Longitudinal follow-up of post-acute COVID-19 syndrome: DL_{CO}, QoL and MRI pulmonary gas-exchange abnormalities.

ONLINE DATA SUPPLEMENT

Material and Methods

Study Participants

We prospectively evaluated people 18-80 years of age who provided written-informed-consent to an ethics-board (HSREB # 113224), Health-Canada approved and registered protocol (ClinicalTrials.gov: NCT04584671). Study participants with a proven positive PCR COVID-19 test were prospectively recruited from a quaternary-care COVID-19 clinic between April and October 2021. Inclusion criteria consisted of: age ≥ 18 and <80 years, a documented case by positive RT-PCR test of COVID-19 infection that resulted in symptoms post-infection. Exclusion criteria consisted of: contraindications to MRI such as implants and severe claustrophobia, mental or legal incapacitation or could not read or understand written material, inability to perform spirometry or plethysmography maneuvers, and pregnancy.

Study Design

The study design consisted of Visit 1 (3-months post +COVID test), an optional Visit 2 (9-months post +COVID test), Visit 3 (15-months post +COVID test) and Visit 4 (27-months post +COVID test). Participants were administered salbutamol upon arrival at our centre according to American Thoracic Society Guidelines(1) and 15 minutes later performed post-bronchodilator (BD) spirometry and DL_{CO} immediately prior to MRI. Participants completed the six-minute-walk-test (6MWT) and Questionnaires (St. George's Respiratory Questionnaire (SGRQ),(2) modified Medical Research Council (mMRC) Questionnaire, Chronic Obstructive Pulmonary Disease

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Assessment Test (CAT),(3) post-COVID-19 Functional Status scale,(4) International Physical Activity Questionnaire (IPAQ),(5) and modified Borg Dyspnoea Scale (mBDS).(6, 7) ^{129}Xe gas-exchange MRI was performed in at least two visits. SpO_2 and heart rate were measured using an 8500 series handheld pulse oximeter (Nonin Medical Inc.) upon participant arrival as well as before and just after the 6MWT.

Pulmonary Function Tests

Pulmonary function tests were performed according to American Thoracic Society guidelines(8, 9) using a *ndd EasyOne Pro LAB system* (ndd Medical Technologies) or a *MedGraphics Elite Series* plethysmograph (MGC Diagnostics Corporation). Post-BD measurements were performed 15 minutes after inhalation of 4×100 µg/inhalation salbutamol sulfate norflurane (Ivax Pharmaceuticals) using an *AeroChamber* (Trudell Medical International). Participants underwent FeNO measurement according to guidelines(10) using a NIOX VERO system (Circassia Pharmaceuticals, Inc.). Participants withheld inhaled medications before study visits according to American Thoracic Society guidelines (e.g. short-acting β-agonists ≥6 hours, long-acting β-agonists ≥12 hours, long-acting muscarinic antagonists ≥24 hours).(8) Questionnaires and the 6MWT were self-administered under supervision of study personnel.

^{129}Xe MRI

Anatomic ^{1}H MRI was acquired using a fast-spoiled gradient-recalled-echo sequence (partial-echo acquisition; total acquisition time, 8 seconds; repetition-time msec/echo time msec, 4.7/1.2; flip-angle, 30°; field-of-view, 40×40cm^2; bandwidth, 24.4 kHz; 128×80 matrix, zero-filled to 128×128; partial-echo percent, 62.5%; 15-17×15mm slices). ^{129}Xe MR spectroscopy was acquired following inhalation breath-hold of a 1.0L gas mixture (4/1 by volume 4He/129Xe) from functional residual capacity (FRC) using a free-induction-decay whole-lung spectroscopy sequence (200 dissolved-

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phase spectra, TR=15ms, TE=0.7ms, flip=40°, BW=31.25kHz, 600μs 3-lobe Shinnar-Le Roux pulse). Spectroscopy was used to determine the echo time for a 90° tissue-plasma/RBC phase difference (TE_{90}). ^{129}Xe MRI was performed following inhalation of a 1.0L gas mixture (1/1 by volume ^{4}He/^{129}Xe) using an interleaved gas/dissolved-phase 3D radial sequence (TR=15ms TE=variable, flip=0.5°/40°, FOV=40cm^3, matrix=72x72x72, BW=62.5kHz, 990 gas/dissolved projections, 600μs 3-lobe Shinnar-Le Roux pulse, frequency shift=7.664kHz). Supine participants were coached to inhale a 1.0L bag (Tedlar; Jensen Inert Products, Coral Springs, FL, USA) (500mL ^{129}Xe + 500mL ^{4}He for ^{129}Xe MRI and 1.0L N_2 for ^{1}H MRI) from the bottom of a tidal breath (functional residual capacity) with acquisition under breath-hold conditions. ^{129}Xe gas was polarised to 30-40% (Polarean; Xenispin 9820, Durham, NC, USA).(11)

Gas-transfer MRI data were reconstructed as previously described using a re-gridding method for non-cartesian acquisition.(12) Receiver phase-offset and local phase inhomogeneity were corrected as previously described.(13)

^{129}Xe gas-exchange MRI were corrected for local phase inhomogeneity using acquired interleaved gas-compartment data. Deviations from uniform phase in the gas image were assumed to result from phase inhomogeneity and voxel-wise phase corrections were applied to eliminate inhomogeneity effects. Receiver phase-offset was corrected using the spectroscopic RBC:TP ratio. A phase correction $\Delta\phi$ was applied such that the ratio of real to imaginary channel signal matched the spectroscopic RBC:TP ratio under the assumption that RBC and TP signal should be perfectly aligned to the real and imaginary channels, respectively, at TE_{90}.

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TABLES

e-Table 1. Participant Demographics

Parameter Mean (SD)	PACS (n=21)
Age yrs	56 (15)
Females n (%)	8 (38)
Hospitalized n (%)	9 (43)
BMI kg/m^2	31 (6)
Asthma n (%)	7 (33)
COPD n (%)	1 (5)
Pack-years	8 (19)

BMI=body mass index; COPD=chronic obstructive pulmonary disease

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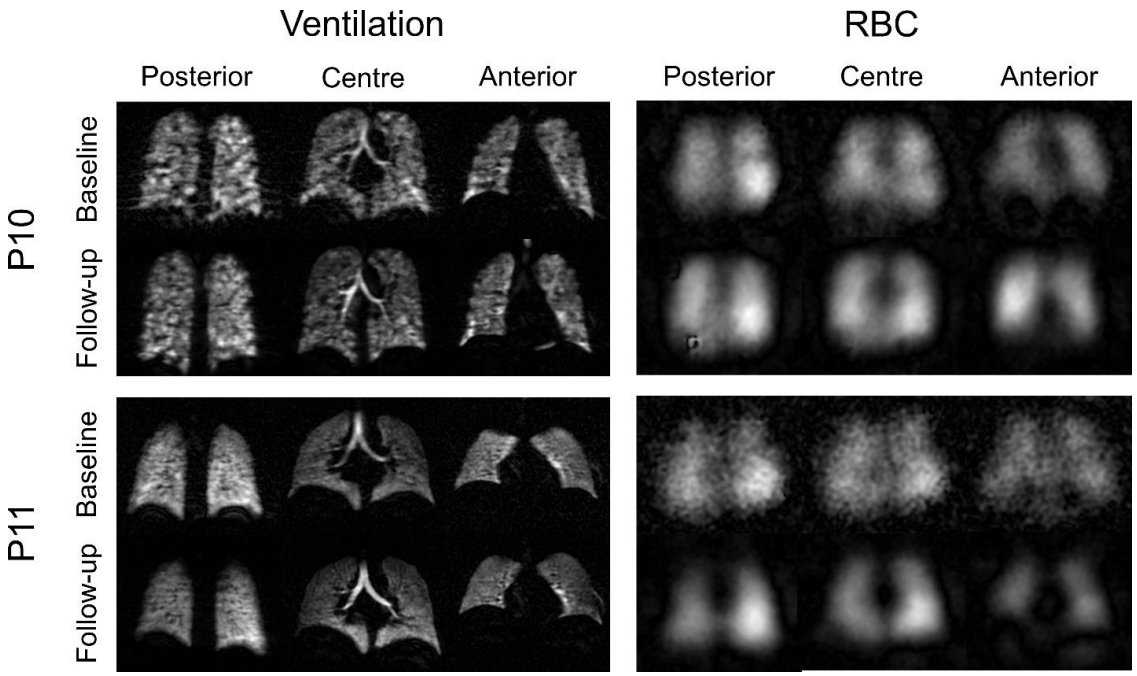
e-Table 2. Participant medications

Participant	Baseline Medications	Follow-up Medications
P01	Anticoagulant, ICS/LABA, SABA	Anticoagulant, ICS/LABA, SABA
P02	ICS/LABA, Anticholinergic, ICS	ICS/LABA, SABA
P03	ICS/LABA, ACE inhibitor, BP	ICS/LABA, ACE inhibitor, BP
P04	ICS/LABA	None
P05	Anticoagulant, stimulant	Anticoagulant, stimulant
P06	Diuretic, anticoagulant, thyroid hormone, BP	ICS/LABA, Diuretic, anticoagulant, thyroid hormone, BP
P07	Alpha blocker, beta blocker, anticoagulant, anti-cholesterol, BP, ICS	Alpha blocker, beta blocker, anticoagulant, anti-cholesterol, BP, ICS
P08	Antidepressant, ICS/LABA	ICS/LABA
P09	Antidepressant	Antidepressant
P10	ICS/LABA, Leukotriene antagonist, LABA, proton pump inhibitor	ICS/LABA, SABA, leukotriene antagonist, LABA, proton pump inhibitor, ICS
P11	ISC/LABA, SABA	ICS/LABA
P12	None	None
P13	BP, anti-cholesterol, alpha blocker, beta blocker, proton pump inhibitor, aspirin, ICS/LABA	BP, anti-cholesterol, alpha blocker, beta blocker, proton pump inhibitor, aspirin, diuretic, ICS/LABA
P14	Thyroid hormone, antidepressant	Thyroid hormone, contraceptive
P15	Insulin, acetaminophen, anti-cholesterol, anticoagulant, anti-inflammatory, proton pump inhibitor, ICS/LABA, SABA, beta agonist	Insulin, acetaminophen, anti-cholesterol, anticoagulant, ani-inflammatory, opioid, BP
P16	Acetaminophen, anticonvulsant, anti-inflammatory, hormone	Anticonvulsant, antidepressant, anti-inflammatory
P17	ACE inhibitor, BP, proton pump inhibitor, prostaglandin analog, anti-cholesterol, LABA, SABA, aspirin, ICS/LABA	ACE inhibitor, BP, proton pump inhibitor, prostaglandin analog, anti-cholesterol, LABA, SABA, aspirin, ICS/LABA
P18	Monoclonal antibody, digestive enzyme, ICS/LABA, SABA, LABA, anti-histamine	Monoclonal antibody, digestive enzyme, ICS/LABA, SABA, LAMA
P19	Antidepressant	ICS/LABA, BP
P20	Anti-cholesterol, prostaglandin analog, diuretic, antacid, SABA	Anti-cholesterol, prostaglandin analog, diuretic, antacid, SABA
P21	None	None



eFigure 1. Ventilation imaging and 2D (three central slices) raw red blood cell component of the dissolved phase images at baseline and follow-up for two participants.

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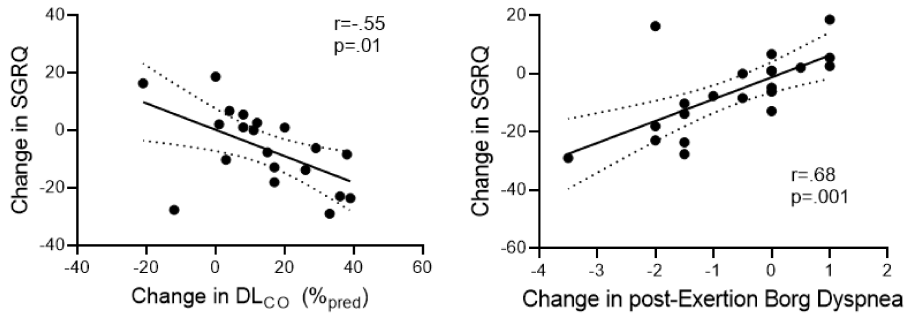

e-Figure 2. Correlations between changes in SGRQ score and clinical measurements. There were moderate correlations between changes in SGRQ score and changes in DL_{CO} as well as post-exertion Borg dyspnoea. (Participants with DL_{CO} measurement n=20).

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