Lung function during and after acute respiratory infection in COVID-19 positive and negative outpatients

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To the Editor:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with prolonged post-acute symptoms in at least 10% of patients [1, 2]. The majority of published data evaluates hospitalised patients with severe SARS-CoV-2 disease (COVID-19) with symptoms and pulmonary function defects several months after discharge [1]. Most of the infected subjects develop mild symptoms and are treated as outpatients. Though they are also reported to suffer from prolonged symptoms, their lung function is studied far less. Furthermore, the prolonged symptoms and objectively measurable findings are usually not compared to a group suffering from airway infection caused by other pathogens [2]. As spirometry and other aerosol-producing procedures are minimised during the pandemic, there are no reports on lung function during acute COVID-19.

Forced oscillation technique (FOT) or airwave oscillometry (AOS) is a non-invasive and effort-independent method to measure airway resistance and airway reactance, enabling safe and admissible evaluation of pulmonary function [3] without producing possibly infective aerosols. FOT has been used in three previous studies to show small airway impairment 1–6 months after discharge in subjects who have recovered from severe COVID-19 [4–6].

Our aim was to evaluate and compare symptoms and pulmonary function at the time of acute infection (visit one) and after 2 months of follow-up (visit two) in outpatients with mild respiratory infection that were either RT-PCR positive (cases) or RT-PCR negative (controls) for SARS-CoV-2.

The final study population consisted of two clinical series, namely 43 cases and 39 controls, who took part in the CANNAS study in Tampere, Finland from 15 January to 18 August 2021 (R20090, NCT04728919). Cases were recruited during contact tracing phone call. Age-matched (±5 years) and gender-matched controls were recruited among subjects tested for SARS-CoV-2 due to acute respiratory infection but who later received a negative test result and gave their contact information (n=138) at local testing sites; 102 people were contacted, 43 matched controls were recruited and, after drop-outs, 39 subjects were included. The exclusion criteria were absence of respiratory symptoms, onset of symptoms more than 10 days previous, pregnancy or breastfeeding, previous vaccination against COVID-19 and inability to arrive at the study site without exposing others.

A standard nasopharyngeal swab sample was obtained and three target genes were analysed by the SARS-CoV-2 RT-PCR protocol (Seegene Inc., Seoul, South Korea). Lung function was measured with AOS (TremoFlo C-100, Thorasys, Montreal, QC, Canada) at both visits and with spirometry (Medikro Pro, Medikro Oy, Kuopio, Finland) at the follow-up visit, according to international standards [7–9], using international and Finnish reference values [10, 11]. A visual analogue scale from “none” (0 mm) to “worst possible” (100 mm) was used to score different symptoms at both visits. Due to skewed distributions (Kolmogorov–Smirnov test), medians (interquartile range) were used to describe the data.

The results are presented in the table 1. Cases and controls did not differ in their demographics. None of the subjects used leukotriene antagonists. Systemic corticosteroids were used only by one subject for a nonidentifiable reason before the control visit (normal AOS and spirometry). Inhaled corticosteroids were

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At acute phase, outpatients with mild COVID-19 had more symptoms, higher small airway resistance and poorer lung elasticity compared to outpatients with other respiratory infections, but there was no difference between the groups after 2 months https://bit.ly/3nalPye

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TABLE 1 Demographics, pulmonary function and symptoms in 43 patients with COVID-19 and 39 controls with other respiratory infections at the time of acute infection (visit 1) and after 2 months' follow-up (visit 2)

	COVID-19 positive cases			COVID-19 negative controls			p-value[¶] (pos to neg)	
	Visit 1 (n=43)	Visit 2 (n=39)	p-value[#] (visit 1 to 2)	Visit 1 (n=39)	Visit 2 (n=35)	p-value[#] (visit 1 to 2)	Visit 1	Visit 2
Demographics								
Females	24 (56)			26 (67)			0.315	
Age (years)	41.0 (28.0–48.0)			39.0 (34.0–46.0)			0.658	
BMI (kg·m^{-2})	27.0 (25.1–31.1)			27.5 (23.3–29.7)			1	
Duration of symptoms (days)	4.6 (4.4–6.5)			5.4 (4.4–8.4)			0.514	
Comorbidities, lung disease[+]	1 (2)			1 (3)			1	
Comorbidities, other	14 (33)			14 (36)			0.752	
Current smoker	10 (23)			9 (23)			1	
Airway allergy	17 (40)			9 (23)			0.110	
Pulmonary function								
FVC (% pred)		94 (88–102)			92 (85–103)			0.623
FEV_1 (% pred)		93 (86–99)			91 (86–105)			0.641
FEV_1/FVC (% pred)		99 (92–102)			100 (93–104)			1
R_5 (cmH_2O·s·L^{-1})	2.88 (2.29–3.61)	3.31 (2.34–3.82)	0.062	2.59 (2.14–3.26)	2.86 (2.20–3.79)	**0.011**		
R_5 (Z-score)	−0.10 (−0.90–0.70)	−0.10 (−0.70–0.73)	0.059	−0.50 (−1.10–0.10)	−0.50 (−0.90–0.40)	0.132	0.113	0.188
R_{20} (cmH_2O·s·L^{-1})	2.67 (2.33–3.39)	2.72 (2.32–3.48)	0.152	2.65 (2.31–3.07)	2.63 (2.18–3.15)	0.255		
R_{20} (Z-score)	−0.20 (−0.90–0.10)	−0.60 (−0.75–0.20)	0.102	−0.50 (−1.00–−0.10)	−0.50 (−1.00–−0.10)	0.113	0.500	0.880
$R_{5–20}$ (cmH_2O·s·L^{-1})	0.09 (−0.05–0.28)	0.32 (0.09–0.70)	**<0.001**	−0.10 (−0.23–0.18)	0.17 (−0.04–0.64)	**<0.001**		
$R_{5–20}$ (Z-score)	0.40 (−0.40–0.70)	0.70 (−0.23–1.50)	**<0.001**	−0.20 (−0.60–0.30)	0.20 (−0.10–1.10)	**0.003**	**0.025**	0.188
X_5 (cmH_2O·s·L^{-1})	−0.92 (−1.24–−0.79)	−0.99 (−1.30–−0.81)	0.052	−0.94 (−1.05–−0.72)	−1.04 (−1.20–−0.77)	**0.048**		
X_5 (Z-score)	0.20 (−0.60–0.70)	−0.05 (−0.90–0.83)	0.075	0.40 (−0.10–0.90)	0.40 (−0.50–0.80)	0.224	0.282	0.129
A_X (cmH_2O·s·L^{-1})	4.28 (2.40–7.17)	4.90 (3.02–8.21)	**<0.001**	2.95 (2.20–4.77)	4.13 (2.43–9.37)	**0.005**		
A_X (Z-score)	0.70 (0.10–1.50)	1.05 (0.25–1.60)	**0.005**	0.30 (−0.20–0.70)	0.50 (0.00–1.40)	**0.018**	**0.045**	0.398
Symptom VAS (0–100 mm)								
Need to blow nose	30 (15–57)	9 (0–24)	**<0.001**	18 (6–33)	8 (0–14)[f]	**0.004**	**0.002**	0.718
Sneezing	22 (9–53)[§]	6 (0–17)	**<0.001**	10 (0–23)	7 (0–15)[f]	0.067	0.057	0.904
Runny nose	31 (8–60)	2 (0–13)	**<0.001**	13 (7–41)	3 (0–12)[f]	**<0.001**	0.119	0.919
Decreased sense of smell/taste	52 (13–87)	1 (0–12)	**<0.001**	0 (0–11)	0 (0–1)[f]	**0.009**	**<0.001**	0.066
Cough	33 (9–59)[§]	0 (0–12)	**<0.001**	12 (0–27)	1 (0–5)[f]	**<0.001**	**0.010**	0.431
Post-nasal discharge	15 (5–42)[§]	0 (0–15)	**<0.001**	18 (5–40)	5 (0–11)[f]	**0.001**	0.915	0.205
Thick nasal discharge	24 (5–41)[§]	0 (0–9)	**<0.001**	5 (0–27)	1 (0–3)[f]	**<0.001**	0.095	0.584
Wet cough	17 (5–39)	0 (0–14)	**<0.001**	4 (0–20)	0 (0–1)[f]	**0.001**	0.185	0.653
Dyspnoea (shortness of breath)	8 (0–22)[##]	0 (0–9)	**0.006**	0 (0–18)	0 (0–3)[f]	0.059	**0.043**	0.842
Fatigue	50 (20–68)	13 (0–50)[¶¶]	**0.001**	24 (7–51)	11 (2–22)[f]	**0.001**	**0.027**	0.816

Data are presented as median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; R_5: total airway resistance; R_{20}: large airways resistance; $R_{5–20}$: small airways resistance; X_5: airway reactance; A_X: area of reactance; Z-score: ratio of the difference between the measured value and that predicted with the residual standard deviation; VAS: visual analogue scale. [#]: related-samples Wilcoxon signed-rank test and; [¶]: independent-samples median test, Fishers exact test or Chi-square (Pearson); [+]: asthma; [§]: n=42; [f]: n=36; [##]: n=41; [¶¶]: n=38. The level of significance was set at p<0.05 (indicated with bold font).

used by 5% of cases (only one of them had the diagnosis of asthma) and 3% of controls (p=1). The median time from visit one to follow-up was 59 (56–64) *versus* 56 (53–67) days (p=0.496), in cases and controls, respectively.

Small airway resistance ($R_{5–20}$) and area of reactance (A_X) were significantly higher in cases during infection (visit one) in comparison to controls, indicating impairment of the peripheral lung. In both cases and controls, there was a small but statistically significant impairment in these parameters from visit one to two (table 1). Proportions of subjects with abnormal results in each oscillometry variable (z-score <−1.65) were small, and there were no differences between cases and controls at either visit. Spirometry results at

follow-up were similar between groups. Some of the subjects in both groups had spirometry values below the lower limit of normal (z-score <1.65) (7.7% *versus* 14.3% in forced vital capacity (FVC), p=0.477; 12.8% *versus* 17.1% in forced expiratory volume in 1 s (FEV_1), p=0.654; 20.5% *versus* 14.2% in FEV_1/FVC, p=0.554; in cases and controls, respectively) but there was no difference between the groups.

During acute infection, cases had higher symptom scores in terms of decreased senses of smell and/or taste, fatigue, coughing, the need to blow their noses and dyspnoea (table 1). There was a significant decrease in symptoms in both groups at the follow-up and no significant difference between the groups.

This is the first study to evaluate outpatient lung function at the acute phase of COVID-19 infection and we had a control group suffering from respiratory infection caused by other pathogens. At the acute phase, cases had, on average, poorer peripheral lung function ($R_{5–20}$ and A_X) in comparison to controls, yet the proportion of abnormal results was low. Although subjects recovering from severe COVID-19 infection may have impaired diffusing capacity, restriction or obstruction [12], our results suggest that mild COVID-19 infection does not impair lung function after 2 months of follow-up when compared to other mild respiratory infections. There were some subjects with lung function below the lower limit of normal, but this is understandable since, by definition, 5% of healthy subjects have abnormal values of each parameter, and our study also included subjects with asthma, a history of smoking (possible undiagnosed chronic obstruction) and obese people with pulmonary restriction. However, the proportion of cases with FEV_1/FVC below lower limit of normal was unexpectedly high (20.5%), but as we do not know their lung function before infection, we do not know if this is because of COVID-19 or undiagnosed prior lung disease. The important finding is that the proportion of abnormal values did not differ between the cases and controls and none of the subjects had FEV_1/FVC <0.70.

Interestingly, the trend of change in our data was slightly worse in R_5, $R_{5–20}$, A_X and X_5 in both groups. This might implicate airway damage after infection [4]. Again, there were no differences between cases and controls, suggesting that mild COVID-19 does not differ from other airway infections in this regard.

COVID-19 patients were more symptomatic than the controls at the acute phase, with the greatest differences being a decreased sense of taste and/or smell, and fatigue, which align with previous results [13, 14]. Both groups had very low levels of symptoms at control visit and there was no difference between the groups, suggesting that long-lasting sequelae are not frequent in subjects with mild COVID-19 treated as outpatients.

The study sample is representative of non-vaccinated adult Finnish outpatients with mild respiratory tract infection, albeit the participation might have been more tempting to people with pulmonary or other health concerns. Measurements at visit one were taken days after the onset of symptoms, not necessarily depicting the culmination of the disease. However, the groups were comparable by background characteristics. The sample size was based on a 90% power with an alpha-error of 5% to find a between-group difference in any continuous variable that was at least 75% of the standard deviation. Thus, we cannot rule out minor differences between the groups.

In conclusion, outpatients with mild COVID-19 had poorer peripheral lung function in comparison to those with other acute respiratory infections, but there were no differences in lung function or symptoms after 2 months of follow-up, suggesting that possible long-standing symptoms after mild COVID-19 may not be due to physical changes in the airways.

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