

Lung function corner

Pathophysiology of pulmonary function anomalies in COVID-19 survivors

Coronavirus disease 2019 (COVID-19) is a disease caused by a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the predisposing and protecting factors have not been fully elucidated. COVID-19 primarily impacts the respiratory system, and can result in mild illness or serious disease leading to critical illness requiring admission to the intensive care unit due to respiratory failure. After hospital discharge, the more commonly described pulmonary function anomalies are alterations in diffusing capacity and the loss of lung volume. Reduction of inspiratory muscle contraction may also be underestimated. This article will focus on the pathophysiology of pulmonary function anomalies in COVID-19 survivors. We will discuss current advances and provide future directions and also present our perspective on this field.

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Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by a new coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which primarily impacts the respiratory system. COVID-19 can result in mild illness or serious disease leading to critical illness requiring admission to an intensive care unit (ICU) due to respiratory failure.

There is intense discussion around potential factors predisposing to and protecting from COVID-19. Children and young people have less severe acute COVID-19 than adults. Severe disease was found to be rare and death exceptionally rare in a large prospective cohort study of children admitted to hospital with laboratory confirmed COVID-19 in the UK [1]. Nonetheless, a study based on data from the National Health Interview Survey in the USA has pointed out that nearly 32% of young adults (aged 18–25 years) and half that (16%)

for nonsmoking young adults were found to be medically vulnerable to severe COVID-19 illness [2]. A word of caution is mandatory here because these findings in young adults need to be compared with other indicators related to severe COVID-19 illness, such as hospitalisation rates and mortality. Smoking appears to be a key factor that confers medical vulnerability among young adults [2]. The risk of severe COVID-19 outcomes is also consistently lower in women than men worldwide, suggesting protective immunomodulatory and anti-inflammatory actions of high physiological concentrations of the steroids 17 β -oestradiol (E2) and progesterone (P4) in women [3]. More research is needed in this area. Another issue is the impact of age \geq 65 years and the pre-existing concurrent cardiovascular or cerebrovascular diseases that are deemed to be predictors for high mortality of COVID-19 pneumonia [4].



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COVID-19 primarily impacts the respiratory system and can result in long-standing alterations in pulmonary function such as anomalies in diffusing capacity and the loss of lung volume

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A major unresolved conundrum is the large spectrum of clinical presentations of patients with COVID-19, ranging from asymptomatic infections or symptomatic mild infections with fever, headache or mild respiratory symptoms (like cough or sore throat) and malaise in 80–85% of patients to flu-like illness and viral pneumonia. Within the “pneumonia phenotype” we also have a large clinical and pathophysiological spectrum that extends from only minor opacification with near normal chest radiographs and mild hypoxaemia (in ~80% of hospitalised patients). Some of these patients develop an acute respiratory failure with severe hypoxaemia and quick progression to a phenotype presenting with greater hypoxaemia and higher respiratory rates (~15% of hospitalised patients) to severe disease manifestations. Seriously ill patients develop severe hypoxaemia requiring high-flow oxygen therapy then mechanical ventilation. Their computed tomography (CT) scans document oedema in the lower lobes and multiple ground-glass opacities, angio-CTs may detect micro-embolic lesions and lung ultrasonography that are consistent with interstitial injury with B lines (white lung). This latter phenotype is compatible with either a diffuse alveolar damage or an organising pneumonia with hypoxic vasoconstriction associated with severe hypoxaemia (~2/3 of patients requiring mechanical ventilation). The last phenotype, less common than the previous one, represents an advanced stage with associated acute lung injury requiring mechanical ventilation [5]. A subset of severe COVID-19 patients also present with coagulation defects with elevated levels of D-dimers and fibrinogen suggesting thrombotic microangiopathy and vasculopathy in the gas-exchange networks and systemically [6–8]. This latter phenotype suggests a combination of respiratory and vascular dysfunction in the lungs of severely ill COVID-19 patients, which was confirmed in several recent pathological studies [9, 10]. The particular feature of SARS-CoV-2 to induce both respiratory and vascular dysfunction has been established in the past year [11, 12].

Increasing evidence suggests that these diverse clinical phenotypes might be explained by an immunological failure to control and restrict SARS-CoV-2 infection of the lung. Failure and skewing of the adaptive immune system, promiscuous infection of epithelial (pneumocytes) and endothelial as well as immune cells, coagulation defects and uncontrolled neutrophilic activation potentially govern the impact of COVID-19 on respiratory function and clinical phenotypes (figure 1) [9, 12–15]. An increased understanding of the respiratory dysfunction underlying the different clinical phenotypes of COVID-19 survivors impacts the management of clinical and pathophysiological consequences of this disease. The pathophysiology of pulmonary function anomalies in COVID-19 survivors will be

at the centre of this article. We will discuss current advances and provide future directions and also present our perspective on this field.

Physiology and pathophysiology of abnormal pulmonary function variables as observed in COVID-19 survivors

Altered lung diffusion capacity is the most common anomaly followed by restrictive ventilatory defect. This section attempts to describe the physiology and pathophysiology that underlies the three most common abnormal pulmonary function variables observed in COVID-19 survivors: transfer factor of the lung for carbon monoxide (T_{LCO}), T_{LCO}/V_A and total lung capacity (TLC). A particular focus will be paid to highlighting the difference between T_{LCO} and K_{CO} and on what is important about having a greater decline in T_{LCO} than in K_{CO} , and how this feeds back to lung pathology.

Altered T_{LCO} or D_{LCO} in COVID-19 survivors

The lung transfer (or diffusing) capacity for carbon monoxide (T_{LCO} or D_{LCO} ; T_{LCO} being more commonly used in Europe whereas D_{LCO} is more commonly used in North America) reflects the capacity of carbon monoxide transfer from the environment to the pulmonary capillary blood and represents the most clinically practical standard methodology to assess gas exchange in the lung. In this article we will use the term T_{LCO} . K_{CO} , the transfer or diffusion coefficient, is the rate constant for carbon monoxide uptake from alveolar gas and is impacted mostly by the thickness and area of the alveolar capillary membrane, the volume of blood circulating in pulmonary capillaries coupling ventilated alveoli and the concentration and properties of haemoglobin in the alveolar capillaries blood (figure 2). K_{CO} and V_A are the two main factors that determine T_{LCO} (figure 2). From a mathematical standpoint, K_{CO} can be calculated as T_{LCO}/V_A under BTPS conditions (Body Temperature, ambient Pressure, Saturated with water vapour). It should be noted that K_{CO} is not a simple ratio, as the relationship between lung volume and carbon monoxide uptake is certainly less than 1:1 [16]. The use of K_{CO} has recently been recommended instead of T_{LCO}/V_A , as T_{LCO}/V_A may be interpreted that T_{LCO} can be normalised for V_A [17].

Factors contributing to altered T_{LCO} or D_{LCO} in COVID-19 survivors

A low T_{LCO} is not exclusively determined by reduced V_A [18]; residual interstitial anomalies

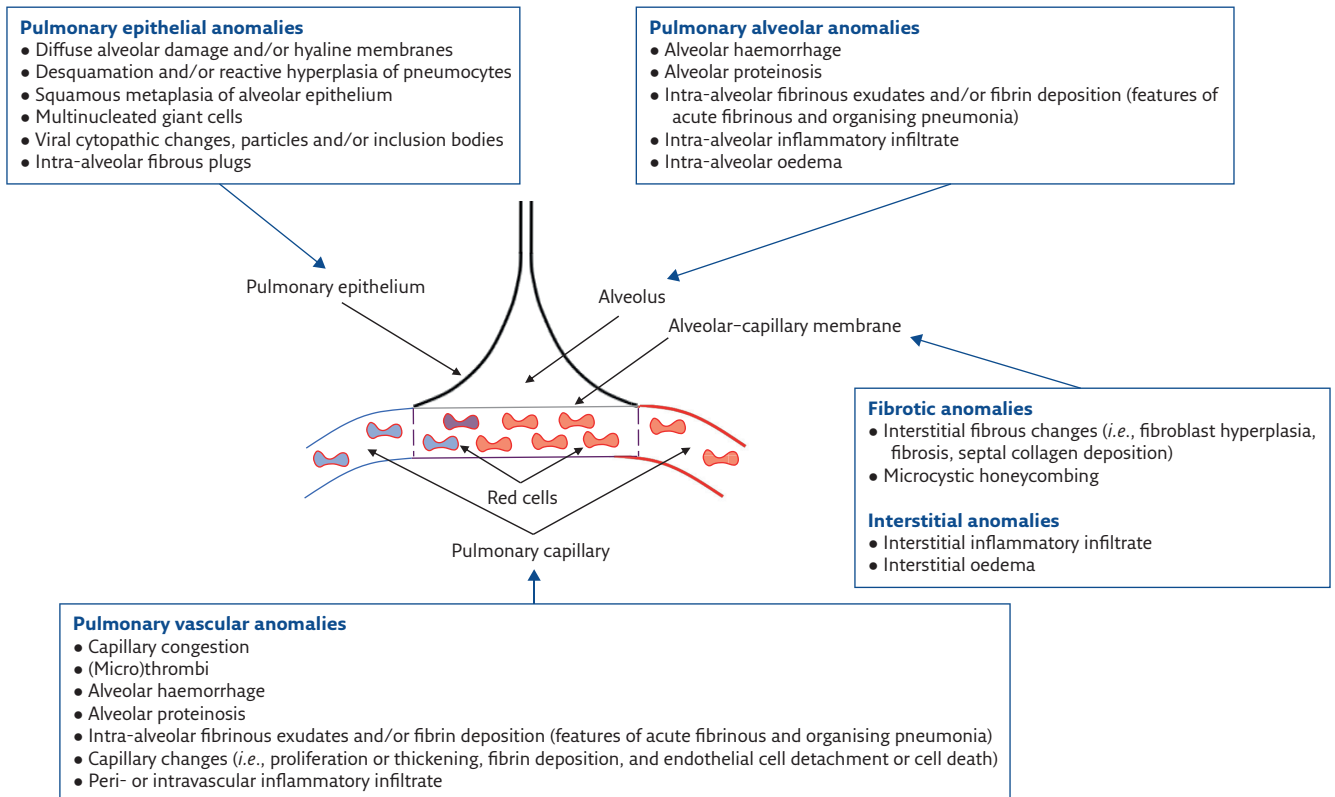


Figure 1 Overview of the most common pulmonary pathology findings observed in post-mortem patients affected by various degrees of severity of COVID-19. See the text for more details and explanations.

[19–21] and pulmonary vascular anomalies (*i.e.* abnormal capillary–alveolar units) [22] may play a fundamental role and this could also be the case in COVID-19 survivors (figure 3). This holds true as the interpretation of low T_{LCO} must consider the complex relationship between V_A , T_{LCO} and K_{CO} , and may inopportune exclude the presence of abnormal gas exchange in the lung (figure 3). To prove this point, we can use data from “severe pneumonia” COVID-19 related patients discussed in this review article to model according to HUCHES and PRIDE [16] what T_{LCO} and K_{CO} responses would be expected if V_A was diminished as a consequence of either suboptimal alveolar expansion or due to loss of alveolar units while having a normal expansion in communicating alveoli. We would then observe two trajectories:

- 1) in the first the decline in T_{LCO} would be largely greater than expected if a decrease in V_A was the unique anomaly, regardless of the mechanism behind the diminished V_A ; and
- 2) the second one is that a decrease in V_A due to either of the abovementioned mechanisms would be associated with an augmentation in K_{CO} , which would be contrary to the diminished K_{CO} observed in many of the discharged patients with severe COVID-19; therefore, the decrease in K_{CO} may suggest that loss of alveolar units is not sufficient to determine the observed alteration in T_{LCO} .

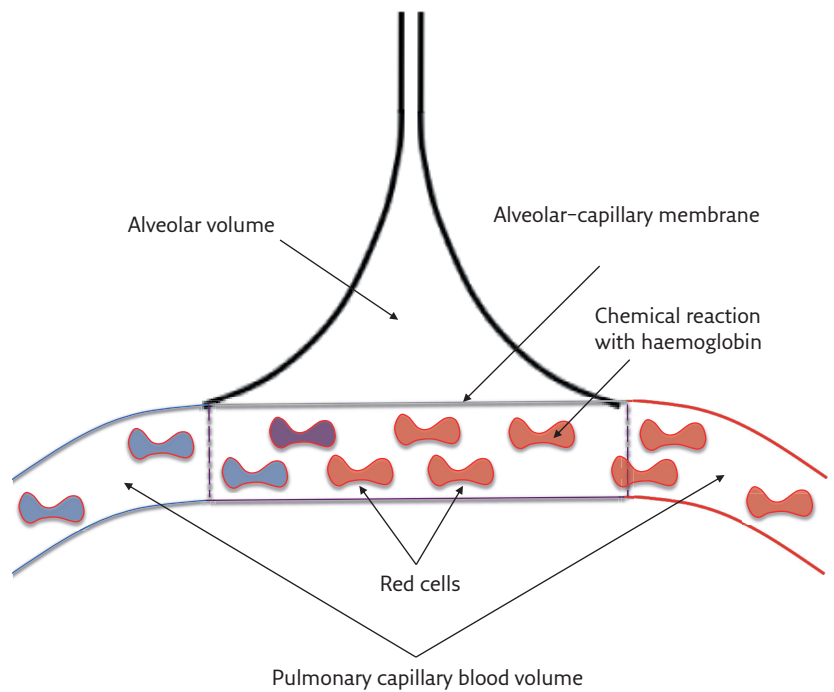


Figure 2 Factors contributing to lung transfer (or diffusing) capacity for carbon monoxide (T_{LCO} or D_{LCO}). See the text for more details and explanations.

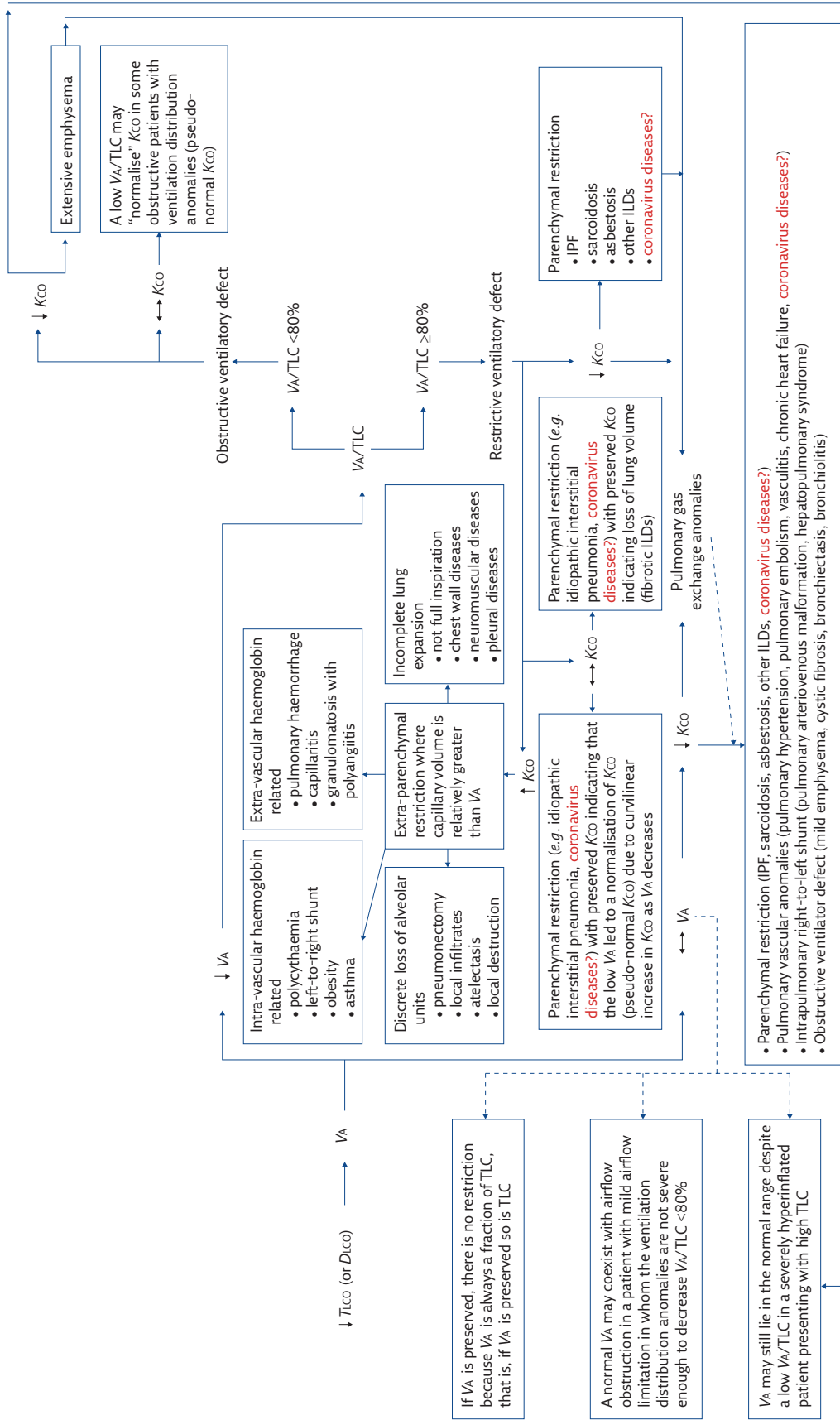


Figure 3 Algorithm allowing physiologists and clinicians to unravel mechanisms of a decreased T_{LCO} (or D_{LCO}). If T_{LCO} (or D_{LCO}) is reduced, the next step is to check whether the V_A is preserved or reduced. If V_A is diminished, the next step is to check whether the V_A/TLC ratio is low ($<80\%$) due to ventilation maldistribution secondary to an obstructive ventilatory defect or is preserved ($\geq 80\%$) due to restrictive ventilatory defect, associated or not with impaired pulmonary gas exchange. If V_A is preserved, please follow the arrows in the algorithm to get some explanations and to see whether the K_{CO} is reduced and if there are pulmonary gas exchange anomalies associated with this. "Coronavirus diseases" appears in red, as potential mechanisms explaining the T_{LCO} (or D_{LCO}) anomalies observed in coronavirus diseases such as COVID-19 (caused by SARS-CoV-2), severe acute respiratory syndrome (SARS; caused by SARS-CoV-1) and Middle East respiratory syndrome (MERS; caused by MERS-CoV) are yet not fully understood. See the text for more details and explanations. IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease.

Altered T_{LCO} or D_{LCO} in COVID-19 survivors: a dangerous interplay between V_A and K_{CO}

While the anomalies in T_{LCO} observed in patients affected by “severe pneumonia” COVID-19 may be partially explained by diminished V_A , the decrease in K_{CO} measured together with the diminished V_A also implies that abnormal gas exchange in the lung occurs (figure 3). Now, the question arises as whether this is due to anomaly of the alveolar–capillary barrier or to abnormal pulmonary blood volume. Unfortunately, this cannot be easily determined based on data presented in the studies discussed in this review article. Lung fibrosis associated with acute respiratory distress syndrome (ARDS) in COVID-19 patients would likely alter alveolar–capillary units, giving rise to loss of alveolar units and altered gas exchange in the lung. The consequence would be a decrease in both V_A and K_{CO} (for that diminished V_A). There is mounting evidence for impaired pulmonary haemodynamics in COVID-19 patients [10], including vascular pruning, decreased pulmonary blood volume and abnormal pulmonary blood volume distribution as measured *via* high-resolution CT [23]. Figure 3 shows that a decrease in K_{CO} may develop in the context of alveolar–capillary damage, microvascular pathology, or anaemia. Factors responsible for a reduced V_A are numerous and may include decreased alveolar expansion, alveolar damage or loss, or inspired gas maldistribution in the context of an obstructive ventilatory defect. Therefore, when K_{CO} turns normal, in the presence of a low T_{LCO} , it is associated with reduced V_A , thus indicating a restrictive ventilatory defect (see below and figure 3). This is because only the functional alveolar units have been sampled thereby providing an erroneous picture toward more preserved areas of the lungs (figure 3). It should be noted that if V_A is preserved, there is no restrictive ventilatory defect because V_A is always a fraction of TLC, *i.e.* if V_A is preserved so is TLC (figure 3). To conclude and for the sake of clarity: the same T_{LCO} may occur with various combinations of V_A and K_{CO} , each suggesting different abnormal respiratory conditions. It is difficult to interpret which one plays the predominant role because both diminished V_A and K_{CO} concur to the pathogenesis of altered lung diffusion capacity. T_{LCO} gives a global evaluation of gas exchange in the lung, while the alveolar–capillary membrane diffusing capacity only depends on molecular diffusion of the membranes. We would thus need more refined techniques capable of measuring more specifically the alveolar–capillary membrane. These could include measurement of T_{LCO} with inhaled gas mixtures containing two or three different oxygen fractions, or combined T_{LCO} and transfer (or diffusing) capacity measurements of the lung for nitric oxide (T_{LNO} or D_{LNO}). Such sophisticated analysis could shed light on the precise mechanisms of reduced T_{LCO} in COVID-19 survivors and may allow distinguishing between interstitial and pulmonary capillary anomalies. On this topic, an Italian study

by BARISONE and BRUSASCO [24] in 94 patients recovering from mild-to-severe COVID-19 found a greater alteration of T_{LNO} than T_{LCO} , suggesting loss of alveolar units with alveolar membrane damage rather than loss of lung capillary bed (see “Future directions, perspectives and conclusions” section).

Restrictive ventilatory defect in COVID-19 survivors

The second most common abnormality in COVID-19 survivors is a restrictive ventilatory defect. A restrictive ventilatory defect is defined by a pathologically decreased TLC. If caused by parenchymal lung disease, restrictive ventilatory defect is accompanied by reduced gas transfer, which may be marked clinically by desaturation during exercise or even at rest (see the above paragraph).

Factors contributing to restrictive ventilatory defect in COVID-19 survivors

TLC is the greatest volume of gas in the lungs achieved after maximal voluntary inspiration. It depends on the static balance between the outward forces generated by inspiratory muscles during a maximal inspiratory effort and the inward elastic forces of the chest wall and lung. It is the lung that normally contributes the most to the elastic recoil forces of the respiratory system at TLC. At TLC, these two sets of forces are equal and opposite in sign. The decrease in TLC usually reflects the reduced lung volumes either because of an alteration in lung parenchyma or because of a disease of the pleura, chest wall, or neuromuscular apparatus that may respectively affect the compliance of the lung or the compliance of the chest wall or the pressure-generating capacity of the inspiratory muscles. Interstitial lung anomalies, such as those observed in some forms of COVID-19 [25], may result in a restrictive ventilatory defect (figures 1 and 3).

Abnormal respiratory function in COVID-19 patients

Respiratory function testing has been performed in COVID-19 survivors at the time of hospital discharge and weeks after hospital discharge. This seems an important issue when dealing with COVID-19 survivors as these respiratory function testing anomalies may have a huge impact on the management, independence and quality of life of these patients as well as on healthcare systems.

At the time of hospital discharge

In the study by FUMAGALLI *et al.* [26], 13 patients with COVID-19 pneumonia were enrolled and the

authors found that at the time of clinical recovery, 10 out of 13 patients presented with a restrictive pattern measured by spirometry: forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were lower than lower limit of normality values, while FEV_1/FVC was higher compared with the upper limit of normality values. These results obtained in a very small sample size should be taken with caution as measurement of TLC, preferably with plethysmography, was not included and the diagnosis of restrictive pattern was made exclusively on the reduced FVC, which is questionable and not acceptable [27]. In addition, T_{LCO} measurement was not employed; this would have permitted a better understanding of the origin and the quality of pulmonary gas exchange damage.

In the study by Mo *et al.* [20], 110 patients with COVID-19 infection were enrolled, which included 24 cases of mild illness, 67 cases of pneumonia and 19 cases of severe pneumonia. Spirometry, plethysmography and T_{LCO} tests were performed on the day of or 1 day before hospital discharge. The authors found that 47% of their patients had anomalies in T_{LCO} , 25% in TLC, 14% in FEV_1 , 9% in FVC, 4.5% in the FEV_1/FVC ratio and 7% in small airway function. The most interesting observation was the significant difference in impaired T_{LCO} among the different groups of severity, which accounted for 30% in mild illness, 42% in pneumonia and 84% in severe pneumonia, respectively ($p < 0.05$). This trend of the gradual decrease in level of T_{LCO} among patients was identical with the varying degree of severity. Of note, in 50% of the T_{LCO} -impaired patients, K_{CO} was still within the normal range, which might indicate that the T_{LCO} decrease was more than the K_{CO} in recovered subjects. In addition, the value of TLC as % of predicted in severe pneumonia cases was much less than that of pneumonia or mild illness, suggesting higher impairment of lung volume in severe cases. No significant difference among the discharged survivors with different severity with regards to other ventilatory defects (*e.g.* reduced FEV_1/FVC) was observed.

These two studies, strongly suggest that respiratory function needs to be carefully investigated in COVID-19 patients, as was already done for other atypical pneumonias such as severe influenza A (H1N1) pneumonia [28]. This is because the lung is the most affected organ in COVID-19 and previous other atypical pneumonias, with anomalies that include diffuse alveolar epithelium destruction, capillary damage/bleeding, hyaline membrane formation, alveolar septal fibrous proliferation, and pulmonary consolidation.

In discharged patients

In the same study by FUMAGALLI *et al.* [26], FVC was still lower than the lower limit of normality

after 6 weeks from hospital discharge. Again, these results obtained in a very small sample size should be taken with caution as measurement of TLC was not included and the diagnosis of restrictive pattern was made exclusively on the reduced FVC, which is questionable and not acceptable [27]. Another study by HUANG *et al.* [29] performed respiratory function testing in 57 COVID-19 patients after 30 days following hospital discharge and found anomalies in 75% of them; 10%, 9%, 44%, 12% and 53% of enrolled patients had FVC, FEV_1 , FEV_1/FVC ratio, TLC, and T_{LCO} values $< 80\%$ of predicted values, respectively, whereas 49% and 23% of patients presented with maximum static inspiratory and expiratory pressure ($P_{I_{max}}$ and $P_{E_{max}}$, respectively) values $< 80\%$ of the corresponding predicted values. Compared with non-severe cases ($n=40$), severe patients ($n=17$) showed higher incidence of T_{LCO} impairment (76% *versus* 43%, $p=0.019$), and significantly lower percentage of predicted TLC. Of note, only 11% of patients showed obstructive and 12% restrictive ventilatory defects [29]. What is also striking, yet surprising, is that a small percentage of patients with no residual imaging abnormalities presented with a slight decrease in T_{LCO} . Similar to this study, FRIJA-MASSON *et al.* [30] observed abnormal lung function in more than 50% of COVID-19 patients after 30 days from hospital discharge. One third of the abovementioned patients had decreased T_{LCO} values indicating that these patients have lung vascular damage, which coincides with the data from HUANG *et al.* [29].

By contrast, ROGLIANI *et al.* [31] have recently pointed out that hospitalised patients with mild-to-moderate forms of COVID-19 are not at risk of developing pulmonary fibrosis. In their study, patients were enrolled within 2 months from hospital discharge and the authors found that FEV_1 and FVC, both expressed as % predicted, were in the normal range. Again, these results should be taken with caution as neither measurement of TLC nor of T_{LCO} was included in the study.

Several studies have explored pulmonary function in COVID-19 survivors at 3 months [21, 32–35] and 4 months [36–38] after hospital discharge. Most of these studies showed alteration in T_{LCO} (in more than 50% of patients), in TLC (in more than 10% of patients), and in pressure-generating capacity of respiratory muscles (in less than 40–50% of patients), but to a much lesser extent alterations in the airway functions (in less than 10% of patients). However, the proportion of altered lung function may be lower in studies that included patients with less severe initial disease [39, 40]. Taken together, these studies strongly converged to the conclusion that the worse the lung involvement during SARS-CoV-2 infection (in those patients who developed ARDS or those who required invasive mechanical ventilation) the worse the impairment in pulmonary function after 3–6 months, especially in terms of T_{LCO} , and the lower the likelihood to normalise pulmonary function over time. Accordingly,

respiratory rehabilitation and gradual physical activity immediately after hospital discharge should be encouraged as it can minimise impairment or improve respiratory function such as TLC and T_{LCO} , quality of life and anxiety in these fragile patients [41].

In conclusion, several mechanisms, sequential or not, may occur and explain the damages induced by SARS-CoV-2 infections of the lungs. They include the microvascular damage with interstitial thickening with clear lungs on radiology examinations along with a severe hypoxaemia [42, 43], the development of alveolar injury inducing a gradual loss of the alveolar spaces [43], and last but not least the diminished V_A that may be explained by changes in mechanical properties of the lungs and the chest wall and by dysfunction of the respiratory muscles after critical illness. These anomalies can be temporary or responsible for a potential long-lasting pulmonary parenchymal dysfunction post-COVID-19 [44].

Potential hypotheses on altered T_{LCO} or D_{LCO} in COVID-19 survivors

Given the interplays discussed above, two hypotheses on reduced T_{LCO} can be proposed in COVID-19 survivors: 1) a reduced T_{LCO} with normal K_{CO} may be in favour of definitive alveolar loss/destruction, with no optimistic perspectives of recovering; 2) a reduced T_{LCO} with diminished K_{CO} may be in favour of alveolar lesions (pulmonary capillary and/or membrane anomalies) that are still evolving, with the optimistic perspective of some and at least partial recovery. We should therefore follow-up COVID-19 survivors to see whether they are able to recover from their T_{LCO} anomalies. Few studies have explored “predictors” for lung function decline, especially for T_{LCO} . Pulmonary interstitial damage (inferred by the chest CT total severity score), the development of acute respiratory distress syndrome, and vascular damage (inferred by high D-dimer levels at the time of hospital admission) have been pointed out as potential predictors for lung function decline, especially for T_{LCO} but also for TLC [21, 22].

Specific features of respiratory dysfunction in COVID-19 compared with other viral pneumonias (SARS, MERS, and influenza A H1N1)

The observations of anomalies in respiratory function, especially in T_{LCO} , in more than 50% of the COVID-19 survivors raises the question of a potential progression towards lung fibrosis in some

patients. Interestingly, the greater decline in T_{LCO} compared with K_{CO} suggests that impaired diffusion across the membrane may be more causative for pulmonary dysfunction than reduced lung volume. Previous studies have demonstrated that patients that recovered from coronavirus pneumonia still have damaged lungs. Impaired lung function was common and lasted for months or even years. In follow-up studies on rehabilitating SARS patients lasting from 6 months to 3 years, impaired T_{LCO} was the most common anomaly, ranging from 15% to 44%, followed by reduced TLC, ranging from 5% to 11% [45–47]. PARK *et al.* [48] showed that 37% of MERS survivors still presented with an impairment of T_{LCO} , but normal TLC at 12 months. In addition, pulmonary function improved significantly in the first 3 months but with no further significant improvement from 3 to 6 months after discharge among survivors of severe influenza A (H1N1) pneumonia [28]. Some other studies showed a complete normalisation of pulmonary function 6 months after H1N1-related ARDS [49]. However, about 80% of survivors of ARDS not provoked by influenza A H1N1 had reduced diffusing capacity, 20% had airway obstruction, and 20% had a restrictive pattern 12 months after recovery [50]. These data are discordant with preliminary follow-up results on COVID-19 survivors highlighting the greater and persistent decline of pulmonary function (T_{LCO} and TLC) in COVID-19 survivors compared with SARS, MERS, and influenza A (H1N1) survivors.

Studies on lung function in COVID-19 survivors at 6 and 12 months from hospital discharge are thus urgently needed in order to monitor the long-term effect of COVID-19 infection on the respiratory system in patients with severe-to-extremely-severe pneumonia. A prediction would be that, at least at 6 months from hospital discharge, these patients may still present with an abnormal T_{LCO} and, to lesser extent, a restrictive ventilatory defect. Indeed, a Chinese study by HUANG *et al.* [51], conducted at 6 months after hospital discharge, found a T_{LCO} <80% of predicted value in 33% of patients, and a TLC <80% predicted in 16% of patients. Moreover, studies with serial pulmonary function testing would be essential to better assess functional trajectories.

Future directions, perspectives and conclusions

Physiological understanding of early as well as chronic lung responses might be helpful for future stratification of surviving COVID-19 patients with chronic respiratory impairment. In our opinion, potential future directions and perspectives are as follows.

- Pathological and lung function evidence for a vascular component among severe COVID-19

- patients, which has long-lasting consequences, should be explored.
- Pathophysiological evidence on deranged adaptive immune function that may drive fibrotic lung diseases and evidence for impaired diffusion capacity in survivors of severe COVID-19 needs to be evaluated.
 - More attention should be paid to COVID-19 survivors presenting with impaired (minor or not) diffusion capacity and perhaps with persistent dyspnoea but with no other associated anomalies in chest or CT scan imaging. Techniques capable of measuring more specifically the alveolar-capillary membrane, such as measurement of T_{LCO} including inhaled gas mixtures containing two or three different oxygen fractions or combined T_{LCO} and T_{LNO} measurements, are welcome to shed light on the precise mechanisms of reduced T_{LCO} in COVID-19 survivors particularly in distinguishing between interstitial and pulmonary capillary anomalies.
 - More particularly, two hypotheses on reduced T_{LCO} could be tested in COVID-19 survivors: 1) a reduced T_{LCO} with normal K_{CO} may be in favour of definitive alveolar loss/destruction, with no optimistic perspectives of recovering; 2) a reduced T_{LCO} with diminished K_{CO} may be in favour of alveolar lesions (pulmonary capillary and/or membrane anomalies) that are still evolving, with potential and optimistic perspective of some recovery, at least in part. We should therefore follow-up COVID-19 survivors to see whether they are able to recover from their T_{LCO} anomalies.
 - A long-lasting follow-up in terms of respiratory function testing is proposed for COVID-19 survivors as results from literature are conflicting as to whether these patients may fully recover or even develop pulmonary sequelae.
- This perspective on physiological abnormalities might foster a better understanding of the disease course and may also shape future stratification of patients and treatment options.

Affiliations

Pierantonio Laveneziana^{1,2}, Lucile Sesé^{3,4}, Thomas Gille^{3,4}

¹Assistance Publique - Hôpitaux de Paris (AP-HP), Groupe Hospitalier Universitaire APHP-Sorbonne Université, sites Pitié-Salpêtrière, Saint-Antoine et Tenon, Service des Explorations Fonctionnelles de la Respiration, de l'Exercice et de la Dyspnée (Département R3S), Paris, France. ²Sorbonne Université, INSERM, UMR1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France. ³Université Sorbonne Paris Nord (USPN), INSERM, UMR 1272 "Hypoxia & the Lung", UFR SMBH Léonard de Vinci, Bobigny, France. ⁴Assistance Publique - Hôpitaux de Paris (AP-HP), Hôpitaux Universitaire Paris-Seine-Saint-Denis (HUPSSD), Hôpital Avicenne, Service de Physiologie et Explorations Fonctionnelles du Département Médico-Universitaire NARVAL, Bobigny, France.

Conflict of interest

P. Laveneziana reports personal fees from Chiesi France, Boehringer Ingelheim France, and Novartis France, outside the submitted work. L. Sesé reports personal fees from Boehringer Ingelheim, Roche and AstraZeneca, and other (congress registration) from Oxyvie (oxygen provider), AstraZeneca and Novartis, outside the submitted work. T. Gille reports personal fees from Boehringer Ingelheim and Roche, other (congress registration) from Oxyvie (oxygen provider), LVL Medical (oxygen provider) and Vitalaire (oxygen provider), outside the submitted work.

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