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Persistent Nasal Inflammation 5 Months after Acute Anosmia in Patients with COVID-19

To the Editor:

Olfactory dysfunction (OD), including hyposmia and anosmia, is frequent in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease (COVID-19) (1). OD has been reported in up to 68% of patients, with a higher proportion of females than males in most cases (2). The underlying mechanisms of smell loss in patients with COVID-19 are still debated. It is likely that OD results from a transient dysfunction of the olfactory epithelium rather than from destruction of olfactory sensory neurons. In any case, local inflammation in the nasal cavity is expected to play a pivotal role in causing olfactory loss. Plasmatic concentrations of systemic inflammatory biomarkers such as CRP (C-reactive protein), fibrinogen, or LDH (lactate dehydrogenase) gradually increased over the first 10 days after the onset of symptoms (3). As the rise of systemic biomarkers does not necessarily reflect local inflammation in the nasal cavity area, we have conducted a prospective study measuring nasal nitric oxide (NO), a local noninvasive biomarker for nasal inflammation (4), in patients with COVID-19 with and without OD.

Between May 5, 2020, and November 5, 2020, we prospectively investigated consecutive patients who had been infected by SARS-CoV-2 as part of our routine post–COVID-19 respiratory function follow-up protocol. All investigations were scheduled in patients in a clinically stable condition (with resolved OD) at least 6 weeks after the onset of respiratory symptoms related to SARS-CoV-2 infection (143 ± 40 d). Respiratory function tests included measurement of FVC and FEV_1 following American Thoracic Society/European Respiratory Society quality standards (Carefusion), fractional exhaled NO (F_{ENO}) (NIOX-VERO; Circassia), nasal NO flow rate, and alveolar concentration of exhaled NO (C_{ANO}) (F_{ENO}^{+} HypAir; MGC Diagnostics) (5). All tests were performed on the same day. Global Lung Initiative reference values were applied for FVC and FEV_1 (6). For nasal NO measurement, subjects performed spontaneous and calm respiration through a mouth cannula with airway pressure control (between −25 and −10 cm H_2O during inspiration, and between 10 and 25 cm H_2O during expiration) causing palate closure while nasal gas was continuously aspirated through a soft line with a disposable foam olive inserted into one nostril. Nasal aspirating flow rate was set at 250 ml/s and a stable plateau of 30 seconds was selected by the device to calculate nasal NO. Two or three reproducible maneuvers (with less than 10% difference) were required to validate the measurement and calculate the mean value of nasal NO (5). We used a written questionnaire to inquire about the existence of ongoing nasal symptoms and treatments with corticosteroids. SARS-CoV-2

Supported by a research grant from the Air Liquide Foundation (France).

Originally Published in Press as DOI: 10.1164/rccm.202011-4258LE on March 8, 2021

Table 1. Demographics, Lung Function Characteristics, and Nasal and Exhaled Nitric Oxide Measurement in Patients with COVID-19

	Total (*n* = 112)	No Anosmia (*n* = 59)	Anosmia (*n* = 53)	*P* Value
Age, yr	51.5 ± 10.9	52.7 ± 9.3	50.2 ± 12.4	0.236
Sex, F	46 (41.1)	21 (35.6)	25 (47.2)	0.214
Height, cm	170.5 ± 8.1	171.1 ± 7.8	169.8 ± 8.5	0.401
Weight, kg	78.5 ± 16.5	79.4 ± 16.8	77.6 ± 16.2	0.546
BMI, kg/m^2	26.9 ± 4.8	27.1 ± 4.8	26.8 ± 4.9	0.800
Obesity	28 (25.0)	13 (22.0)	15 (28.3)	0.444
Smoker				0.952
Active	8 (7.1)	4 (6.8)	4 (7.5)	
Former	18 (16.1)	9 (15.3)	9 (17.0)	
Comorbidities				
Lung disease	18 (16.1)	8 (13.6)	10 (18.9)	0.445
Heart disease	7 (6.3)	6 (10.2)	1 (1.9)	0.117*
Hypertension	25 (22.3)	14 (23.7)	11 (20.8)	0.706
Diabetes	19 (17.0)	12 (20.3)	7 (13.2)	0.315
Time from COVID-19, d	143 ± 40	139 ± 45	148 ± 34	0.250
COVID-19 severity				
Mild	43 (38.4)	18 (30.5)	25 (47.2)	0.117
Moderate	27 (24.1)	14 (23.7)	13 (24.5)	
Severe	42 (37.5)	27 (45.8)	15 (28.3)	
Nasal nitric oxide, nl/min	311 ± 127	263 ± 107	363 ± 127	<0.001
F_{ENO}-50, ppb	22.8 ± 11.9	21.8 ± 9.8†	23.9 ± 13.9‡	0.388
C_{ANO}, ppb	4.05 ± 1.89	4.08 ± 1.7§	4.03 ± 2.09‡	0.898
Spirometry (GLI-2012)				
FVC, L	3.43 ± 0.88	3.48 ± 0.82	3.36 ± 0.94	0.469
FVC, % predicted	84 ± 16	85 ± 18	84 ± 13	0.662
FEV_1, L	2.79 ± 0.71	2.80 ± 0.67	2.78 ± 0.75	0.877
FEV_1, % predicted	86 ± 16	86 ± 18	86 ± 13	0.883
FEV_1/FVC, %	82 ± 7	81 ± 8	83 ± 6	0.115
Obstructive pattern (FEV_1/FVC < LLN)	3 (2.7)	3 (5.1)	0 (0)	0.245*

Definition of abbreviations: BMI = body mass index; C_{ANO} = alveolar concentration of exhaled nitric oxide; COVID-19 = coronavirus disease; F_{ENO}-50 = fractional exhaled nitric oxide concentration at expiratory flow rate of 50 ml/s; GLI = Global Lung Initiative; LLN = lower limit of normal. Data are presented as mean ± SD or *n* (%). Comparisons between patients with COVID-19 with anosmia and without anosmia were performed using Student's *t* test for continuous variables.

*Comparisons were performed using chi-squared or Fisher exact tests for categorical variables.

†*n* = 55 patients, as some failed to measure exhaled nitric oxide.

‡*n* = 49 patients, as some failed to measure exhaled nitric oxide.

§*n* = 50 patients, as some failed to measure exhaled nitric oxide.

infection was identified by multiplex real-time RT-PCR on nasopharyngeal swabs, or retrospectively by serological quantification of anti–SARS-CoV-2 IgG antibodies. SARS-CoV-2 infection was classified as mild disease (mild symptoms, with or without radiographic evidence of pneumonia, and no requirement for supplemental oxygen), moderate pneumonia (evidenced by chest high-resolution computed tomography, and requirement of oxygen therapy up to 12 L/min), and severe disease (respiratory failure requiring nasal high-flow oxygen or mechanical ventilation, septic shock, and other organ failure with admission into the ICU) according to World Health Organization interim guidance and guidance from China (7). Results are summarized in Table 1. Statistical analyses were performed using a Student's *t* test for continuous variables after normal distribution was tested and chi-squared or Fisher exact tests for categorical variables (IBM SPSS 20.0).

All patients were free of nasal symptoms at the time of the study, none actually reported previous upper airways disorders before infection by SARS-CoV-2, and none were treated with nasal corticosteroids either during COVID-19 infection or at the time of the study. Nasal NO measurements were systematically performed twice or thrice in all patients. The coefficients of variations of these measurements were 5.1 ± 3.5% and 5.8 ± 4.1% (mean ± SD) in patients with COVID-19 with and without anosmia, respectively. This is consistent with data from the literature and coefficients of variation ranging from 7% to 13% (8). Comparisons between patients with COVID-19 with and without anosmia showed that the former had significantly higher levels of nasal NO than the latter (363 ± 127 vs. 263 ± 107 nl/min, $P < 0.001$). Nasal NO in 25 age-matched (52.1 ± 13.7 yr) healthy control subjects was significantly lower than that in the whole group of patients with COVID-19 (226 ± 48 vs. 311 ± 127 nl/min, $P < 0.001$). This difference, however, only reached statistical significance when a comparison was made between control subjects and patients with COVID-19 with anosmia ($P < 0.001$), with no difference being found between control subjects and patients with COVID-19 without anosmia. None of the other variables, including anthropometric data, smoking status, comorbidities, COVID-19 severity, lung function tests, and F_{ENO} and C_{ANO} results, differed between patients with COVID-19 with and without anosmia (Table 1). Regarding sex, anosmia was numerically but nonsignificantly more frequent in females (54%, 25/46) than in males (42%, 28/66); the higher nasal NO values that were observed in patients with COVID-19 with anosmia were similarly found in men and women as compared with patients without anosmia

(366 ± 128 vs. 258 ± 101, $P < 0.001$ in men with and without anosmia and 360 ± 128 vs. 273 ± 119 nl/min, $P < 0.05$ in women with and without anosmia).

Increasing evidence suggests that inflammatory processes are involved in COVID-19–related OD. First, epithelial olfactory cells are susceptible to SARS-CoV-2 entry and subsequent replication as they express high levels of both the cell surface angiotensin-converting enzyme 2 and its activating enzyme transmembrane protease serine subtype 2 (TMPRSS2) (1). Second, in animal models, the instillation of SARS-CoV-2 in the nasal cavity caused tissue injury with transient destruction of the olfactory epithelium and its supportive cells, as well as massive infiltration of immune cells (9). Third, postmortem analyses in humans revealed increased levels of tumor necrosis factor-α and prominent leukocytic infiltrates in damaged olfactory epithelium and olfactory nerves in lethal cases of patients with COVID-19 with anosmia (10). All patients with COVID-19 with anosmia in our study fully recovered from OD by the time nasal NO was measured. As the earliest time-point of nasal NO measurement took place 6 weeks after symptoms onset, our results are consistent with data from the literature showing that 98% of patients with COVID-19 could recover from their anosmia within 28 days (11). Although anosmia is a transient symptom that resolves within 1, or a few, week(s) in most cases, whether the underlying inflammation persists after recovery of olfaction was previously unknown. The results of this study strongly suggest the persistence of nasal inflammation up to 5 months after the onset of symptoms in patients with COVID-19 from both sexes with anosmia as compared with those without anosmia and healthy control subjects. The lack of differences in NO production in intrathoracic conducting airways and alveoli region (as shown by comparable results of Fe_{NO} and Ca_{NO}) between patients with COVID-19 with and without OD (Table 1) suggests that increased residual inflammation accompanying the loss of smell is only restricted to the olfactory epithelium. This may relate to the infectivity gradient from the upper to the lower respiratory tract, as a consequence of the greater expression of both angiotensin-converting enzyme 2 and TMPRSS2 in ciliated and goblet cells from the nasal cavity as compared with lower airways and alveolar epithelial cells (12). Whether Fe_{NO} and Ca_{NO} also remain elevated in patients with COVID-19 with versus without pneumonia or acute respiratory distress syndrome is unknown. Whether nasal inflammation is more prominent during the acute phase of infection in patients with anosmia is also uncertain. It is, however, likely that high nasal NO levels in patients with COVID-19 with anosmia is a local consequence of ongoing background activation of inducible NO synthase by proinflammatory cytokines (4, 5) even after recovery.

In conclusion, there is clear evidence of persistent inflammation 5 months after the onset of symptoms in patients with COVID-19 who have recovered from their OD. Whether this will lead to chronic rhino-sinus diseases is yet to be investigated. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank all medical and nurse teams from both clinical units and the technicians and nurses of the Respiratory Physiology unit for their commitment to the care of the patients and conducting technical measurements, including nasal and expired NO.

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Balanced Crystalloids versus Saline in Critically Ill Adults with Hyperkalemia or Acute Kidney Injury: Secondary Analysis of a Clinical Trial

To the Editor:

Hyperkalemia is common in critically ill patients and is associated with an increased risk of cardiac arrhythmia, cardiac arrest, and death (1). Intravenous fluids affect plasma electrolyte concentrations (2). Saline (0.9% sodium chloride) causes hyperchloremia and metabolic acidosis, which may move potassium from the intracellular space into the interstitial fluid and plasma (3). Balanced crystalloids, such as lactated Ringer's solution or Plasma-Lyte A, contain 4.0–5.0 mmol/L of potassium—a concentration similar to that of normal human plasma. The theoretical risk of hyperkalemia from supplemental potassium is a frequently cited concern with balanced crystalloids (4). However, balanced crystalloids also contain buffers such as lactate and acetate, which may prevent acidosis-induced potassium shifts (3). To evaluate the effect of fluid composition on the incidence of hyperkalemia and renal replacement therapy (RRT), we performed a secondary analysis of a large, pragmatic trial comparing balanced crystalloids with saline among critically ill adults (2).

Some of the results of this study have been previously reported in the form of an abstract (5).

Methods

Patient populations. SMART (Isotonic Solutions and Major Adverse Renal Events Trial) compared balanced crystalloids versus saline among 15,802 critically ill adults (2). We identified the following two cohorts of patients in SMART at risk of severe hyperkalemia: patients with hyperkalemia at ICU admission and patients with acute kidney injury (AKI) at ICU admission. Hyperkalemia at baseline was defined as a plasma potassium concentration of ⩾6.5 mmol/L in the 24 hours before ICU admission (or in the 6 h after ICU admission if no potassium values were available before ICU admission). A potassium concentration of ⩾6.5 mmol/L was used to define hyperkalemia in the original SMART and other prior trials of balanced crystalloids (2, 6). AKI at baseline was defined as a plasma creatinine concentration in the 24 hours before ICU admission (or in the 6 h after ICU admission if no creatinine values were available before ICU admission) meeting criteria for stage 2 or greater kidney injury according to the Kidney Disease: Improving Global Outcomes creatinine criteria (7). The method for identifying baseline creatinine and calculating a value when a measured value was unavailable has been previously described (2).

Study outcomes. Outcomes included severe hyperkalemia, defined as a plasma potassium concentration ⩾7.0 mmol/L (8), between ICU admission and hospital discharge; highest potassium concentration from ICU admission to hospital discharge; death; new receipt of RRT; and incident AKI by the Kidney Disease: Improving Global Outcomes creatinine criteria. All outcomes were censored at the first of hospital discharge or 30 days. Patients who had received RRT before ICU admission were ineligible to meet criteria for incident AKI or new receipt of RRT but were eligible for other outcomes.

Statistical analysis. Analyses used the same approach to modeling as the original SMART (2). Binary outcomes were analyzed with a generalized, linear, mixed-effects model that included group assignment as a fixed effect and the ICU to which the patient was admitted as a random effect. Continuous outcomes were analyzed using a proportional odds logistic regression model that included group assignment as an independent variable and used robust covariance matrix estimates to adjust for within-ICU correlation. For outcomes that included potassium, models included baseline potassium as a fixed effect.

Results

A total of 254 patients had a baseline potassium concentration of ⩾6.5 mmol/L, of whom 67 were excluded for artifactual hyperkalemia from hemolysis, and 187 were included in the analysis (94 in the balanced crystalloids group and 93 in the saline group). Among 15,016 patients in SMART who had not received RRT before ICU admission, 1,324 patients had AKI at baseline (681 in the balanced crystalloid group and 643 in the saline group). The characteristics of patients randomized to the balanced crystalloid and saline groups in each cohort are displayed in Table 1.

Among patients with hyperkalemia at baseline, eight patients (8.5%) in the balanced crystalloid group and 13 patients (14.0%) in the saline group went on to experience severe hyperkalemia (adjusted odds ratio, 0.57; 95% confidence interval [CI], 0.22–1.46; $P = 0.24$) (Figure 1 and Table 1). New or worsening AKI (25.3% vs. 42.0%; adjusted odds ratio, 0.47; 95% CI, 0.23–0.94; $P = 0.03$) and new receipt of RRT (13.9% vs. 29.0%; adjusted odds ratio, 0.40; 95% CI, 0.17–0.90; $P = 0.03$) occurred less frequently in patients in the balanced crystalloid group compared with those in the saline group (Figure 1 and Table 1). The receipt of potassium-lowering therapies, including sodium polystyrene, insulin/dextrose, sodium bicarbonate, and calcium gluconate/chloride, was similar between the two groups (Table 1).

Among patients with AKI at baseline, three patients (0.4%) in the balanced crystalloid group and nine patients (1.4%) in the saline group experienced severe hyperkalemia (adjusted odds ratio, 0.33; 95% CI, 0.09–1.25; $P = 0.10$) (Figure 1 and Table 1). A total of 97 patients (14.2%) in the balanced crystalloid group received new RRT

Supported in part by Vanderbilt Clinical and Translational Science Award grant UL1TR002243 from the National Center for Advancing Translational Sciences/NIH. J.D.C. was supported in part by the NIH (K12HL133117 and K23HL153584). M.W.S. was supported in part by the NHLBI (K12HL133117 and K23HL143053). T.W.R. was supported in part by the NIH (R34HL105869). E.D.S. was supported in this work by the Vanderbilt Center for Kidney Diseases. Data collection used the Research Electronic Data Capture tool developed and maintained with Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from the National Center for Advancing Translational Sciences/NIH).

Authors Contributions: Study concept and design: A.H.T., M.W.S., T.W.R., and J.D.C. Acquisition of data: A.H.T., M.W.S., J.P.W., and J.D.C.; Analysis and interpretation of data: A.H.T., M.W.S., L.W., and J.D.C. Drafting of the manuscript: A.H.T., M.W.S., and J.D.C. Critical revision of the manuscript for important intellectual content: A.H.T., M.W.S., W.H.S., G.R.B., L.W., E.D.S., J.L.S., J.P.W., T.W.R., and J.D.C.

Originally Published in Press as DOI: 10.1164/rccm.202011-4122LE on January 27, 2021