Persistent isolated impairment of gas transfer following COVID-19 pneumonitis relates to perfusion defects on dual-energy computed tomography

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To the Editor:

Breathlessness is common in patients after coronavirus disease 2019 (COVID-19) [1]. Patients may have an isolated impairment of gas transfer (diffusing capacity of the lung for carbon monoxide (D_{LCO})) at lung function testing, often without obvious interstitial lung disease or classical pulmonary emboli on imaging. Iodine maps from post-COVID-19 patients undergoing dual-energy computed tomography (DECT) demonstrate hypoenhancement in areas of normal lung parenchyma [2] (figure 1). We hypothesised that in breathless patients recovering from COVID-19, low D_{LCO} would correlate with a computed tomography (CT) marker of lung perfusion, measured using DECT-derived iodine enhancement, including in patients where parenchymal disease was absent. As an even more specific indicator for the pulmonary vascular compartment, we hypothesised that the transfer coefficient of the lung for carbon monoxide (K_{CO}) (*i.e.* D_{LCO} corrected for alveolar volume) would even better correlate with DECT perfusion, and more so than forced vital capacity (FVC) and CT measures of interstitial lung involvement.

Consecutive patients attending a post-COVID-19 clinic at Royal Brompton Hospital (London, UK) underwent Medical Research Council (MRC) dyspnoea scoring, full pulmonary function testing and DECT [3] analysed by an experienced thoracic radiologist using validated automated CT processing software (Syngo.via; Siemens, Erlangen, Germany), 6 months after a positive COVID-19 test. CT scores of mean lung density (MLD) and ground-glass opacity (GGO)% used a lung density threshold < −200 HU [4] (table 1). CT predictors of pulmonary hypertension (ventricular and aortopulmonary ratio) and the "Qanadli" score (number and size of pulmonary arterial occlusions) were scored. Iodine perfusion in Hounsfield units [5] corrected for total lung volume (TLV) to offset haemoconcentration in pathologically small lungs generated a novel volume-corrected iodine perfusion score (IP_v).

Statistical analysis used Chi-squared (categorical), Mann–Whitney or t-tests (continuous). Linear regression assessed the association between IP_v and radiological or lung function measurements (STATA version 15). Patients were stratified by physiological lung volume (FVC <80% or FVC ⩾80%) and diffusion impairment to carbon monoxide corrected for Hb (D_{LCOc}) (D_{LCOc} <80% or D_{LCOc} ⩾80%).

Ethical approval with informed consent for this cross-sectional study was approved by the National Health Service Health Research Authority (HRA) (approval number 20/HRA/1434).

78 patients (51% male) with mean±SD age 49±12 years were studied. 16 (21%) were smokers. Comorbidities included obesity (n=11), hypertension (n=16), hyperlipidaemia (n=8) and asthma (n=8). 45 patients required intensive care for a median (interquartile range) 27 (18–38) days, many of whom required extracorporeal membrane oxygenation (ECMO) (n=17). Other treatments included therapeutic anticoagulation (n=32), thrombolysis (n=3), steroid therapy (n=23) and pulmonary vasodilators (n=9).

Across the group, there was a correlation between disease severity, symptoms, pulmonary function and pulmonary IP_v: MRC scores were 1 (n=26, 33%), 2 (n=26, 33%), 3 (n=16, 21%), 4 (n=9, 12%) and 5 (n=1, 1%).

Shareable abstract (@ERSpublications)
A novel iodine perfusion score correlates with breathlessness and D_{LCO} in patients post-#COVID19 without obvious interstitial disease on CT, suggesting that lung perfusion assessment may be useful in patients without another cause of dyspnoea https://bit.ly/3U6E2f5

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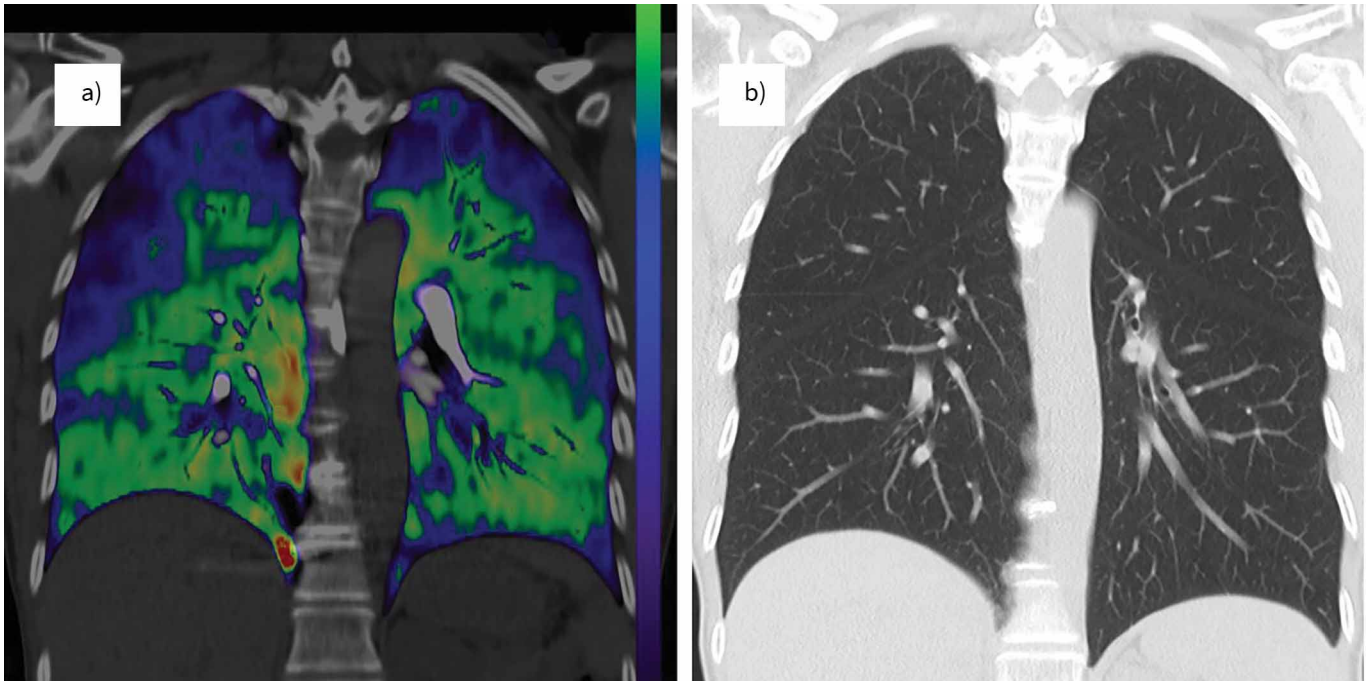

FIGURE 1 a) Coronal dual-energy computed tomography perfused blood volume iodine map with computed tomography overlay in a 59-year-old female with dyspnoea, fatigue and chest pain imaged 11 months after onset of mild coronavirus disease 2019 pneumonia. Diffusing capacity of the lung for carbon monoxide was 72% predicted with otherwise normal spirometry. Upper-lobe subpleural iodine distribution defects (represented as blue and black overlay, approximating <40 HU) in the subpleural apices bilaterally correspond with similar unmatched defects on perfusion scintigraphy. Computed tomography angiography did not demonstrate pulmonary arterial thrombus. b) Corresponding coronal computed tomography image shows normal lung parenchyma.

Patients with a higher MRC (more breathlessness) had a lower D_{LCO} ($p<0.05$) and lower IP_v ($p<0.05$). 21 patients had low physiological lung volumes (FVC <80% in 26.6%) (table 1).

In all patients, the IPv score correlated with D_{LCO} (R^2 0.054, 95% confidence interval (CI) 0.0005–0.34; $p<0.05$) and K_{CO} ($R^2=0.09$, 95% CI 0.066–0.48; $p<0.01$), but not FVC ($R^2=0.004$, 95% CI −0.11–0.19; nonsignificant), or with CT parenchymal markers including GGO% ($R^2=0.0029$, 95% CI −0.080–0.129; nonsignificant) and MLD ($R^2=0.0036$, 95% CI −1.43–0.8445; nonsignificant).

The prominent lung function abnormality in the whole cohort was impaired gas transfer (D_{LCO} <80% predicted in 72.2%) (table 1). The pulmonary artery obstruction (Qanadli) index was abnormal in only four patients, and none had CT features of pulmonary hypertension (pulmonary artery/aorta ratio 0.88±0.12 (normal <1), right ventricle/left ventricle ratio 1.04±0.23 (normal <1)). As expected, CT-derived TLV positively correlated with FVC (R=0.57, $p<0.0001$) and CT-derived GGO% negatively correlated with D_{LCO} (R= −0.51, $p<0.0001$) and FVC (r= −0.50, $p<0.0001$). CT measures of parenchymal abnormality (TLV, MLD, GGO%) were abnormal in those with low FVC, and in those with low D_{LCO} (TLV, MLD, but not GGO%).

39 (50%) patients had an "isolated low D_{LCO} phenotype", with normal lung volumes, no pulmonary embolism (Qanadli <1) and no parenchymal disease or suggestion of pulmonary hypertension on CT (table 1).

There was a positive correlation between IP_v score and D_{LCO} in this group ($p<0.0001$), in the whole group (D_{LCO} and IP_v, R=0.568, $p<0.0001$), and in patients who had received ECMO. MLD and GGO scores were similar to those with normal D_{LCO}, but lung volumes (both FVC and CT-derived) were smaller ($p=0.04$).

Finally, to test the hypothesis that barotrauma might impact on diffusion capacity, IP_v was compared in patients who had needed mechanical ventilation and those who had not. Whereas patients needing

TABLE 1 Demographic, full lung function and computed tomography (CT) data in a post-coronavirus disease 2019 clinic population at 6-month follow-up, split by lung function phenotype

	All patients	FVC ⩾80% pred	FVC <80% pred	D_{LCO} ⩾80% pred	D_{LCO} <80% pred	FVC ⩾80% and D_{LCO} ⩾80%	FVC ⩾80% and D_{LCO} <80% "isolated low D_{LCO}"
Patients, n	78	57	21	21	57	18	39
Age, years	48.8±12.4	47.7±12.7	52.3±11.1	48.4±2.5	49.0±12.7	47.6±13.4	47.7±11.6
Male	45 (56)	30 (52)	15 (71)	10 (45)	35 (61)	10 (48)	20 (54)
MRC score							
1	26 (33)	19 (33)	7 (33)	8 (38)	18 (32)	8 (40)	11 (29)
2	26 (33)	19 (33)	7 (33)	4 (19)	22 (39)	2 (20)	17 (41)
3	16 (21)	11 (19)	5 (24)	6 (29)	10 (18)	6 (30)	5 (14)
4	9 (12)	7 (12)	2 (10)	2(10)	7 (12)	1 (5)	6 (16)
5	1 (1)	1 (2)	0	1 (5)	0	1 (5)	0
Lung function							
FEV_1 % pred	90.3±21.3	97.2±17.9	71.6±18.8***	100±26.1	86.8±18.2	100.±26.6	96.3±10.6
FVC % pred	93.7±19.7	NA	NA	109.2±17.5	87.9±17.3	111.3±15.2	97.3±12.5**
FEV_1/FVC %	92.6±16.1	98.9±12.8	75.0±10.3***	104.8±14.4	88.3±14.4	105.9±13.9	95.3±10.6
TLC % pred	81.2±14.7	89.3±9.6	65.6±9.5***	77.5±96.6	96.6±11.7	99.8±5.56	85.4±7.6
D_{LCOc} % pred	66.9±18.4	73.2±15.7	49.4±13.4***	NA	NA	90.6±7.2	64.8±11
K_{COc} % pred	81.6±13.8	82.0±12.3	80.4±17.4	NA	NA	90.3±11.3	77.9±10.8
S_{aO_2} %	96.7±2.2	96.8±2.3	96.5±1.6	96.6±2.3	97.3±1.22	97.3±1.23	96.6±2.57
CT data[#]							
Iodine perfusion	45.7±15.3	46.2±15.6	44.2±14.7	45.1±10.8	45.9±16.8	45.0±11.0	47.0±17.9
Iodine perfusion (volume-corrected)[¶]	182.8±79.3	198±80.8	140.2±57.7**	213±73.8	170.9±78.8*	219.2±69.5	186±85.3

Data are presented as n, mean±SD or n (%). FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; MRC: Medical Research Council; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; D_{LCOc}: D_{LCO} corrected for haemoglobin; K_{COc}: transfer coefficient of the lung for carbon monoxide corrected for haemoglobin; S_{aO_2}: arterial oxygen saturation; NA: not appropriate. [#]: CT measurements included those using noncontrast CT where standard measurements included total lung volume (normal range 5060±1353 mL), mean lung density (normal range −839.6±21.8 HU), Hounsfield units and ground-glass opacification score (normal 3.9±0.58%). Using dual-energy CT, a dynamic comparison was made between a set volume of contrast and noncontrast using whole-lung CT average global iodine perfusion enhancement; [¶]: volume adjustment was made per litre of lung volume, to correct for changes in lung volume between subjects. Data compared between columns were significant with *: p<0.05, **: p<0.01, ***: p<0.001.

mechanical ventilation had lower FVC (85.5±17.0% pred *versus* 104.2±17.9% pred, p<0.0001) and D_{LCO} (60.2±18.3% pred *versus* 75.9±14.4% pred, p=0.0001), IP_v (46.5±14.8 *versus* 48.2±13.7 $HU \cdot mL^{-1}$, p=0.6) and K_{CO} (80.8±15.8% pred *versus* 82.7±10.5% pred, p=0.6) were no different between these groups.

This is the first report to correlate advanced lung imaging findings with full lung function 6 months after COVID-19. We and others observe that breathless patients with long COVID often have isolated low D_{LCO} with normal lung volumes, where DECT-derived volume-corrected iodine perfusion (IP_v) remains impaired. Compared to patients with normal D_{LCO}, this group with diffusion impairment have similar GGO and MLD scores, and FVC was only mildly impaired, often remaining within normal limits. As well as D_{LCO}, K_{CO} is also reduced, and is even more strongly associated with IP_v. K_{CO} is considered a marker of pulmonary vascular involvement as it corrects for alveolar volume, as shown in patients with fibrotic lung diseases [6]. We assessed the potential impact of mechanical ventilation on diffusion capacity. Those ventilated did have lower FVC and D_{LCO}, in keeping with the potential impact of barotrauma on the interstitial compartment, but K_{CO} and IP_v, as potential markers of the pulmonary vascular compartment, were no different between these groups. This supports the hypothesis that the pulmonary microcirculation as well as the alveolar membrane is affected in breathless survivors of COVID-19 [7]. This novel DECT score, IP_v, also correlated with breathlessness scores in a spectrum of patients recovering from COVID-19.

In acute COVID-19 pneumonitis, endothelialitis is a frequent feature [8], which induces intravascular immune activation and *in situ* thrombotic angiopathy [9]. It is possible that alongside alveolitis, pulmonary vascular dysfunction is a residual feature in survivors with breathlessness. This observation may not be limited to patients after COVID-19. Indeed, persistent gas transfer impairment with normal spirometry was reported in patients a year after acute lung injury due to multiple causes [10]. Whether this finding relates to pulmonary vascular abnormalities is unknown, and lung biopsy data are lacking in post-COVID-19

patients. Structural changes to lung vessels including neoangiogenesis and vascular proliferation are recognised in COVID-19, which may contribute to apparent parenchymal changes on CT [11].

Limitations to this study include potential pre-existing perfusion defects, subtle emphysema (smokers), gas trapping (asthma and smokers), obesity-related artifacts or hypoventilation, which may occur in a normal appearing lung on CT. This could be improved in future studies using age- and comorbidity-matched controls. Further limitations include the sample size and population heterogeneity. That said, we have shown that breathlessness after COVID-19 infection, ranging from mild to severe disease, is associated with a range of radiological and lung function measures representing interstitial and/or pulmonary vascular disease.

We propose that this "isolated low D_{LCO}" with mottling of lung perfusion on DECT scanning is an under-reported phenotype and could be a target for therapeutics in this post-COVID-19 syndrome. Alternative advanced imaging modalities including ventilation/perfusion scanning show a mottling in lung perfusion [12]; a hyperpolarised lung magnetic resonance imaging (MRI) study also reports an alveolar capillary diffusion abnormality in patients with normal CT scans [13]. Whether these imaging findings relate to persistent impairment of the pulmonary microcirculation, alveolar inflammation, or both, needs further understanding. The apparent onset of microthrombosis in patients with long COVID [14] is potentially relevant here. Indeed, endothelial activation is associated with low D_{LCO} in similar patients [15], suggesting a potential mechanism for this gas exchange deficit if long COVID drives persistent pulmonary endothelial abnormalities.

We describe for the first time a complete dataset of full lung function testing alongside DECT in a cohort of post-COVID-19 patients, where 50% of patients have persistent low gas transfer, relatively normal CT scans and an apparent pulmonary perfusion abnormality on DECT. This phenotype has also been suggested in the studies of lung MRI. Using automated imaging software, we propose a validated perfusion score in this setting. The correlation with symptoms and lung function suggests that this imaging marker is clinically relevant in patients after COVID-19. The use of advanced perfusion imaging may guide future therapeutic trials in these patients, potentially using therapies targeting the pulmonary microcirculation.

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