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Gas exchange abnormalities in Long COVID are driven by the alteration of the vascular component

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ABSTRACT

Background: There are uncertainties whether the impairment of lung diffusing capacity in COVID-19 is due to an alteration in the diffusive conductance of the alveolar membrane (Dm), or an alteration of the alveolar capillary volume (Vc), or a combination of both. The combined measurement DL_{NO} and DL_{CO} diffusion, owing to NO higher affinity and faster reaction rate with haemoglobin compared to CO, enables the simultaneous and rapid determination of both Vc and Dm. The aim of the present study was to better identify the precise cause of post-COVID-19 diffusion impairment.

Methods: Using the combined NO and CO gas transfer techniques (DL_{NO} and DL_{CO}), it is possible to better understand whether gas exchange abnormalities are due to membrane or alveolar capillary volume components. The present study was aimed at evaluating pulmonary gas exchange one year after severe COVID-19.

Results: The cohort included 33 survivors to severe COVID-19 (median age 67 years, 70% male) with no pre-existing lung disease, who underwent clinical, lung function and imaging assessments at 12 months due to persistence of respiratory symptoms or radiological impairment. The gas exchange abnormalities were mainly determined by the compromise of the vascular component as demonstrated by vascular pattern of gas exchange impairment (*i.e.,* $DL_{NO}/DL_{CO} \geq 110\%$, 76% of the sample), and by a reduction of the Vc (73%), while the Dm was reduced only in 9% of the entire sample. We did not find a correlation between the gas exchange impairment and the extent of the chest CT alterations (DL_{CO} p = 0.059 and DLNO p = 0.054), which on average were found to be mild (11% of the parenchyma).

Conclusion: In COVID-19 survivors who are still symptomatic or have minimal CT findings at one year, gas exchange abnormalities are determined by impairment of the vascular component, rather than the diffusive component of the alveolar membrane.

Key words: COVID-19, gas exchange, DL_{CO}, DL_{NO}, capillary volume, alveolar-capillary membrane.

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Ethic approval: This observational study was approved by the local Ethics Committee (Comitato Etico di Bergamo, Italy. N°37/2020); Informed consent was obtained from the patients.

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Introduction

The sequelae of SARS-CoV-2 infection are an element of concern. Many studies show an increased prevalence of pulmonary function abnormalities at 3 and 6 months, in particular a mild impairment of pulmonary gas diffusion is described. This is often associated with persistence of radiological abnormalities, such as the presence of ground-glass areas or reticular opacities at chest CT scan [1, 2]. The pulmonary diffusing capacity of carbon monoxide (DL_{CO}) is the most sensitive pulmonary function test in the assessment of gas exchange at the alveolar-capillary membrane. Specifically, this examination is determined by two resistances arranged in series: the pulmonary membrane diffusing capacity (Dm) for carbon monoxide (CO) and the rate of carbon monoxide uptake by blood in the alveolar capillary volume (Vc). Notably, both components are involved in SARS-CoV-2 infection [3]. However, a reduction of the classical DL_{CO} is mainly driven by the vascular compartment, with the potential risk of shadowing alterations of Dm in the study of COVID-19 sequelae. This is, because DL_{CO} can better measure the defects in microvascular alterations while DL_{NO} is affected more by the membrane defects [4]. To overcome this limitation, it is possible to evaluate the transfer of nitric oxide (DL_{NO}) in association with DL_{CO}. Indeed, nitric oxide (NO) has a higher affinity and faster reaction with haemoglobin than CO, making the contribution of the second resistance negligible (i.e., NO uptake by blood) and eventually allowing the isolated measurement of the diffusive component (i.e., Dm). Thus, using the combined NO and CO gas transfer techniques, it is possible to obtain the evaluation of Dm and Vc in a single breath experiment [3, 4]. In COVID-19 survivors, radiological studies have shown that DL_{CO} is negatively correlated with the rate of lung volume involvement [1]. Furthermore, 3-6 months after infection, DL_{NO} and DL_{CO} inversely correlated with persisting CT ground glass opacities, but these were more frequently associated with DL_{NO} than DL_{CO} decrease. These data suggest that an impairment of DL_{NO} may be present during the recovery from COVID-19, possibly due to loss of alveolar units with alveolar membrane damage, but relatively preserved capillary volume [5].

The aim of the present study was to evaluate gas exchange one year after COVID-19, using the combined DL_{NO}/DL_{CO} technique in patients with radiological abnormalities or symptoms that persist 12 months after discharge; moreover, the correlation between gas exchange impairment and CT radiological findings was investigated.

Methods

This observational study was approved by the local Ethics Committee (Comitato Etico di Bergamo, Italy. N°37/2020). Informed consent was obtained from the patients.

Patients

The cohort under study includes severe COVID-19 survivors without pre-existing pulmonary disease admitted to our hospital (Papa Giovanni XXIII, Bergamo, Italy) between February 25 and May 2, 2020 (first wave), who underwent repeated clinical and pulmonary function evaluation up to 12 months after discharge. Patients with persistent symptoms (*i.e.*, dyspnea with a mMRC≥1 or cough) and/or with the persistence of chest-CT abnormalities have been enrolled. The exclusion criteria were: (a) suboptimal pulmonary function tests (PFT) reproducibility, (b) low-quality CT data, and c) onset of severe COVID-19 unrelated complications after discharge.

Procedures

Spirometry and plethysmography were assessed using the Platinum Elite Body Plethysmograph equipped with rapid gas analysers (MGC Diagnostics Corporation, USA), while the simultaneous measurement of DL_{NO} and DL_{CO} was assessed with the HypAir System (Medisoft, Belgium) with a breath-hold of 4 seconds, using the following gas mixtures: He 14%, CO 0.3%, O_2 21% balanced with N_2, and 40 ppb NO balanced with N_2 for DL_{NO}. DM and Vc were directly obtained from DL_{NO}, assuming a ΘNO of 4.5 mL blood/min/mmHg, and directly measuring ΘCO from Hb and PAO_2 [3]. All tests were performed by trained respiratory technicians following current ATS/

ERS standards. Pulmonary function tests (PFTs) results were interpreted by two experienced pulmonologists (CC and GI), in accordance with current guidelines at time of testing [6]. Standard PFTs parameters included: forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1), FEV_1/FVC ratio, and total lung capacity (TLC). Diffusing capacity for nitric oxide (DL_{NO}), diffusing capacity for carbon monoxide during combined testing (DL_{CO}no, DL_{CO} from here on), alveolar membrane diffusing capacity (DM), pulmonary capillary blood volume (VC), and alveolar volume during combined testing (VAno, VA DL_{NO} from here on) were recorded. The dyspnea intensity was assessed using the modified Medical Research Council (mMRC) dyspnea scale.

Unenhanced Chest CT scans were acquired supine at complete inspiration, covering the lung bases to the apex, using a 64- or 16-slice scanner (Brilliance 64 and MX 16-slice; Philips Medical Systems, Best, Netherlands) with the parameters previously specified [1]. Qualitative evaluations included the assessment of the presence of consolidation.

Chest CT scans were analyzed using the 3D Slicer open-source software, version 4.8.1 (https://www.slicer.org), which allowed the quantification of the percentage of compromised lung tissue. As formerly described [1], the lung parenchyma was first segmented and separated from the airways via the Chest Imaging Platform extension and the Airway Segmentation Module. The regions with an image density over -800 HU were finally classified as pathological. A manual editing step addressed any inaccuracies before the measurement.

Statistical Analysis

Standard PFTs parameters were expressed as absolute values, and z-scores and considered impaired when lower than the lower limit of normal range (LLN) defined by the Global Lung Function Initiative reference equations for spirometry and lung volumes. Combined DL_{NO}/DL_{CO} values were expressed as absolute values and z-score and considered impaired when lower than the LLN defined by most recent reference equations by Zavorsky et al [7]. The severity of DL_{CO} and DL_{NO} impairment was evaluated also based on z-score results, assuming a prior evidence of lung disease [7]. DL_{CO} and DL_{NO} ratio, expressed as absolute and as a percentage of the median value taken from a reference healthy population [3], was used to classify the prevalent combined DL_{NO}/DL_{CO} result (vascular pattern if more than 110%, interstitial pattern if less than 95%, indeterminate pattern for values in between) [8]. Descriptive statistics were used to summarize the baseline characteristics of patients. Continuous variables were expressed as median and interquartile range (IQR). Comparison of continuous variables was conducted using the Mann-Whitney U test. Categorical variables were expressed as absolute counts and percentages and were analyzed with Fisher's exact test. Correlation was assessed using the Pearson's correlation coefficient. All reported p are two sided and a $p < 0.05$ was considered significant. Statistical analysis was done using SPSS 27.0 (SPSS, Inc., Chicago, IL, USA).

Results

This study included 33 patients. Anthropometric and clinical data are reported in table 1, while functional and imaging characteristics of the patients are showed in table 2. Median age was 67 (61-70) and males were 70% of our sample. One patient showed obstruction in the year after enrolment (3%), 14 (54%) had reduced DL_{CO}, and median DL_{CO} values were mildly reduced (DL_{CO} z-score value -1.64 (-2.55 - -0.85)). DL_{CO} reduction was mild in 49%, moderate in 6% and severe in any patients. Median values for DL_{NO} were within normal range in our sample (DL_{NO} z-score -1.55 (-2.53 - -0.62)). Fifteen patients (46%) showed a DL_{NO} reduction, that was mild in 39% and moderate in 6% of pathologic cases (no severe alteration), while 14 (42%) had both DL_{CO} and DL_{NO} values reduced. VA was reduced in 10 (30%) patients, while FVC and TLC in 1 and 4 cases, respectively (3% and 12%).

Median Vc was mildly reduced, with z-score values of -2.12 (-3.12 - -1.59), and impaired in 24 patients (73%), while Dm median value was normal, with z-score 0.30 (-1.04 – 1.61), and lower than the LLN in 3 (9%).

Figure 1 shows single cases data of Vc z-score

Table 1. Patients' anthropometric characteristics, symptoms score and biochemistry data (whole sample and according to gas exchange pattern).

	All patients	Interstitial and indeterminate pattern	Vascular pattern	P
Number	33	8	25	
Age (years)	67.0 (61.0-71.0)	62.0 (55.5 – 66.8)	67.0 (63.0 – 72.0)	0.107
Males (%)	70	88	64	0.212
Number of days from admission to testing date (days)	491 (475 – 537)	501 (477 – 556)	491 (475 – 538)	0.578
Height (cm)	170 (164-177)	173 (170 – 179)	169 (161 – 177)	0.150
Weight (kg)	84 (72 – 95)	106 (84 – 122)	80 (72 – 88)	0.022
BMI (kg/m^2)	29.1 (26.1-33.4)	33.4 (28.6 – 39.7)	28.0 (25.7 – 32.2)	0.067
Hb (mg/L)	14.5 (13.6-15.7)	16.2 (14.7 – 16.9)	14.4 (13.3 – 15.1)	0.012
D-dimer (ng/ml)	367 (277-593)	318 (215 – 463)	466 (277 – 709)	0.331
mMRC (n)	1 (0-1)	1 (0-2)	1 (0-1)	0.206

Data are reported as median (IQR) (continuous/numerical variables) or number (%) (binary/categorical variables). Abbreviations: mMRC = modified Medical Research Council.

and Dm z-score in patients grouped according to the DL_{CO} status. Eighteen patients (55% of the whole sample) showed a reduced DL_{CO}, while 15 patients (45%) showed a normal DL_{CO}, seven out of which with Vc under the LLN. Four patients demonstrated a contemporary reduction of both Dm and Vc.

Gas exchange abnormality pattern and correlation with imaging

The radiological impairment detectable with long-term chest CT scan was low, about 10% of the overall parenchyma (Table 2). We found a close correlation between DL_{CO} and DL_{NO} (figure 1), with r = 0.95 (p < 0.001). Correlation between DL_{CO}, DL_{NO} and the amount of abnormal CT involvement resulted modest and non significant in both cases (r = -0.332, p = 0.059, and r = -0.338, p = 0.054, respectively). Eight patients (24% of the whole sample) demonstrated an interstitial or indeterminate pattern (*i.e.,* a DL_{NO}/DL_{CO}<110%), while 25 (76%) a vascular pattern of gas exchange (*i.e.,* DL_{NO}/DL_{CO}≥110%) (Table 1). The only significant differences between these two groups included Vc absolute value, lower as expected in patients with vascular impairment, the level of haemoglobin, significantly reduced in patients with the vascular pattern, BMI, lower in those with vascular pattern and VA z-score, abnormally low in the non-vascular pattern group. We found no significant correlation between the values of DL_{NO}/DL_{CO} % and the CT percent involvement, as showed in figure 2.

Discussion

The main findings of this study, aimed at evaluating the one-year effects of COVID-19 infection on gas exchange and correlation with CT imaging abnormalities, can be summarized as follows: (a) DL_{CO} has a high sensitivity in the assessment of long-term COVID-19 sequelae, with 54% of patients either symptomatic or with radiological abnormalities 12 months after infection still having impairment of this test; (b) however, most patients (76%) demonstrates a vascular pattern of gas exchange (*i.e.,* DL_{NO}/DL_{CO}≥110%) and there are patients with normal DL_{CO} showing a significant decrease in capillary volume, which is the most common impairment in these patients (73%), while Dm is reduced only in 9% of the whole sample; (c) there is no correlation between gas exchange abnormalities and the extent of CT abnormal involvement which was on average mild.

The predominant histological pattern of lung injury in COVID-19 deceased patients is diffuse alveolar damage, often associated with hyaline membrane formation and atypical hyperplasia of pneumocytes. How-

Table 2. Patients' lung function and imaging (whole sample and according to gas exchange pattern).

	All patients	Interstitial and indeterminate pattern	Vascular pattern	P
Number	33	8	25	-
FVC (L)	3.69 (3.12 – 4.19)	3.75 (3.25 – 4.24)	3.61 (3.01 – 4.19)	0.578
FVC (z-score)	-1.13 (-0.88 – 0-61)	-0.91 (-1.33 – 1.03)	0.06 (-0.60 – 0.61)	0.107
FEV_1 (L)	2.84 (2.40 – 3.43)	3.20 (2.35 – 3.60)	2.75 (2.40 – 3.43)	0.606
FEV_1 (z-score)	-0.07 (-0.62 – 0.56)	-0.58 (-0.94 – 0.21)	0.07 (-0.59 – 0.77)	0.098
FEV_1/FVC (n)	0.80 (0.73 – 0.85)	0.79 (0.73 – 0.86)	0.80 (0.73 – 0.85)	0.885
FEV_1/FVC (z-score)	0.12 (-0.62 – 0.92)	0.29 (-1.57 – 1.35)	0.12 (-0.47 – 0.92)	0.984
TLC (L)	5.98 (5.09 – 6.48)	5.68 (5.29 – 6.24)	6.02 (4.91 – 6.62)	0.821
TLC (z-score)	-0.29 (-1.14 – 0.52)	-1.31 (-1.98 – 0.20)	0.00 (-0.77 – 0.58)	0.107
VA (L)	5.40 (4.53 – 5.86)	5.17 (4.50 – 5.55)	5.40 (4.52 – 5.93)	0.696
VA (z-score)	-0.84 (-1.90 – 0.11)	-2.02 (-2.19 - -0.52)	-0.58 (-1.51 – 0.28)	0.032
DL_{NO} (mLmin/mmHg)	99 (79 – 114)	105 (94 – 128)	93 (77 – 112)	0.138
DL_{NO} (z-score)	-1.55 (-2.53 - -0.62)	-2.00 (-2.39 - -0.78)	-1-13 (-2.81 - -0.45)	0.821
DL_{CO} (mLmin/mmHg)	17.7 (13.8 – 20.8)	21.3 (18.1 – 26.8)	17.2 (13.1 – 19.4)	0.009
DL_{CO} (z-score)	-1.67 (-2.55 - -0.85)	-1.46 (-2.14 - -0.58)	-1.75 (-2.87 - -0.85)	0.352
Vc (mL)	34 (31 – 45)	44 (36 – 52)	33 (28 – 41)	0.02
Vc (z-score)	-2.12 (-3.12 - -1.59)	-2.28 (-2.6 - -1.31)	-2.07 (-3.14 - -1.63)	0.496
Dm	124 (99 – 143)	125 (110 – 144)	124 (93 - 144)	0.726
Dm (z-score)	0.30 (-1.04 – 1.61)	-0.47 (-1.27 – 0.74)	0.67 (-0.90 – 1.80)	0.374
DL_{NO}/DL_{CO} (n)	5.57 (5.29 – 5.82)	5.06 (4.86 – 5.15)	5.65 (5.5 – 5.86)	-
DL_{NO}/DL_{CO} (%)	116 (110 – 122)	106 (102 – 108)	118 (115 – 122)	-
Breath hold time (s)	4.6 (4.5 – 5.2)	4.8 (4.5 – 5.2)	4.6 (4.5 – 5.2)	0.918
FVC reduction (%)	3	13	0	0.242
Obstruction (%)	3	13	0	0.242
Restriction (%)	12	25	8	0.241
VA reduction (%)	30	63	20	0.036
DL_{NO} reduction (%)	46	62	40	0.240
DL_{CO} reduction (%)	54	50	56	0.541
DL_{NO} and DL_{CO} reduction (%)	42	50	40	0.461
Vc reduction (%)	73	63	76	0.374
Dm reduction (%)	9	0	12	0.422
Vc and Dm reduction (%)	9	0	12	0.505
CT lung involvement (%)	11 (9-13)	10 (0-14)	11 (8-14)	0.757
Consolidation (%)	6	0	10	0.646

Data are reported as median (IQR) (continuous/numerical variables) or number (%) (binary/categorical variables). Vascular pattern: $DL_{NO}/DL_{CO} \geq 110\%$; interstitial or indeterminate pattern: $DL_{NO}/DL_{CO} < 110\%$. p are computed between the two groups with different gas exchange pattern by the independent Mann-Whitney test (continuous variables) or Fisher test (binary variables). Abbreviations: DL_{CO} = diffusion capacity for carbon monoxide, DL_{NO} = diffusion capacity for nitric oxide, VA = alveolar volume, Dm = alveolar membrane diffusing capacity, Vc = capillary volume, FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity, TLC = total lung capacity, LLN = lower limit of normal, mMRC = modified Medical Research Council.

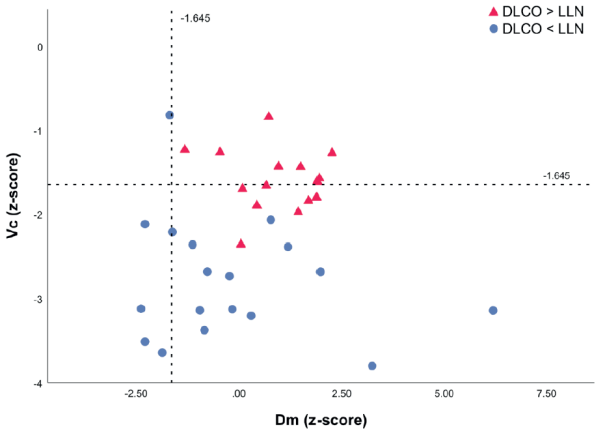

Figure 1. Vc (pulmonary capillary blood volume) and DM (alveolar membrane diffusing capacity) single patients' data of cases grouped according to DL_{CO} reduction.

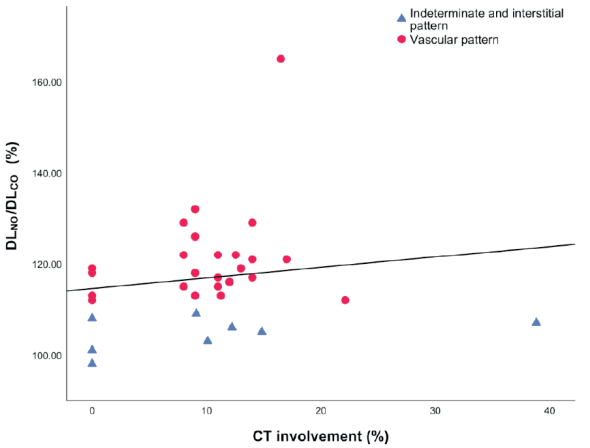

Figure 2. Correlation between lung involvement % at CT (computerized tomography) and DL_{NO}/DL_{CO} ratio, (the gas exchange pattern), (i.e. vascular pattern if more than 110%, interstitial pattern if less than 95%, indeterminate pattern for values in between).

ever, capillary endothelitis and fibrinous microthrombi with angiogenesis within the interalveolar septa are also described [9]. An analysis of morpho-phenotypic changes by transbronchial lung cryobiopsy in patients with persistent symptoms and residual parenchymal lung disease on average 3 months after recovery from COVID-19 revealed three different clusters of cases: chronic fibrosing, acute/subacute and a vascular form. The latter cluster was characterized by diffuse vascular increase and dilatation or distortion (capillaries and venules) within the otherwise normal parenchyma [10]. In the present study, in patients still symptomatic or with persistent chest CT abnormalities one year after COVID-19, decreased Vc was identified as the primary mechanism of gas exchange impairment. A previous article by Barisione *et al.* investigated the role of DL_{NO} in patients recovering from mild to severe COVID-19 pneumonia. The authors found a DL_{CO} reduction in 20% of the cases, but a DL_{NO} reduction in 57% of the patients, therefore they concluded that the discrepancy is likely due to loss of alveolar units by alveolar membrane damage. We found a higher percentage of patients with DL_{CO} alteration after one year of severe COVID-19 pneumonia, with a reduction of DL_{NO} and DL_{CO} (46 and 54%, respectively), but only 9% have an agreement between the two tests. Furthermore, only 9% of the whole sample showed a reduction in Dm, while 73% showed a reduction in Vc. Considering these results, we found that capillary volume impairment is the predominant alteration in long COVID-19. Given the greater sensitivity of DL_{CO} for capillary volume and of DL_{NO} for Dm, the conclusions of Barisione *et al.* (i.e loss of alveolar units by alveolar membrane damage) are reasonable. At least three major differences between the present study and that of Barisione *et al.* can be described. First, we enrolled only patients with severe COVID-19, while they also enrolled patients with mild COVID-19 who did not require hospitalization. Second, we evaluated patients after a longer time post infection, specifically 12 months. Finally, in our population the parenchymal involvement of CT scans is mild on average (about 10% vs 20% in the study by Barisione *et al.*). Núñez-Fernández and colleagues also assessed the role of DL_{NO} in COVID-19 survivors, both at 3 and 12 months, showing a reduction in diffusion mainly explained by Dm reduction secondary to the damage and loss of alveolar units [11]. In their study VC and VA significantly improved over time, while DMCO increased less. This led the authors to conclude that COVID-19 survivors diffusion improves over time due to an expansion of the perfusion component, with the reduction in the alveolar surface area being greater than the microvascular damage, a hypothesis against the conclusion of our study where diffusion alterations are mainly explained by Vc reductions.

Our results are instead similar to two recently

published studies. Dal Negro *et al.* demonstrated that patients still symptomatic after 12-16 months showed lower values of DL_{CO}, DL_{NO} and Vc despite a complete radiological resolution of COVID-19 [12]. Seccombe *et al.* also described a population of severe COVID-19 survivors who, after 2 months, showed a mild reduction both in Dm and Vc (z-score –1.19 ±1.05 and –1.41±1.20), with patients after 4 and 8 months showing a normalization of Dm (z-score -1.41±0.78) but persistent Vc impairment (-2.29±0.56) [13].

These contradictory findings still lack a definite explanation, but we hypothesize that the heterogeneity of diagnostic devices and examined populations may contribute to the varied results in combined DL_{NO}/DL_{CO} evaluation. For example, compared to the population studied by Núñez-Fernández *et al.*, our sample is predominantly composed of males (56% vs 67%), slightly older (62 vs 67 years old), and none of our patients had a prior COPD diagnosis. Notably, differences are observed in the combined DL_{NO}/DL_{CO} status, with our patients more frequently experiencing a reduction in DL_{CO} (9.6% vs 54%) and DL_{NO} (19.3% vs 46%) one year after hospitalization.

The choice of diagnostic equipment may also contribute to the different results reported in the literature. Our measurements were conducted using the HypAir system, similar to the approach taken by Dal Negro and Seccombe, whereas patients in the studies by Barisione and Núñez-Fernández were tested with the MasterScreen PFT system. To address these potential differences, our results were calculated using the most recent reference equations published by Zavorsky *et al.*, which also account for the diagnostic equipment.

Symptomatic patients 12 months after infection can be identified as "long-covid" cases, once other cardiopulmonary or neurological diseases have been excluded. Although definitive results are still lacking, there is evidence suggesting systemic capillary compromise in these patients. For instance, in a study including long-term COVID-19 patients with persisting symptoms, population was evaluated by sublingual video microscopy. The Authors found that COVID-19 leaves a persistent capillary rarefaction up to 18 months after infection [14]. Our results are consistent with this hypothesis. In fact, more than seven out of ten patients show a reduction in capillary volume, and most patients (76%) demonstrates a vascular pattern of gas exchange (*i.e.,* $DL_{NO}/DL_{CO} \geq 110\%$) despite non-specific imaging and a DL_{CO} sometimes within normal limits. In these cases, we can hypothesize that the reduction in capillary volume is balanced by an increase in membrane conductance, in terms of efficiency or surface area.

This study has some limitations. First, it is a single centre study with no formal a priori assessment of sample size. However, the number of enrolled patients is comparable with previous pathophysiological studies. Second, we did not include a control group of asymptomatic patients with normal chest CT or without an history of COVID-19 infection; in any case, if we had found the same pattern in these subjects, our conclusions would not have changed. Finally, we did not apply more sophisticated imaging techniques or processing procedures to study pulmonary vasculature – it was not distinguished from dense alterations, assuming the same contribution across patients – that could have helped to better define the degree and characteristics of gas exchange impairment.

Conclusion

In conclusion, in COVID-19 survivors who are still symptomatic or have minimal CT impairment at one year, gas exchange abnormalities are determined by the vascular component. This condition may be present despite normal DL_{CO}. Our findings are consistent with previous works, describing systemic capillary impairment in patients with long COVID-19.

Abbreviations:

ATS: American Thoracic Society;
Chest CT: computed tomography of the chest;
CO: carbon monoxide;
COVID-19: Coronavirus Disease 2019;
CT: computerized tomography;
DL_{CO}: diffusing capacity of carbon monoxide;
DL_{NO}: diffusing capacity of nitric oxide;
DM: alveolar membrane diffusing capacity;
DMCO: membrane diffusing capacity for carbon monoxide;
ERS: European Respiratory Society;
FEV_1: forced expiratory volume in the first second;

FVC: forced vital capacity;
TLC: total lung capacity;
IQR: interquartile range;
LLN: lower limit of normal range;
mMRC; modified Medical Research Council;
NO: nitric oxide;
ϴNO: nitric oxide's diffusion;
PFT: pulmonary function tests;
VA: alveolar volume;
VAno or VA DL_{NO}: alveolar volume during combined testing;
Vc: pulmonary capillary blood volume;

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