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Early View

Research letter

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

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

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Background

Breathlessness is common in patients after COVID-19 (1). Patients may have an isolated impairment of gas transfer (diffusion of the lung for carbon monoxide, DLCO) at lung function testing, often without obvious interstitial lung disease or classical pulmonary emboli (PE) on imaging. Iodine maps from post-COVID patients undergoing dual energy computed tomography (DECT) demonstrate hypoenhancement in areas of normal lung parenchyma (2) (**Figure 1**). We hypothesized that in breathless patients recovering from COVID-19, low DLCO would correlate with a 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 hypothesized that KCO (DLCO 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.

Methods

Consecutive patients attending a post-COVID clinic at Royal Brompton Hospital, UK, underwent Medical Research Council (MRC) dyspnea 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), six months after a positive COVID test. CT scores of mean lung density (MLD) and ground glass opacity (GGO)% used a lung density threshold < -200 Hounsfield units (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 (IP) in HU (5) corrected for total lung volume (TLV) to offset haemoconcentration in pathologically small lungs, generated a novel volume-corrected iodine perfusion score (IPv).

Statistical analysis used Chi-squared (categorical), Man Whitney or t-tests (continuous). Linear regression assessed the association between IUv and radiological or lung function measurements (STATA version 15). Patients were stratified by physiologic lung volume (FVC<80% or FVC≥80%) and diffusion impairment to carbon monoxide corrected for Hb DLCOc (DLCO) (DLCO<80% or DLCO≥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).

Results

78 patients (51% male) with mean±SD age 49±12 years were studied. Sixteen (21%) were smokers. Co-morbidities included obesity (n=11), hypertension (n=16), hyperlipidemia (n=8) and asthma (n=8). 45 patients required intensive care for 27 (18-38) days, many of whom required extra-corporeal 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 IPv: MRC scores were 1 (26, 33%), 2 (n=26, 33%), 3 (n=16, 21%), 4 (n=9, 12%) and 5 (n=1, 1%). Patients with a higher MRC (more breathlessness) had a lower DLCO ($p<0.05$) and lower IPv ($p<0.05$). Twenty-one patients had low physiologic lung volumes (FVC<80% in 26.6%) (**Table 1**).

In all patients, the IPv score correlated with DLCO (R2 0.054, confidence interval (CI) 0.0005 to 0.34, $p<0.05$), KCO (R2=0.09 (CI 0.066 to 0.48, $p<0.01$), but not FVC (R2=0.004, CI -0.11 to 0.19, NS)**, or** with CT parenchymal markers including GGO% (R2=0.0029 (CI -0.080 to 0.129), NS and MLD (R2=0.0036, CI -1.43 to 0.8445, NS).

The prominent lung function abnormality in the whole cohort was impaired gas transfer (DLCO<80% pred. in 72.2%, **Table 1**). The pulmonary artery obstruction (Qanadli) index was abnormal in only 4 patients, and none had CT features of pulmonary hypertension (PA:Ao ratio 0.88+-0.12 (normal < 1), RV:LV 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 DLCO (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 DLCO (TLV MLD but not GGO).

39 patients (50%) had an 'isolated low DLCO phenotype', with normal lung volumes, no PE (Qanadli<1) and no parenchymal disease or suggestion of pulmonary hypertension on CT (**Table 1**).

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

Finally, to hypothesize that barotrauma might impact on diffusion capacity, IPv was compared in patients who had needed mechanical ventilation or not. Whereas patients needing mechanical ventilation had lower FVC (85.5+-17.0 vs 104.2+-17.9%, $p<0.0001$) and DLCO (60.2+-18.3 vs 75.9+-14.4, $p=0.0001$), IPv (46.5+-14.8 vs 48.2+-13.7, $p=0.6$) and KCO (80.8+-15.8 vs 82.7+-10.5, $p=0.6$) were no different between these groups.

Discussion

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 DLCO with normal lung volumes, where DECT-derived volume-corrected iodine perfusion (IPv) remains impaired. Compared to patients with normal DLCO, 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 DLCO, KCO is also reduced, and is even more strongly associated with IPv. KCO is considered a marker of pulmonary vascular involvement as it corrects for alveolar volume, as shown in patients with fibrotic lung diseases

(Corte TJ et al, Respirology. 2012 May;17(4):674-80). PMID: 22212399). We assessed the potential impact of mechanical ventilation on diffusion capacity. Those ventilated did have lower FVC and DLCO, in keeping with the potential impact of barotrauma on the interstitial compartment, but KCO and IPv, 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 (6). This novel DECT score, IPv, also correlated with breathlessness in a spectrum of patients recovering from COVID-19.

In acute COVID-19 pneumonitis, endothelialitis is a frequent feature (7), which induces intravascular immune activation and in-situ thrombotic angiopathy (8). 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 also reported in patients a year after acute lung injury due to multiple causes (9). Whether this finding relates to pulmonary vascular abnormalities is unknown, and biopsy data are lacking in post-COVID patients. Structural changes to lung vessels including neoangiogenesis and vascular proliferation are recognized in COVID-19, which may contribute to apparent parenchymal changes on CT (10).

Limitations to this study include potential pre-existing perfusion defects, subtle emphysema (smokers), gas trapping (asthma and smokers), obesity related artifact 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 DLCO’ with mottling of lung perfusion on DECT scanning is an under-reported phenotype and could be a target for therapeutics in this post COVID syndrome. Alternative advanced imaging modalities including VQ scanning show a mottling in lung perfusion (11); hyperpolarized lung MR also report a alveolar capillary diffusion abnormality in patients with normal CT scans (12). Whether these imaging findings relate to persistent impairment of the pulmonary microcirculation, alveolar inflammation, or both, needs further understanding. The onset of microthrombosis in patients with long COVID (13) is potentially relevant here. Indeed, endothelial activation is associated with low DLCO in similar patients (14), 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 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 automated perfusion score in this setting. The correlation with symptoms and lung function suggests 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.

	All patients n=78 (%)	FVC≥80% predicted (n=57)	FVC<80% predicted (n=21)	DLCO≥80% predicted (n=21)	DLCO<80% predicted (n=57)	FVC≥80% and DLCO≥80% (n=18)	FVC≥80% and DLCO<80% (n=39) 'Isolated low DLCO'
Age	48.8+-12.4y	47.7+-12.7y	52.3+-11.1	48.4+-2.5	49.0+--12.7	47.6+-13.4	47.7+-11.6
Sex, 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							
FEV1 % 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**
FEV1/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
DLCOc %pred.	66.9+-18.4%	73.2+-15.7	49.4+-13.4***	Na	Na	90.6+-7.2	64.8+-11
KCOc %pred.	81.6+-13.8%	82.0+-12.3	80.4+-17.4	Na	Na	90.3+-11.3	77.9+-10.8
SaO_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/vol (IPv)	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

Table 1. Demographic, full lung function and CT data in a post-COVID clinic population at six-month follow up, split by lung function phenotypes.

Computed tomography (CT) measurements included those using non-contrast CT where standard measurements included total lung volume (TLV) (normal range 5060+-1353ml), mean lung density (MLD) (normal range -839.6 HU+/-21.8) Hounsfield units (HU), and ground glass opacification score (GGO)%, (normal = 3.9% +/- 0.58). Using dual energy CT, a dynamic comparison was made between a set volume of contrast and non-contrast was made 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 *($p<0.05$), **($p<0.01$), ***($p<0.001$ or less).

Abbreviations: % pred. predicted, FEV1 forced expiratory volume in one second, FVC forced vital capacity, TLC total lung capacity, DLCOc diffusion of the lung for carbon monoxide corrected for haemoglobin (Hb), KCOc carbon monoxide transfer coefficient corrected for Hb, SaO_2 oxygen saturations, DECT dual-energy computed tomography, GGO ground glass

opacification, PA pulmonary artery, Ao aorta, RV right ventricle, LV left ventricle, IPv Iodine perfusion/lung volume, Na not appropriate

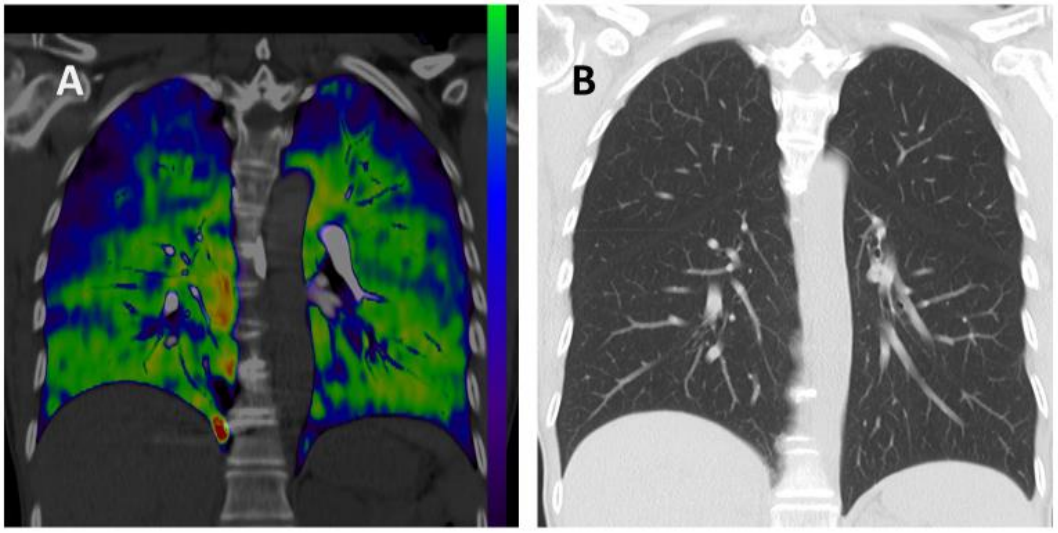

Figure 1

A: Coronal dual energy CT perfused blood volume iodine map with CT overlay in a 59 year old female with dyspnoea, fatigue and chest pain imaged 11 months after onset of mild COVID-19 pneumonia. DLCO was 72% predicted with otherwise normal spirometry. Upper lobe subpleural iodine distribution defects (represented as blue and black overlay, approximating < 40HU) in the subpleural apices bilaterally correspond with similar unmatched defects on perfusion scintigraphy. CT angiography did not demonstrate pulmonary arterial thrombus.

B: Corresponding coronal CT image shows normal lung parenchyma.

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DN and NJ did the acquisition, BG, CB, JH, BP, SP, GJ, WM, SS, CR, LP did analysis, or interpretation of data for the work. All had involvement in drafting the work or revising it critically for important intellectual content. All authors had final approval of the version to be published.

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REFERENCES

1. Zhang S, Bai W, Yue J, Qin L, Zhang C, Xu S, et al. Eight months follow-up study on pulmonary function, lung radiographic, and related physiological characteristics in COVID-19 survivors. Sci Rep. 2021;11(1):13854.
2. Remy-Jardin M, Duthoit L, Perez T, Felloni P, Faivre JB, Fry S, et al. Assessment of pulmonary arterial circulation 3 months after hospitalization for SARS-CoV-2 pneumonia: Dual-energy CT (DECT) angiographic study in 55 patients. EClinicalMedicine. 2021;34:100778.
3. Ridge CA, Desai SR, Jeyin N, Mahon C, Lother DL, Mirsadraee S, et al. Dual-Energy CT Pulmonary Angiography (DECTPA) Quantifies Vasculopathy in Severe COVID-19 Pneumonia. Radiol Cardiothorac Imaging. 2020;2(5):e200428.
4. Lyu P, Liu X, Zhang R, Shi L, Gao J. The Performance of Chest CT in Evaluating the Clinical Severity of COVID-19 Pneumonia: Identifying Critical Cases Based on CT Characteristics. Invest Radiol. 2020;55(7):412-21.
5. Arru CD, Digumarthy SR, Hansen JV, Lyhne MD, Singh R, Rosovsky R, et al. Qualitative and quantitative DECT pulmonary angiography in COVID-19 pneumonia and pulmonary embolism. Clin Radiol. 2021;76(5):392 e1- e9.
6. McGonagle D, Bridgewood C, Meaney JFM. A tricompartmental model of lung oxygenation disruption to explain pulmonary and systemic pathology in severe COVID-19. Lancet Respir Med. 2021;9(6):665-72.
7. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-8.
8. Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, et al. Pulmonary Angiopathy in Severe COVID-19: Physiologic, Imaging, and Hematologic Observations. Am J Respir Crit Care Med. 2020;202(5):690-9.
9. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med. 2003;348(8):683-93.
10. Doglioni C, Ravaglia C, Chilosi M, Rossi G, Dubini A, Pedica F, et al. Covid-19 Interstitial Pneumonia: Histological and Immunohistochemical Features on Cryobiopsies. Respiration. 2021;100(6):488-98.
11. Dhawan RT, Gopalan D, Howard L, Vicente A, Park M, Manalan K, et al. Beyond the clot: perfusion imaging of the pulmonary vasculature after COVID-19.

Lancet Respir Med. 2021 Jan;9(1):107-116.

12. James T Grist, Mitchell Chen, Guilhem J Collier, Betty Raman, Gabriele Abueid, et al. Hyperpolarized ^{129} Xe MRI Abnormalities in Dyspneic Patients 3 Months after COVID-19 Pneumonia: Preliminary Results**.** Radiology. 2021 Oct;301(1):E353-E360.

13. Pretorius E, Vlok M, Venter C, Bezuidenhout JA, Laubscher GJ, Steenkamp J, Kell DB. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. Cardiovasc Diabetol. 2021 Aug 23;20(1):172

14. Raúl Méndez, Paula González-Jiménez, Ana Latorre, Mónica Piqueras, Leyre Bouzas, Katheryn Yépez et al. Acute and sustained increase in endothelial biomarkers in COVID-19. Thorax. 2022 Apr;77(4):400-403.