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Research Article

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Maximal Breath Hold Associated with Inappropriate Change in Respiratory Rate in Hospitalized Covid-19 Patients Indicates a Blunted Ventilatory Response

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Abstract

Background: *Some patients with severe acute respiratory syndrome coronavirus 2 associated disease (COVID-19) presented with hypoxemia without exhibiting dyspnea. This phenomenon was called "silent" or "happy" hypoxia. The cause of "silent hypoxia" was unknown. It was suspected that COVID-19 might be altering structures vital to the normal respiratory drive. Oxygen sensing glomus cells of the carotid bodies, express the angiotensin-converting enzyme 2 receptors used by COVID-19 to infect cells. In a healthy person, hypoxemia stimulates carotid body neural activity triggering reflex stimulation of breathing and tachycardia. If COVID-19 infected the carotid bodies, the cells might not respond to hypoxemia.*

Methods: *We performed a prospective observational pilot study where the ventilatory responses to breath holding tests in hospitalized patients with COVID-19 were compared to healthy controls in a single medical center. The aim was to determine whether ventilatory responses to hypoxia produced by breath holding in COVID-19 patients were different from those in volunteers without COVID-19.*

Results: *In comparison to the control group, COVID-19 patients had significantly less post breath-holding respiration rate increase after maximal breath hold effort. COVID-19 patients also had significantly less post breath-holding desaturation after maximal breath hold effort in unadjusted analysis but not statistically significant in the adjusted model. This prospective observational study demonstrated that COVID-19 infection is associated with a statistically significantly smaller breath-holding increase in respiratory rate.*

Conclusions: *The findings indicate that COVID-19 may cause a blunted hypoxic ventilatory response in the infected patients during the early stages of pandemic.*

Keywords: Ace2 Receptors, Carotid Bodies, COVID-19, Silent Hypoxia

1. Introduction

In the early months of the pandemic caused by the severe acute respiratory syndrome coronavirus 2 associated disease (COVID-19), there were clinical reports of patients with COVID-19 who did not exhibit dyspnea [1], despite having hypoxemia and evidence of impaired pulmonary gas exchange [2]. This phenomenon was described as "happy" or "silent hypoxia."

To pathophysiologically explain "silent hypoxia" it was hypothesized that COVID-19 may be invading and altering structures vital to the normal respiratory drive. In an otherwise

healthy person, carotid bodies are peripheral chemoreceptors for monitoring arterial blood oxygen levels, and hypoxemia stimulates carotid body neural activity triggering reflex stimulation of breathing and tachycardia [3,4]. Peripheral chemoreceptors work together with central chemoreceptors to further regulate respiratory output by detecting carbon dioxide and acidemia [4]. In cases of hypoxemia, hypercapnia, or acidemia an inappropriate ventilatory response may indicate chemoreceptor insensitivity [5]. Since coronavirus has been known to infect neuronal cells [6], including those in the medullary cardiorespiratory center [7], it was suggested that COVID-19 may also infect the carotid bodies via the angiotensin-converting enzyme 2 receptor [8]. Moreover, both coronavirus RNA and protein have been detected in the carotid bodies of patients who died of COVID-19 [9,10]. However, despite this potential pathophysiologic mechanism, silent or happy hypoxia had not been empirically confirmed beyond isolated anecdotal case reports.

As a result, the purpose of this study was to test for a blunted hypoxic ventilatory response in hospitalized patients with COVID-19. We hypothesized that hospitalized patients with COVID-19 would exhibit: 1) less change in respiratory rate in response to breath holding, and 2) greater tolerance to oxygen-hemoglobin desaturation.

2. Methods

2.1. Study Design

We performed a prospective observational study at the University of Chicago Medical Center (UCMC) where the ventilatory responses in hospitalized patients with COVID-19 were compared to the ventilatory responses in healthy controls. The study was approved by the UCMC IRB #20-0898. Clinical Trial Registration was NCT04954157.

2.2. Recruitment

Forty study participants at the UCMC were recruited from July through December of 2020, and enrolled according to the following inclusion criteria: COVID-19 positive and ≥18 years old. COVID-19 positivity was determined by laboratory PCR test drawn at the time of presentation to the hospital emergency room. Patients eligible for study participation were identified using the electronic health record (EHR) and recruited by an attending physician not involved in the patient's care. Non-English-speaking patients, patients requiring intubation or high flow (>6L O2) nasal cannula, and patients not admitted to the general medicine services were excluded. Forty healthy control subjects were also recruited and enrolled through advertising the study and its aims across the UCMC. Healthy controls were recruited from May through June of 2021. Figure 1 illustrates the participant flow diagram. For both COVID-19 and healthy control subjects' consent was obtained via a Redcap database.

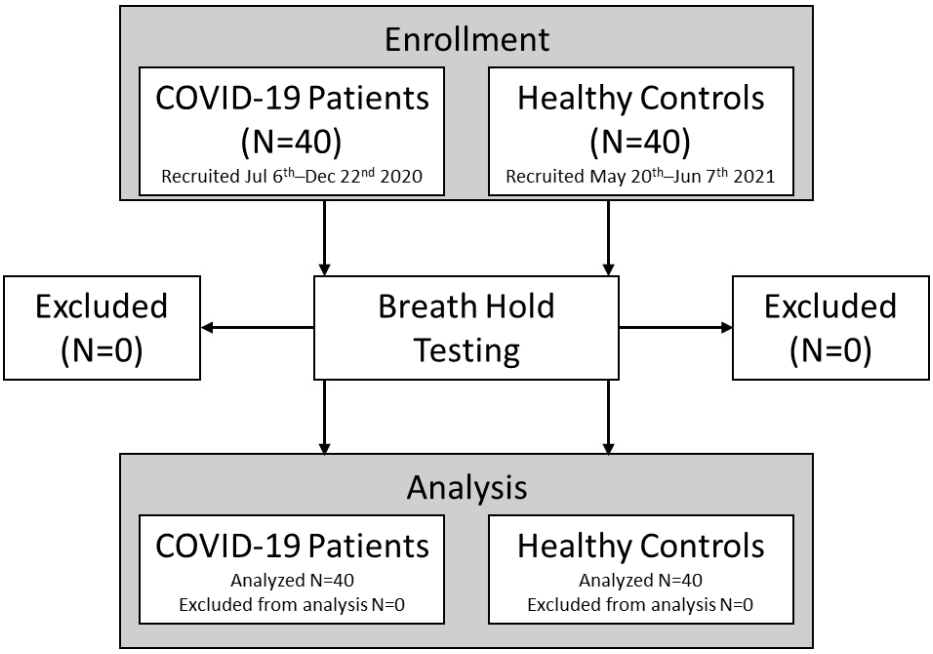

Figure 1: Participant Flow Diagram

2.3. Breath Holding Test for Ventilatory Response

Participants, under supervision of a study attending physician, were instructed to perform a trial of holding their breath beginning at functional residual capacity (i.e., after a normal inhalation and exhalation) for a maximal effort duration while in the sitting position. For each subject three trials were attempted with a 5-minute interval between each trial. Peripheral oxygen saturation (SpO2), respiratory rate (RR), heart rate (HR), and blood pressure were monitored by telemetry (Intellivue X3, Philips, Amsterdam NL) and recorded before the first trial as a baseline and after every trial. To ensure patient safety the attending physician monitored subjects during the trial and if they experienced dizziness, if their SpO2 fell below 85% or by an absolute drop of more than 8%, or if their HR changed more than 30% from baseline, subjects were told to discontinue the breath hold attempt and resume breathing. After discontinuing

the trial, patients were allowed to recover to the baseline before attempting another trial. If patients felt any discomfort, they were allowed to stop the trials completely and end their study participation. While COVID-19 patients underwent the study procedures in their rooms on the inpatient wards, healthy subjects participated in research rooms equipped with normal medical equipment to allow for close subject monitoring. Breath holding tests were administered during daytime hours.

2.4. Additional Data

In addition to the data collected during the breath-holding test, routine demographic, and clinical data (age, sex, race, height, and weight) were captured from the EHR on consenting patients. Height and weight were used to calculate body mass index (BMI). Whether the patient had a history of smoking, diabetes, pulmonary and/or cardiovascular disease was also captured from the EHR. The heterogenuous nature of the patient population made exact matching of the control group to them difficult.

2.5. Statistical Analysis

The data from the breath hold trial with the maximal breath hold time for each patient was used as the primary test for statistical consideration. If multiple trials from the same patient shared the same breath hold time, the following criteria were used in descending priority to select a single trial: greatest drop in SpO2 (desaturation), greatest rise in RR, greatest rise in HR.

We created two separate linear regression models to evaluate the association between COVID-19 infection and inappropriate ventilatory response:

• COVID-19 infection (independent variable) and post breath-holding RR increase after maximal breath hold effort (dependent variable). Post breath-holding RR increase after maximal breath hold effort was defined as the RR after maximal breath hold effort minus the patient's baseline RR.

• COVID-19 infection (independent variable) and post breath-holding desaturation after maximal breath hold effort (dependent variable). Post breath-holding desaturation after maximal breath hold effort was defined as the patient's baseline SpO2 minus their SpO2 after maximum breath hold effort.

• From these regression models we calculated both unadjusted and adjusted estimates of the association between the independent and dependent variables. Based on literature review [11–26] we controlled for and included the following variables in the adjusted models: age (≥50 vs. <50), sex (male vs. female), race (Black/African-American vs. all others), obesity (BMI ≥30 vs. <30), current smoking status (yes/no), history of asthma (yes/no), history of COPD (yes/no), history of congestive heart failure (yes/no), history of hypertension (yes/no), history of type 2 diabetes (yes/no), maximal breath hold time (seconds), baseline desaturation (<95% vs. ≥95%), and whether the subject was on nasal cannula oxygen at the time of conducting the study (yes/no). T-tests (continuous variables) and Fisher's exact tests (categorical variables) were used to compare the baseline characteristics of COVID-19 and healthy control subjects. Prism 9.4.1 (GraphPad, San Diego, CA) was used to perform all statistical analyses. A p-value of 0.05 was used to determine statistical significance.

• It is possible that CO2 levels were changing during breath holding, producing concomitant changes in pH which would be detected by central and peripheral chemoreceptors. The relatively brief nature of the breath holding by the COVID-19 patients suggests that these changes may be small. During the early stages of the pandemic when the study was carried out, end tidal measurements of CO2 were not possible, nor was it permissible to alter O2 levels breathed by COVID-19 patients from 100%.

3. Results

Baseline characteristics for COVID-19 and control group are described in Table 1. COVID-19 patients were more likely to be older, black, have higher BMI, have history of type 2 diabetes mellitus, history of hypertension and have shorter maximal breath hold time. At baseline, COVID-19 patients were also more likely to have lower diastolic blood pressure, higher heart rate, higher respiratory rate and lower SpO2. Fifteen (15, 37.5%) COVID-19 patients were on nasal cannula oxygen at the time of conducting the study compared to no subjects on nasal cannula oxygen in the healthy control group.

Characteristic	COVID-19 Patients (n=40)	Control Volunteers (n=40)	p-value
Age	58 [53, 63]	51 [47, 55]	<0.05
Female	18 (45)	18 (45)	
Race/Ethnicity			
Black/African American	29 (73)	15 (38)	<0.01
All Others	11 (29)	25 (63)	
BMI	32 [30, 34]	29 [27, 31]	<0.05
Current Cigarette Smoker	2 (5)	2 (5)	
Comorbidities			
Asthma	10 (25)	6 (15)	0.40
COPD	5 (13)	1 (3)	0.20
Diabetes Mellitus	13 (32.5)	2 (5)	<0.01
Hypertension	21 (52.5)	4 (10)	<0.01

Congestive Heart Failure	4 (10)	0	0.12
Nasal Cannula	15 (38)	0	<0.01
Baseline Vital Signs			
Systolic blood pressure, mm Hg	121 [117, 126]	127 [121, 133]	0.13
Diastolic blood pressure, mm Hg	74 [71, 78]	81 [77, 85]	<0.05
Heart rate, beats/min	82 [78, 86]	73 [69, 77]	<0.01
Respiratory rate, breaths/min	18 [17, 20]	14 [13, 15]	<0.01
SpO2, %	96 [95, 97]	99 [98, 99]	<0.01
Mild desaturation at baseline, <95% SpO2	14 (35)	0	<0.01
Breath Holding Measurements			
Breath Hold time, seconds	27 [23, 30]	46 [41, 52]	<0.01
Desaturation, %	3 [2, 3]	5 [4, 6]	<0.01
Change in Respiratory Rate, breaths/min	4 [3, 5]	6 [5, 8]	<0.01
Change in Heart Rate, beats/min	4 [2, 6]	8 [6, 11]	<0.05

Table 1. Baseline Characteristics

Continuous data are expressed as Mean [95% Confidence Interval] and categorical data expressed as N (%). Unpaired t-test was used to compare two means. Fisher's exact test was used to compare two categorical variables with binary outcomes.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; SpO2, peripheral oxygen saturation.

Variable	β Estimate	95% Confidence Interval	P value
COVID-19	-2.96	-5.32, -0.61	0.01
Nasal Cannula	1.57	-1.10, 4.25	0.24
Age≥50	-1.29	-3.03, 0.46	0.15
Black	2.64	0.91, 4.37	0.00
Female	0.73	-0.99, 2.45	0.40
Current Smoker	2.58	-0.95, 6.10	0.15
Breath Hold time	0.06	0.00, 0.11	0.04
Desaturation	0.16	-0.09, 0.41	0.21
Mild Desaturation at Baseline	0.31	-2.13, 2.75	0.80
Obese	0.25	-1.58, 2.07	0.79
Asthma	0.56	-1.52, 2.64	0.59
COPD	-1.98	-5.21, 1.24	0.22
Diabetes Mellitus	1.80	-0.98, 4.59	0.20
Hypertension	0.64	-1.60, 2.88	0.57
Congestive Heart Failure	-1.50	-5.94, 2.95	0.50

Table 2: Association Between Breath Holding Variables and Change in Respiratory Rate

All subjects (COVID-19 patients and control groups) were able to complete at least one trial of the breath holding. COVID-19 patients had significantly less post breath-holding RR increase after maximal breath hold effort in both unadjusted (β=-2; 95% CI -4 to -1; p-value <0.01) as well as adjusted analysis. (β=-3; 95% CI -5 to -1; p-value 0.01) (Table 2). COVID-19 patients also had significantly less post breath-holding desaturation after maximal breath hold effort in unadjusted analysis (β=-2; 95% CI -3 to -1; p-value <0.01). However, this difference was not statistically significant in the adjusted model (β=-2; 95% CI -4 to 0.1; p-value 0.06) (Table 3).

Variable	β Estimate	95% Confidence Interval	P value
COVID-19	-2.15	-4.39, 0.09	0.06
Nasal Cannula	-0.43	-3.04, 2.19	0.75
Age≥50	-1.89	-3.53, -0.25	0.02
Black	-0.44	-2.13, 1.24	0.60
Female	-1.52	-3.16, 0.12	0.07
Current Smoker	-0.97	-4.41, 2.47	0.57
Breath Hold time	0.04	-0.01, 0.09	0.15
Mild Desaturation at Baseline	0.60	-1.79, 2.98	0.62
Obese	0.83	-0.94, 2.60	0.35
Asthma	1.36	-0.65, 3.36	0.18
COPD	-0.11	-3.25, 3.04	0.95
Diabetes Mellitus	0.33	-2.40, 3.05	0.81
Hypertension	2.20	0.07, 4.32	0.04
Congestive Heart Failure	-0.41	-4.76, 3.93	0.85

The β estimate describes the change in desaturation for every unit of change in the variable. The variables that had a significant β estimate ($p<0.05$) were Age and Hypertension. Reference levels are as follows: No COVID-19, no nasal cannula, age < 50 years old, not Black, male, not a current smoker, no mild desaturation at baseline (≥ 95% SpO_2), not obese, no history of asthma, no history of COPD, no history of type II diabetes mellitus, no history of hypertension, no history of congestive heart failure.

Table 3: Association Between Breath Holding Variables and Desaturation

4. Discussion

This prospective observational study demonstrated that after a maximal breath holding effort, COVID-19 infection is associated with a statistically significantly smaller post breath-holding increase in respiratory rate, and a non-statistically significant higher post breath-holding oxygen-hemoglobin desaturation. Although the effect of COVID-19 on post breath-holding oxygen-hemoglobin desaturation did not meet the threshold for statistical significance, the confidence interval was skewed negative, suggesting that the effect is real, but our study was not powered to detect it. A post breath-hold smaller increase in respiratory rate and greater oxygen-hemoglobin desaturation due to COVID-19 are consistent with each other and indicative of a poor ventilatory response, suggesting that the effects we observed are indeed real. Moreover, we believe that our breath holding experiment likely induced the necessary decreased PaO2 and increased PaCO2 levels to trigger a ventilatory response, based on previous data demonstrating a ventilatory response in healthy subjects holding their breath for over 35 seconds [27]; in our study the mean breath hold times for COVID-19 and control groups were 26.5 and 46.4 seconds, respectively. Additionally, increases in ventilation in relation to PCO2 may manifest as an increase in tidal volume or an increased respiratory rate [28], and as such our study may have undermeasured the degree to which COVID-19 suppresses a patient's ventilatory response. As a result, this study is the first to empirically assess the silent hypoxemia phenomenon that was described in the initial stages of the COVID-19 pandemic, and our findings suggest that COVID-19 may cause a blunted hypoxic ventilatory response.

These findings have several important implications. First, although the availability of vaccination and biologic therapeutics has mitigated the worse effects of COVID-19 both globally and in individual patients, triaging patients with COVID-19 who may be likely to decompensate and need acute hospitalization remains a significant challenge. Our study suggests that breath-holding tests could be included as part of a bundle of clinical tests and signs that are used as a triage tool [29] to identify the highest risk patients with COVID-19. Second, our results suggest that the pathways and physiologic mechanisms of hypoxemia and respiratory response with COVID-19 infection are to date incompletely described in the literature. Given that COVID-19 appears to have become endemic [30], building on our work future investigations are warranted to better understand how the different strains of coronavirus generally and COVID-19 specifically affect critical physiologic functions. This is important for developing interventions and targeted therapeutics in the future that address and can reduce the risk of the most serious adverse outcomes of a coronavirus infection.

As an observational study there are limitations to our findings. Our sample size is consistent with a pilot study, and we were most likely underpowered to detect the associations we examined. The strains and the presentations of COVID-19 also changed during our recruitment period, and although it seems unlikely, different strains could have different effects on ventilatory response. We also did not measure end-tidal or arterial CO2 given COVID-19 clinical protocols, and so we had to use respiratory rate and oxygen-hemoglobin desaturation as surrogate markers for a patient's ventilatory response. Last, we did not remove the low flow O2 nasal cannula for patients on it at the time of their tests due to the concerns of patient safety, which could have affected the results. However, we found no difference in the results between the COVID-19 patients with or without an O2 nasal cannula in our sensitivity analysis.

Interpretation

COVID-19 infection may cause a blunted hypoxic ventilatory response, a phenomenon known as “happy hypoxemia”. A blunted hypoxic ventilatory response may be predictive of severity of coronavirus infection and can be easily and safely administered at the bedside to evaluate patients with COVID-19.

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Financial/Nonfinancial Disclosures

The authors have reported to CHEST the following: None.

Conflict of Interest: None.

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Data Sharing

Raw data (after de-identification) that underlie the published results on request can be shared with researchers who provide a methodologically sound proposal, provided that our data indeed serve to achieve the aims in that proposal.

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