion criteria were: current and former-smokers; age < 18 years; the presence of major comorbidities affecting the diffusion

measurements (such as: anaemia (blood Hb < 12 g/L); heart failure; COPD; lung fibrosis; vasculitis; liver and renal failure; diabetes); the persistence of COVID-related parenchymal abnormalities; the presence of physical limitations and/or cognitive impairment enabling procedures for lung function tests; the refusal of the informed consent.

Further to age, gender, BMI, and other possible comorbidities not interfering with diffusion measures, the following parameters were collected in all patients:

- Hb (blood haemoglobin, in g/L);
- SpO₂ (O₂ saturation, in %);
- VC (vital capacity) and FEV₁ (forced expiratory volume in 1 sec), both reported as % predicted);
- DL_{CO} (diffusing capacity for carbon oxide); Kco ($DL_{CO} / VA -$ alveolar volume); DL_{NO} (diffusion capacity for nitric oxide); Kno ($DL_{NO} / VA -$ alveolar volume); Vc (capillary blood volume), and DL_{NO} / DL_{CO} . All parameters were reported as % predicted.

Spirometrical parameters were obtained by means of a Plethysmography Platinum DX Elite (MedGraphics, Saint Paul, MN, USA). Diffusion parameters were measured by means of the “Stand-Alone” Hypair Compact System (MGC Diagnostics International, Sorinnes, Belgium) that allows the simultaneous assessment of DM and Vc as a function of the standard single-breath method. This method is based on the principle by Roughton and Forster [22] of two reactions of THETA fractions: one for CO, and the other one for NO, according to the values fixed in the ERS/ATS Task-Force 2017 [23], during the usual single breath manoeuvres. Due to the use of an electrochemical analyser for NO, the usual DL_{CO} measure apnoea time duration of 10 sec, is reduced for DL_{NO} around 5 sec. Two gas mixtures are required for these measures: i) helium (He) 14%; CO 0.280%; oxygen (O₂) 18–21, and nitrogen (N₂), and ii) nitric oxide in nitrogen (NO in N₂) 400 ppm. According to standard procedures, measure of DL_{CO} and DL_{NO} required breath-hold times of 10 and 5 sec, respectively.

Current dyspnoea was checked and graded in each patient according to the modified British Medical Research Council (mMRC) dyspnoea score [24], and its duration after discharge was also reported.

The whole sample was then divided in two groups of patients to compare: i) those who did not report any significant dyspnoea (Dys-), and ii) those still claiming dyspnoea (DYS+).

Statistics

Continuous data were presented as means and standard deviation (SD), while sex as absolute and relative frequencies. Differences in all variables collected in the two groups were tested by *t*-test for continuous data and by Fisher exact test for categorical data; $p < 0.05$ was accepted for statistical significance. Furthermore, correlation analysis was performed to explore the linear association between all the lung function parameters in the whole sample.

All statistical calculations were carried out by means of STATA (StataCorp 2017. Stata Statistical Software: Release 15; StataCorp LLC, College Station, TX, USA); $p < 0.05$ was assumed as the limit of statistical significance.

Ethics statement

At recruitment, all subjects gave their informed consent also to the anonymous use of their own data for research purposes. The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session of May 2nd, 2021.

Results

General data

The whole sample consisted of 40 patients: 21 patients still reporting persisting dyspnoea at different extent for 12-16 weeks after their discharge, and 19 without any significant dyspnoea over the same period. General data are reported in Table 1.

Patients of the two groups were well matched for all general variables considered, including comorbidities that were evenly distributed in the two groups, both in terms of their frequency and type. Obviously, the dyspnoea duration after discharge and the current dyspnoea score proved significantly much higher in patients of group B.

Specific parameters in the whole sample

Mean blood Hb values and mean values for all lung function parameters assessed in the whole sample are reported in Table 2.

The whole sample of patients showed mean basal values for Hb, SpO₂, VC and FEV₁ in their predicted normal range. DL_{CO} and DL_{NO} mean values were slightly lower than predicted while only mean Vc values were dramatically reduced than predicted and proved to be significantly and negatively related to the values for the DL_{NO}/DL_{CO} ratio (-0.3636).

Specific parameters in the two groups

Mean values for all variables obtained in the two groups of patients are also reported in Table 2 together with the results of the corresponding statistical comparisons.

Patients of groups A and B had comparable mean basal values for blood Hb and O₂ saturation. Mean spirometrical lung volumes were in their normal range and comparable in both groups regardless of whether reporting dyspnoea or not. In particular, two patients in group A and three patients in group B had CV values lower than predicted (72% and 63% in group A, and 73%, 65%, and 63% in group B, respectively). Only one patient in group A and two patients in group B had FEV₁ values lower than predicted (68% in group A, and 73% and 68% in group B, respectively).

Nevertheless, patients in group A and B were significantly different in terms of mean values for all parameters related to CO and NO diffusion. Mean values for DL_{CO}, K_{CO}, DL_{NO}, K_{NO}, and Vc were significantly lower than predicted only in patients of group B, such as in those still claiming long-lasting dyspnoea (p<0.011; p<0.0036; p<0.02; p<0.038; p<0.001, respectively), while the DL_{NO}/DL_{CO} ratio was significantly higher (p<0.001). Moreover, three and four patients in group A, and fourteen and eleven patients in group B showed DL_{CO} and DL_{NO} absolute values lower than predicted, respectively (such as <80%). To underline that mean values for Vc proved dramatically lower than predicted in patients of group B (Table 2).

Table 1. General characteristics of the whole sample, together with those of the two groups, with corresponding statistical comparisons (means \pm SD, and statistical significance). Comorbidities are reported as relative frequency.

	Whole sample	Group A dyspnoea	Group B dyspnoea +	p
n	40	19	21	
Males/females	17/23	9/10	8/13	0.39
Age (y)	49.3 \pm 19.3	48.4 \pm 16.7	48.9 \pm 20.6	0.92
BMI	24.9 \pm 4.6	24.7 \pm 4.1	24.3 \pm 4.9	0.86
Comorbidities				
mild hypertension	6		3	3
thyroiditis	1		1	-
atopy	2		1	1
Dyspnoea duration after discharge (weeks)	5.3 \pm 10.7	1.1 \pm 0.4	12.7 \pm 3.1	0.001
Dyspnoea score	0.9 \pm 1.3		0.1 \pm 0.1	1.7 \pm 0.4 0.001

Table 2. Blood haemoglobin and lung function parameters in the whole sample and in two groups of patients, together with corresponding statistical comparisons.

	Whole sample	Dyspnoea -	Dyspnoea +	p
Hb (g/L)	14.11 \pm 0.1	14.06 \pm 0.4	14.14 \pm 0.5	0.59
SpO ₂ (%)	97.2 \pm 1.8	97.8 \pm 1.1	96.7 \pm 1.6	0.77
VC (% predicted)	99.1 \pm 16.3	97.05 \pm 12.1	99.14 \pm 20.9	0.71
FEV ₁ (% predicted)	96.4 \pm 15.1	95.79 \pm 11.5	96.57 \pm 17.6	0.87
DL _{CO} (% predicted)	83.7 \pm 16.9	90.5 \pm 16.5	76.9 \pm 15.6	0.011
K _{CO} (% predicted)	89.1 \pm 11.6	94.3 \pm 12.8	83.5 \pm 9.1	0.0036
DL _{NO} (% predicted)	82.3 \pm 16.9	91.7 \pm 14.0	77.9 \pm 15.9	0.022
K _{NO} (% predicted)	96.1 \pm 11.5	99.7 \pm 11.8	92.0 \pm 10.9	0.038
Vc (% predicted)	56.2 \pm 13.1	62.5 \pm 12.8	49.6 \pm 10.2	0.001
DL _{NO} /DL _{CO} (% predicted)	116.6 \pm 9.1	111.4 \pm 5.0	121.8 \pm 8.6	0.001

Discussion

After more than two years of pandemic, it is now accepted that a significant proportion of patients hospitalized for COVID pneumonia may experience long-term effects after discharge [11,13,25-27]. This condition is known as “long-COVID syndrome” or “post-COVID syndrome.” It is distinguished by varying lung function limitations as well as the persistence of some respiratory and extra-respiratory clinical signs [11,15,25].

Long-term dyspnoea is the most common symptom reported for several weeks, regardless of normalized lung volumes. The cause of long-term dyspnoea in these cases is still unknown. Unfortunately, the majority of cases in clinical practice remain unsolved because standard diagnostic procedures do not substantiate any cardiac involvement (the very first and practically only aspect investigated) and are generally inconclusive. In the absence of a clear cardiogenic cause, a psychological cause of persistent dyspnoea is frequently proposed. In these cases, it is generically related to the patients’ anxiety, most likely due to the great fear of an impending COVID-19 relapse, but the results are equally poor. The diagnostic path usually ends here, and a time-dependent spontaneous resolution is currently anticipated.

In contrast, the cause of this long-term dyspnoea should not be overlooked in these patients. It should be looked into further based on the accumulating evidence of COVID-19-induced microangiopathy involving the lung capillary bed. This unusual disorder may be the most likely cause of the hidden gas exchange abnormalities that result in symptomatic alveolar-perfusion mismatch. In other words, these types of disorders can be perceived by post-COVID patients, and dyspnoea may be their main persistent symptom despite being defined as “clinically and morphologically recovered” [10-11].

Despite the fact that several studies only report a generic reduction in CO diffusing capacity (DL_{CO}) as the only lung function limitation in these cases [12-15], additional studies reported reduced values of the DL_{CO} -to-alveolar volume ratio (DL_{CO}/VA) in a variable proportion of COVID-19 patients, even lasting for several weeks after discharge [28-29]. Further physiological studies have recently investigated and confirmed the additive value of measuring NO diffusing capacity (DL_{NO}) in post-COVID-19 conditions [19]. The evaluation of both of these measurements (and of other related parameters) in particular helped to clarify some relevant aspects of post-COVID lung function abnormalities and to distinguish DM from Vc disorders, which can persist for several weeks after their presumed “clinical recovery” [16-19].

When considering the different affinity of NO and CO to blood haemoglobin and then the different power of DL_{NO} and DL_{CO} measurements in discriminating changes in blood volume, the hypothesis that the persistence of dyspnoea could be related to the underlying alveolar-perfusion mismatch due to the involvement of the vascular side of lung diffusion is strongly supported in these cases (Vc) [19].

For the first time, simultaneous measurements of DL_{CO} , DL_{NO} , and Vc were used in this study to investigate the potential role of hidden abnormalities in blood gas exchange in supporting long-term post-COVID dyspnoea in patients who were otherwise defined as “clinically and morphologically recovered” from COVID pneumonia. Surprisingly, the current study found that DL_{CO} and K_{CO} are significantly impaired only in patients who continue to complain of long-term dyspnoea: their values were lower than those of DL_{NO} and K_{NO} , strongly implying the presence of impaired (such as reduced) capillary blood flow within the lung in these cases. These findings, which are supported by an increased

DL_{NO}/DL_{CO} ratio, point to the active role of disorders in the vascular side of pulmonary diffusion in these cases [16-19,28,29]. The evidence that Vc, such as capillary blood volume, was significantly reduced only in patients who reported dyspnoea for several weeks lends further credence to this hypothesis. This factor is critical in assessing the natural evolution of long-COVID because it is well known that the impact of symptomatic sequelae can be significant in a significant proportion of patients, even if a longitudinal improvement can be expected over the next twenty-four months from discharge [29].

The current study has some limitations: i) it is a monocentric study conducted in a small sample of post-COVID patients; ii) the original severity of COVID pneumonia was impossible to quantify because the majority of patients did not have a CT scan performed at the time of their hospital admission; and iii) the follow up period was only 12-16 weeks. Points of strength include: i) patients were carefully selected in clinical terms; ii) patients in both groups were equally investigated after a comparable period of time from their discharge from COVID pneumonia; iii) at recruitment, all patients were provided with a relatively recent CT scan showing complete resolution of any COVID-induced parenchymal abnormalities; iv) for the first time in clinical practice, the simultaneous single-breath assessment of DL_{CO} , DL_{NO} , and Vc was used to investigate both the alveolar and vascular sides of lung diffusive function; v) dyspnoea was used as a probe for discriminating the different values of these measures in still symptomatic long-COVID patients.

Conclusions

A significant proportion of patients who were deemed “recovered” from COVID pneumonia claim to have experienced long-term dyspnoea. Its cause is frequently regarded as “unexplained” and ignored, owing to the difficulty of investigating it in daily clinical practice. The occurrence and persistence of hidden abnormalities in blood gas exchange are difficult to detect and, in these cases, can elude common investigations of lung function.

Even in the presence of complete resolution of previous CT parenchymal lesions, the single-breath simultaneous assessment of DL_{CO} , DL_{NO} , and Vc provided reliable information about the origin of hidden, but still present, disorders in blood gas exchange. Despite the normality of spirometric volumes, significant limitations in lung capillary blood volume were discovered.

As these measures are simple to obtain, take little time, and are inexpensive, they can be recommended for investigating all post-COVID patients who claim “unexplained” dyspnoea for long periods after discharge or their supposed “complete clinical recovery.”

Finally, the main message of the present study is that the origin of “unexplained” long-lasting dyspnoea in these patients can be clarified when we pay attention to the vascular side of blood gas abnormalities.

Data from the current study, if confirmed by larger studies on similar patients, may lead to some novel and original suggestions for future therapeutic approaches against residual and symptomatic signs of long-COVID.

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