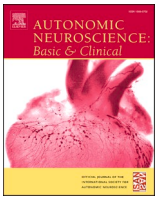
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Autonomic Neuroscience: Basic and Clinical 235 (2021) 102855

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu



Characteristics and predictors for silent hypoxemia in a cohort of hospitalized COVID-19 patients

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ARTICLE INFO

Keywords:
COVID-19
Happy hypoxemia
SARS-CoV-2
Silent hypoxemia

ABSTRACT

Background: An intriguing feature recently unveiled in some COVID-19 patients is the "silent hypoxemia" phenomenon, which refers to the discrepancy of subjective well-being sensation while suffering hypoxia, manifested as the absence of dyspnea.
Objective: To describe the clinical characteristics and predictors of silent hypoxemia in hospitalized COVID-19 patients.
Methods: We conducted a prospective cohort study including consecutive hospitalized adult ($\geq$ 18 years) patients with confirmed COVID-19 presenting to the emergency department with oxygen saturation (SpO2) $\leq$ 80% on room air from March 15 to June 30, 2020. We analyzed the characteristics, disease severity, and in-hospital outcomes of patients presenting with dyspnea and those without dyspnea (silent hypoxemia).
Results: We studied 470 cases (64.4% men; median age 55 years, interquartile range 46–64). There were 447 (95.1%) patients with dyspnea and 23 (4.9%) with silent hypoxemia. The demographic and clinical characteristics, comorbidities, laboratory and imaging findings, disease severity, and outcomes were similar between groups. Higher breathing and heart rates correlated significantly with lower SpO_2 in patients with dyspnea but not in those with silent hypoxemia. Independent predictors of silent hypoxemia were the presence of new-onset headache (OR 2.919, 95% CI 1.101–7.742; $P = 0.031$) and presenting to the emergency department within the first eight days after symptoms onset (OR 3.183, 95% CI 1.024–9.89; $P = 0.045$).
Conclusions: Patients with silent hypoxemia sought medical attention earlier and had new-onset headache more often. They were also likely to display lower hemodynamic compensatory responses to hypoxemia, which may underestimate the disease severity.

1. Introduction

In late December 2019, an outbreak of pneumonia of unknown etiology emerged in Wuhan City, Hubei Province of China. By January 7, 2020, a new strain of β-coronavirus, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified (Zhu et al., 2020). The disease spread worldwide rapidly, and on March 11, 2020, it was declared a pandemic by the World Health Organization (World Health Organization, 2020). SARS-CoV-2-associated disease (COVID-19) can lead to massive respiratory tract damage and fatal lung failure, mainly secondary to pulmonary vascular pathology (Ackermann et al., 2020; Hariri et al., 2021; Salazar-Orellana et al., 2021). Still, the reported symptoms have substantial variations among series. According to two meta-analyses, the most frequent symptoms are fever (88.7–91.0%), cough (57.6–67.0%), fatigue (29.4–51.0%), and dyspnea (30–45.6%) (Latin American Network of Coronavirus Disease 2019-COVID-19 Research (LANCOVID-19). Electronic address: https://www.lancovid.org et al., 2020; Yang et al., 2020). Given the extensive lung damage that

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https://doi.org/10.1016/j.autneu.2021.102855
Received 21 February 2021; Received in revised form 8 June 2021; Accepted 12 July 2021
Available online 17 July 2021

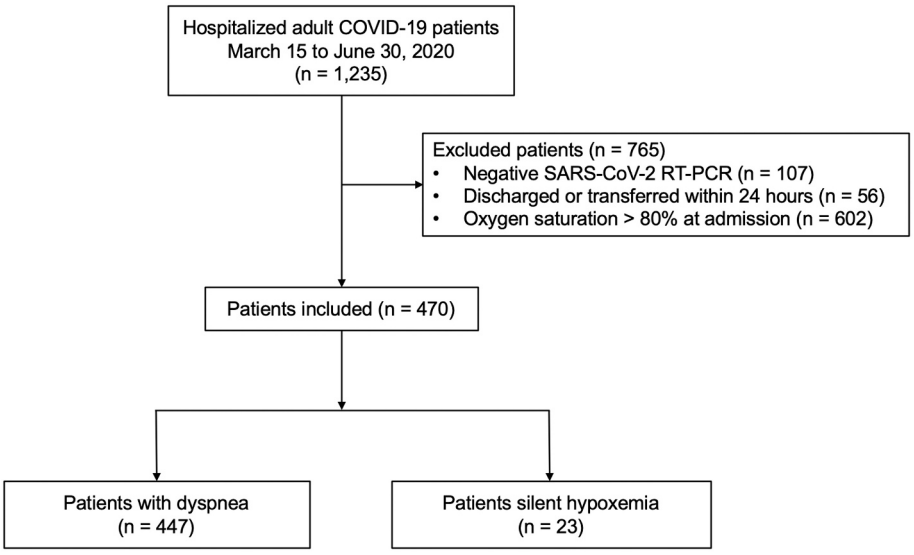

Fig. 1. Patient selection flowchart.

some patients exhibit, the low percentage of dyspnea as the presenting symptom by several studies is remarkable. Many reports have addressed this observation using terms like "silent," "apathetic," or "happy" hypoxemia to describe the lack of self-awareness to hypoxia, with or without signs of respiratory distress (Dhont et al., 2020; González-Duarte and Norcliffe-Kaufmann, 2020; Ottestad et al., 2020).

Dyspnea, defined as the subjective experience of breathing discomfort, consists of qualitatively distinct sensations that vary in intensity that must be distinguished from objective signs of respiratory distress such as tachypnea, use of accessory muscles, and intercostal retractions (Parshall et al., 2012). Emerging hypotheses implicate the neuroinvasive potential of SARS-CoV-2, or the loss of function of the peripheral afferent receptors may play a key role in its development (Dhont et al., 2020; González-Duarte and Norcliffe-Kaufmann, 2020; Jiménez-Ruiz et al., 2020; Li et al., 2020; U.R., 2020). However, the evidence for this phenomenon in COVID-19 patients derives only from a few case reports (Ottestad et al., 2020; Wilkerson et al., 2020). Herein, we aimed to describe the clinical characteristics and predictors of silent hypoxemia in a cohort of hospitalized patients with confirmed COVID-19.

2. Methods

2.1. Study design, setting and participants

This prospective cohort study was conducted at the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán*. A third-level hospital converted as a referral center for COVID-19 patients in Mexico City. Early after conversion, standardized case assessment formats, diagnostic and care protocols for COVID-19 patients were implemented at our center. All patients under invasive mechanical ventilation (IMV) were admitted to the intensive care unit (ICU) or other ICU-adapted areas, while non-IMV patients were treated in general medical wards. When beds in the ICU were unavailable, patients requiring IMV were referred to other hospitals with ICU bed availability (Olivas-Martínez et al., 2021). All patients or relatives signed written informed consent at admission as part of an institutional consent for observational studies during the COVID-19 pandemic. The Local Research and Ethics Committee approved the conduction of this study (NER-3497-20-20-1).

As part of an ongoing study on COVID-19-associated neurologic manifestations, clinical data of all hospitalized patients with confirmed COVID-19 were captured using standardized case report formats and entered into a secure online database derived from electronic medical records used for multiple observational studies (Flores-Silva et al., 2021). Here we present specifically the analysis on silent hypoxemia. We analyzed consecutive patients from March 15 to June 30, 2020, who had confirmed COVID-19 pneumonia by chest computed tomography (CT) scans and positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (rt-RT-PCR) in respiratory fluids from nasal swabs. Our study included adult ($\geq$ 18 years) hospitalized patients who presented to the Emergency Department (ED) with severe hypoxemia defined as an oxygen saturation (SpO_2) $\leq$ 80% on room air. We excluded patients with negative rt-RT-PCR for SARS-CoV-2 and those discharged or transferred to other hospitals within the first 24 h after admission.

2.2. Data collection

Data for this analysis were extracted from the electronic medical records using a standardized case report format created for this analysis and recorded in an electronic database. Data collection included demographic characteristics; comorbidities (hypertension, diabetes, active smoking, and obesity), history of cardiovascular (myocardial infarction, peripheral artery disease, stroke, heart failure or atrial fibrillation), and pulmonary disease (chronic obstructive pulmonary disease, asthma, idiopathic interstitial pneumonia or chronic pulmonary hypertension). COVID-19-associated symptoms (fever, rhinorrhea, cough, headache, anosmia/dysgeusia, myalgia/arthralgia, nausea/vomiting, and diarrhea), time from symptoms onset to hospital presentation, pre-admission treatments for COVID-19 (nonsteroidal anti-inflammatory drugs [NSAIDs] and steroids), initial vital signs (blood pressure, heart rate, breathing rate, temperature and SpO2 on room air); laboratory evaluation including complete blood count, blood chemistries (renal and liver function tests, creatine kinase and lactate dehydrogenase [LDH]), inflammatory response biomarkers (serum ferritin, D-dimer, C-reactive protein and fibrinogen), arterial blood gas (ABG) analysis all of them with local reference values, chest CT scan findings, requirement of IMV/ICU, hospital length of stay, and in-hospital outcome. Two researchers reviewed all data, and a third researcher adjudicated any difference in interpretation between the two primary reviewers.

2.3. Definitions

According to the American Thoracic Society, we defined dyspnea as the sensation of "air hunger, breathlessness, uncomfortable, difficult, or labored" breathing reported by the patient on arrival, regardless of the presence of objective signs of respiratory distress such as tachypnea, use of accessory muscles, and intercostal retractions (Parshall et al., 2012).

Table 1
Baseline characteristics.

	Total (n = 470)	Dyspnea (n = 447)	No dyspnea (n = 23)	*P*-value
Gender, male, n (%)	312 (64.4)	296 (66.2)	16 (69.6)	0.824
Age, years, median (IQR)	55 (46–64)	55 (46–64)	52 (42–67)	0.459
Days from symptoms onset, median (IQR)	8 (6–11)	8 (6–12)	6 (2–8)	0.001
≤8 days from symptoms onset, n (%)	256 (54.5)	238 (53.2)	18 (78.3)	0.019
Risk factors, n (%)				
Diabetes	157 (33.4)	148 (33.1)	9 (39.1)	0.651
Hypertension	164 (34.9)	157 (35.1)	7 (30.4)	0.823
Cardiovascular disease	26 (5.5)	26 (5.8)	0	0.234
Pulmonary disease	24 (5.1)	23 (5.1)	1 (4.3)	0.865
Smoking	64 (13.6)	61 (13.6)	3 (13)	0.934
Obesity, BMI ≥ 30 kg/m^2	228 (48.5)	216 (48.3)	12 (52.2)	0.831
Symptoms, n (%)				
Fever	393 (83.6)	375 (83.9)	18 (78.3)	0.477
Rhinorrhea	59 (12.6)	58 (13)	1 (4.3)	0.223
Cough	358 (76.2)	344 (77)	14 (60.9)	0.084
Headache	170 (36.2)	157 (35.1)	13 (56.5)	0.045
Anosmia/Dysgeusia	23 (4.9)	22 (4.9)	1 (4.3%)	0.901
Myalgia/Arthralgia	158 (33.6)	151 (33.8)	7 (30.4)	0.824
Diarrhea	59 (12.6)	56 (12.5)	3 (13)	0.942
Nausea/vomiting	32 (6.8)	32 (7.2)	0	0.184
Altered mental status	9 (1.9)	9 (2)	0	0.492
Pre-admission treatments, n (%)				
Steroids	24 (5.1)	24 (5.4)	0	0.254
NSAIDs	112 (23.8)	106 (23.7)	6 (26.1)	0.803
Vital signs, median (IQR)				
SpO_2 on room air, %	70 (58–76)	70 (57–76)	76 (60–79)	0.024
Breathing rate, bpm	30 (26–35)	30 (26–36)	22 (20–26)	<0.001
Tachypnea, >20 bpm	443 (94.3)	442 (94.4)	21 (91.3)	0.386
Heart rate, bpm	104 (91–116)	104 (91–116)	102 (85–117)	0.438
Systolic BP, mmHg	126 (110–136)	125 (110–136)	126 (120–140)	0.205
Diastolic BP, mmHg	74 (68–82)	74 (64–82)	78 (69–80)	0.718
Temperature, °C	37 (36.5–37.4)	37 (36.5–37.3)	37.1 (36.5–37.5)	0.266

Abbreviations: IQR, interquartile range; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; SpO_2, oxygen saturation; BP, blood pressure.

SpO_2 and vital signs were obtained with a Dräger Vista 120 patient monitor (Dräger Medical GmbH, Lübeck, Germany). Silent hypoxia was defined as the absence of dyspnea with a $SpO_2 \leq 80\%$ on room air, measured upon arrival to the ED. In addition, all patients had critical an arterial partial pressure of oxygen to inspired oxygen fraction ratio ($PaO_2/FiO_2 < 300$ mmHg) upon admission. Obesity was defined as having a body mass index (BMI) ≥ 30 kg/m^2. In all patients, a chest CT was performed and evaluated by experienced radiologists. They semi-quantitatively classified the lung involvement's severity by visual assessing the total pulmonary consolidation/ground-glass opacities as mild (extension of the disease in less than 20% of the pulmonary parenchyma), moderate (20–50%), or severe (>50%). We calculated the arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio, and the alveolar-arterial oxygen (A-a O_2) gradient (adjusted for barometric pressure and age) (Pérez Padilla and Vázquez García, 2000; Petersson and Glenny, 2014), using the estimated FiO_2 provided by each oxygen delivery device (nasal cannula or simple face mask) according to the oxygen flow rate (L/min) when the first arterial blood samples for ABGs measurement were obtained (Hardavella et al., 2019). We categorized the disease severity at admission according to the National Early Warning Score 2 (NEWS2) (Royal College of Physicians, 2017), and the risk of progression with the comorbidities, age, lymphocyte count, and LDH (CALL) scoring model (Ji et al., 2020).

2.4. Statistical analysis

We compared the characteristics of severely hypoxemic ($SpO_2 \leq 80\%$) patients presenting with dyspnea and those without dyspnea (silent hypoxemia). Categorical variables are reported as frequencies and proportions, and continuous variables are described as median with interquartile range (IQR). Analyses of differences for independent groups between categorical variables were performed with the X^2 test or Fisher's exact test as appropriate and for non-parametric continuous variables with the Mann-Whitney *U* test. For relevant relative frequencies (prevalence), we calculated the 95% confidence intervals (CI) as an estimation of the systematic error, with the maximum likelihood estimate method, given the sample size. Pearson correlation coefficient was used in the continuous association between SpO_2, heart rate, and breathing rate between groups. We performed a binary logistic regression analysis to determine predictors of silent hypoxia, including all the independent co-variables based on biological plausibility and those with a *P*-value ≤0.1, and evaluated by the Hosmer-Lemeshow goodness of fit test, which was considered reliable when the *P*-value was ≥0.20. The final model was adjusted for model adjusted for age, sex, comorbidities, pre-admission treatments, COVID-19 clinical manifestations, vital signs, SpO_2 on room air, arterial blood gases, PaO_2/FiO_2 ratio, glucose, creatinine, serum lactate, hemoglobin, inflammatory response biomarkers, neutrophil/lymphocyte ratio, and chest CT findings. Odds ratios (OR) with 95% CI were calculated. All values were two-tailed and considered significant when *P*-value was ≤0.05. All statistical analyses were performed with IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA).

3. Results

During the study period, 1235 patients with COVID-19 were hospitalized in our center. We excluded 765 cases for the following reasons: 107 had negative (one or multiple) SARS-CoV-2 rt-RT-PCR, 56 were discharged or transferred to other hospitals within the first 24 h after admission, and 602 with a SpO_2 on room air >80% (Fig. 1). We studied 470 cases (64.4% men; median age 55 years, IQR 46–64), presenting within the first eight days after symptoms onset in 54.5%. The most common comorbidities were obesity in 48.5% of cases, followed by hypertension and diabetes in 34.9% and 33.4%, respectively. None of the patients with silent hypoxemia had a history of using opioids, benzodiazepines, or bronchodilators. The most frequent symptoms were fever in 393 (83.6%) cases, dry cough in 358 (76.2%), and new-onset headache in 170 (36.2%). There were 447 (95.1%) patients with dyspnea and 23 (4.9%) with silent hypoxemia. We present the baseline characteristics of patients with dyspnea and those without dyspnea in Table 1.

There were no demographic differences in comorbidities and pre-admission treatments for COVID-19 between groups. Patients with silent hypoxemia arrived two days earlier than those with dyspnea (median 6 days, IQR 2–8 vs. 8, IQR 6–15; $P < 0.001$). Also, patients with silent hypoxia had a higher frequency of new-onset headache (56.5% vs. 35.1%; $P = 0.045$). Patients with dyspnea had a lower SpO_2 (70% vs. 76%; $P = 0.024$) and higher breathing rate (median 30 bpm, IQR 26–36 vs. 22 IQR 20–26; $P = 0.008$). Higher breathing and heart rates correlated significantly with lower SpO_2 in patients with dyspnea but not in those with silent hypoxemia (Fig. 2). On blood gas analysis, there were no significant differences in pH, arterial partial pressure of oxygen (PaO_2), and arterial partial pressure of carbon dioxide ($PaCO_2$) levels among groups. The exception was that patients with dyspnea had lower serum bicarbonate (HCO_3-) levels but near normality (median 21.2 mmol/L, IQR 18.8–23.5 vs. 23.6, IQR 30.6–25.6; $P = 0.008$) (Table 2).

There were no differences in the percentage of lung involvement measured by chest CT scan or PaO_2/FiO_2 ratio. Patients with dyspnea

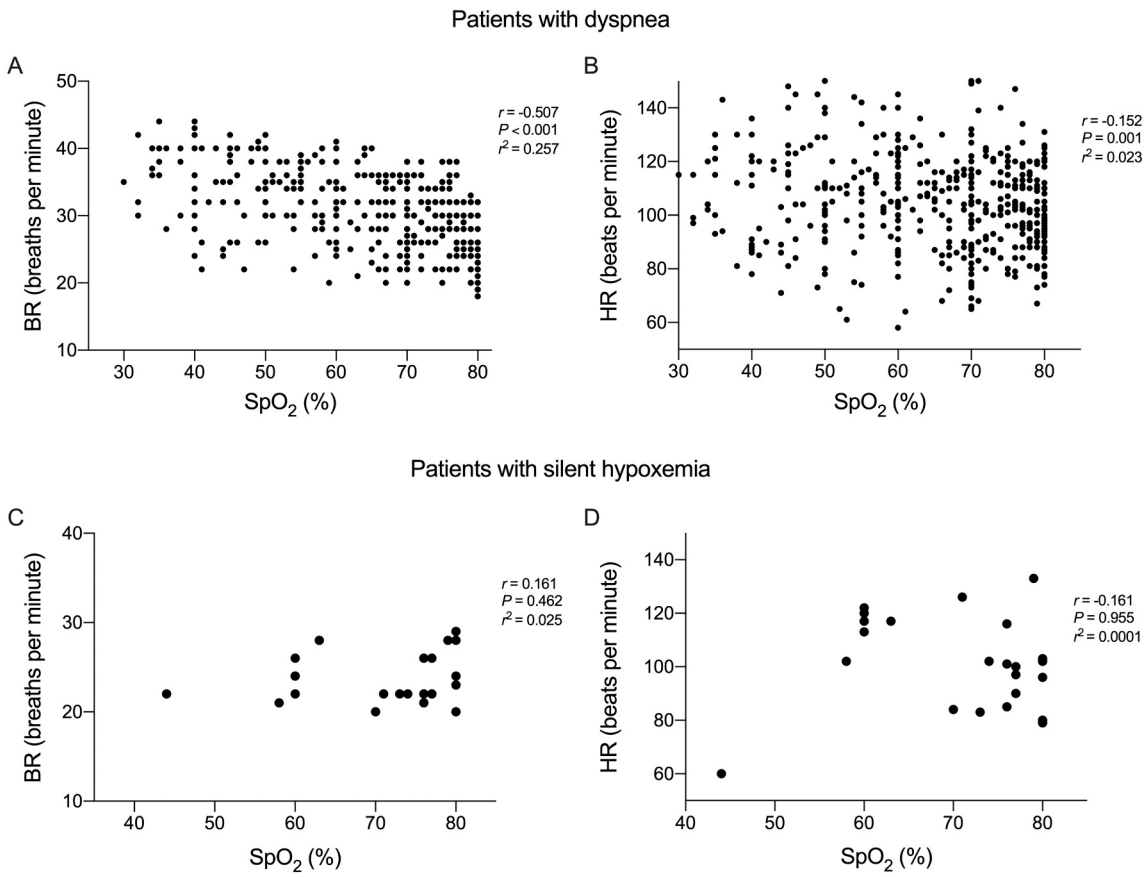

Fig. 2. Correlation between breathing rate and heart rate with oxygen saturation on room air at admission.
Plots show a statistically significant correlation between (A) breathing and (B) heart rates with lower SpO_2 levels in patients with dyspnea and no correlation between (C) breathing, (D) heart rates, and lower SpO_2 levels in patients with silent hypoxemia.
Abbreviations: SpO_2, oxygen saturation; BR, breathing rate; HR, heart rate.

had higher serum glucose levels (median 144 mg/dL vs. 109 mg/dL; $P = 0.002$), lactate (median 1.8 mmol/L, IQR 1.4–2.5 vs. 1.5, IQR 1–2.1; $P = 0.027$) and neutrophil/lymphocyte ratio (median 12.08, IQR 7.57–20.46 vs 8.26, IQR 5.89–12.29; $P = 0.015$). According to the NEWS2 score and CALL scoring model, the disease severity and the risk of illness progression were similar for both groups. Overall, there were no differences in the requirements of IMV/ICU, hospital length of stay, or in-hospital mortality rates (Table 3). In an adjusted multivariable model constructed to identify potential independent predictors of silent hypoxemia, the only factors associated with this clinical condition were presenting in ≤8 days after symptoms onset (OR 3.18, 95% CI 1.02–9.87; $P = 0.046$) and the presence of new-onset headache (OR 2.85, 95% CI 1.08–7.57; $P = 0.035$) (Hosmer-Lemeshow goodness of fit test: X^2 3.01, 2 df, $p = 0.22$).

4. Discussion

This study describes the clinical and laboratory characteristics of hospitalized patients with COVID-19 and silent hypoxemia in a tertiary hospital converted as a referral center for COVID-19 patients. In our cohort, the prevalence of silent hypoxemia was 4.89% (95% CI 3.13–7.25). Following the first descriptions of silent hypoxemia in COVID-19, many mechanistic hypotheses for this phenomenon were proposed (González-Duarte and Norcliffe-Kaufmann, 2020; Jounieaux et al., 2020; Tobin et al., 2020). Jounieaux and colleagues suggested silent hypoxemia could be the result of an acute vascular distress syndrome due to an increased physiological right-to-left intrapulmonary shunting resulting in ventilatory inhibition (Jounieaux et al., 2020; Jounieaux et al., 2021). However, the fact that patients have the same degree of inflammatory markers and pulmonary damage makes it difficult to support that only the shunts are solely responsible.

In this series, the $PaCO_2$ levels in our silent hypoxemia cases were near normality and, slightly higher than those observed in patients reporting dyspnea. Furthermore, demographics, comorbidities, systemic inflammatory response biomarkers, the extension of pulmonary parenchyma involvement measured by chest CT scan, and severity by PaO_2/FiO_2 ratio were similar between both groups. These similarities suggest that silent hypoxemia is not related to lung damage extension or increased systemic inflammation, yielding the possibility of neurologic dysfunction (González-Duarte and Norcliffe-Kaufmann, 2020; Li et al., 2020; U.R., 2020).

Supporting this hypothesis, we found that patients with silent hypoxemia had impaired hypoxia's hemodynamic compensatory physiological responses. In normal conditions, tachycardia and tachypnea are typically observed during systemic hypoxia. Hypoxic tachycardia is a consequence of a reduction in efferent vagal outflow to the heart from the primary afferent impulses of the respiratory centers located at the medulla oblongata. Likewise, hypoxemia and hypercapnia also raise breathing rates by increasing the respiratory center output. The inappropriate low respiratory rate and heart rate response suggest impaired chemoreflex sensitivity in patients with silent hypoxia (Dhont et al., 2020; González-Duarte and Norcliffe-Kaufmann, 2020; Tobin et al., 2020). In our series, $PaCO_2$ levels were similar despite that respiratory rates were significantly slower in silent hypoxemia patients. Furthermore, A recent series of silent hypoxemia found similar conditions where silent and dyspneic hypoxemic patients had similar $PaCO_2$ but significantly different respiratory rates, 24 bpm vs. 11.3 bpm respectively ($P = 0.002$) (Busana et al., 2021). The decreased physiological

Table 2
Laboratory and chest computed tomography findings.

	Total (n = 470)	Dyspnea (n = 447)	No dyspnea (n = 23)	*P*-value
Blood gas analysis, median (IQR)				
pH	7.44 (7.4–7.46)	7.44 (7.4–7.46)	7.44 (7.41–7.47)	0.398
$PaCO_2$, mmHg	31.2 (27.8–34.9)	31.1 (27.8–34.7)	33.4 (29.5–37.2)	0.71
HCO_3-, mmol/L	21.3 (18.9–23.7)	21.2 (18.8–23.5)	23.6 (20.6–25.8)	0.008
PaO_2, mmHg	63.5 (52.9–77.1)	63.5 (53.1–77.1)	66.4 (49–77.6)	0.922
FiO_2, %	60 (40–60)	60 (40–60)	60 (40–60)	0.935
PaO_2/FiO_2 ratio, mmHg	124.67 (96.67–173)	124.67 (96.67–172.75)	129.33 (82–196.67)	0.597
Elevated A-a O_2 gradient[a], n (%)	447 (95.1)	426 (95.3)	21 (91.3)	0.386
Blood workup, median (IQR)				
Glucose, mg/dL	141 (113−211)	144 (114–214)	106 (96–140)	0.002
Creatinine, mg/dL	1 (0.77–1.3)	1 (0.77–1.3)	1 (0.87–1.28)	0.885
Ureic nitrogen. mg/dL	20.5 (14.3–30.2)	20.55 (14.4–30.3)	18.9 (12.225.9)	0.28
Serum lactate, U/L	1.8 (1.4–2.5)	1.8 (1.4–2.5)	1.5 (1–2.1)	0.027
Lactic dehydrogenase, U/L	465 (365–596)	470 (365–598)	429 (333–572)	0.143
Creatine kinase, U/L	103.5 (56–211)	103 (56–207)	157 (60–350)	0.364
Ferritin, ng/dL	696.4 (408.8–1203.4)	708.25 (417.7–1222.4)	627 (315.7–916)	0.161
D-dimer, ng/dL	1092 (715–1997)	1092 (715–2009)	1100 (734–1834)	0.775
Fibrinogen, mg/dL	757 (630–906)	758 (630–913)	693 (544–798.5)	0.149
C-reactive protein, mg/dL	19.68 (14.07–28.23)	19.8 (14.25–28.24)	16.93 (6.5–25.68)	0.099
Hemoglobin, g/dL	15 (13.8–16.2)	15 (13.9–16.2)	14.6 (13.3–15.7)	0.118
Neutrophils, 10^9/L	8.63 (6.15–12.09)	8.68 (6.2–12.2)	7.52 (4.19–9.22)	0.017
Lymphocytes, 10^9/L	0.69 (0.48–0.99)	0.69 (0.46–1)	0.77 (0.61–0.93)	0.342
Neutrophil/lymphocyte ratio	11.79 (7.43–19.98)	12.08 (7.57–20.46)	8.26 (5.89–12.29)	0.015
Platelets, 10^9/L	245 (198–330)	245 (197–335)	254 (201–286)	0.797
Chest CT severity, n (%)				0.175
Mild, <20%	4 (0.9)	3 (0.7)	1(4.3)	
Moderate, 20%–50%	62 (13.2)	59 (13.3)	3 (13)	
Severe, >50%	402 (85.9)	383 (86.1)	19 (82.6)	

Abbreviations: IQR, interquartile range; $PaCO_2$, arterial partial pressure of carbon dioxide; HCO_3-, bicarbonate; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; A-a O_2, alveolar–arterial oxygen; CT, computed tomography.
[a] Adjusted for barometric pressure and age.

Table 3
Severity scores and in-hospital outcomes.

	Total (n = 470)	Dyspnea (n = 447)	No dyspnea (n = 23)	*P*-value
CALL Score, n (%)				0.254
Low risk	134 (28.5)	125 (28)	9 (39.1)	
Intermediate risk	184 (39.1)	174 (38.9)	10 (43.5)	
High risk	152 (32.2)	148 (33.1)	4 (17.4)	
NEWS2 Score, n (%)				0.051
Low risk	19 (4)	17 (3.8)	2 (8.7)	
Medium risk	88 (18.3)	80 (17.9)	8 (34.8)	
High risk	363 (77.2)	350 (78.3)	13 (56.8)	
Invasive mechanical ventilation, n (%)	172 (36.6)	166 (37.1)	6 (26.1)	0.376
Days of in-hospital stay, median (IQR)	7 (3–15)	7 (2–15)	7 (4–13)	0.86
Dead, n (%)	200 (42.6)	193 (43.2)	7 (30.4)	0.281

Abbreviations: CALL, comorbidities, age, lymphocyte count and lactic dehydrogenase; NEWS2, National Early Warning Score 2; IQR, interquartile range.

reactions and diminished self-awareness of dyspnea making patients not feeling ill, resulting in ignoring the severity of their illness. This may explain the so-called “happy hypoxemia” that became popular with the disease.

Recently, Busana et al., described the prevalence and outcome of silent hypoxemia in patients with COVID-19 (Busana et al., 2021). Similar to our findings, they found that silent and dyspneic hypoxemia patients had different respiratory rates and that the presence of dyspnea was associated with a more severe clinical condition. This study also described dyspnea upon presentation to the Emergency Department, based on the patients' subjective feeling of shortness of breath. They found a higher prevalence of 32%, but they also found no relationship to previous comorbidities or laboratory variables. Also of note is that silent hypoxemia patients had less respiratory and more extra-pulmonary symptoms than patients with dyspnea, highlighting our findings that those symptoms drove patients to seek medical attention instead of dyspnea. Finally, as in our series, patients with dyspnea had a more severe clinical condition than silent patients.

The brain gives the sensation of dyspnea or “air hunger” when it receives the signal of internal hypoxia. Three different inputs fine-tune the neural pathway of respiration: (1) PCO_2, and PO_2 sensed by the peripheral chemoreceptors, (2) cerebral PCO_2 sensed by the neurons in the brainstem, and (3) the neural feedback from muscles (Fig. 3) (Guyenet and Bayliss, 2015). Since none of the patients had alterations in the muscle control of breathing, the muscle neural feedback mechanisms are not involved. Jounieaux et al., and Busana et al., suggested that a ventilatory shunt produced by direct damage to the lungs may explain the absence of dyspnea. However, the carotid chemoreceptors are as capable as the pulmonary receptors to generate responses to hypoxemia (Busana et al., 2021; Jounieaux et al., 2021). Moreover, patients with silent hypoxemia patients had a similar degree of damage in the lugs and similar levels of hypoxia in our and Busanas' series.

We hypothesize that there is an abnormal autonomic control of respiration. Impairment may be localized in the afferent system, the pulmonary and aortic chemoreceptors, glossopharyngeal and vagal afferents, or directly into the brainstem. The absence of compensatory tachypnea and tachycardia suggests that the information was not transmitted to the somatosensory cortex (responsible for driving the air-hunger sensation) nor to the periphery to generate the compensatory hemodynamic responses to hypoxemia.

Interestingly, in this study, the development of new-onset headache was a predictor of silent hypoxemia, supporting a possible direct brainstem invasion by SARS-CoV-2, especially to the nucleus of the solitary tract, which participates in both pathophysiological processes (Benarroch, 2006). This tract has implications in pain modulation due to activation of the trigeminovascular system (Bolay et al., 2020; Caronna

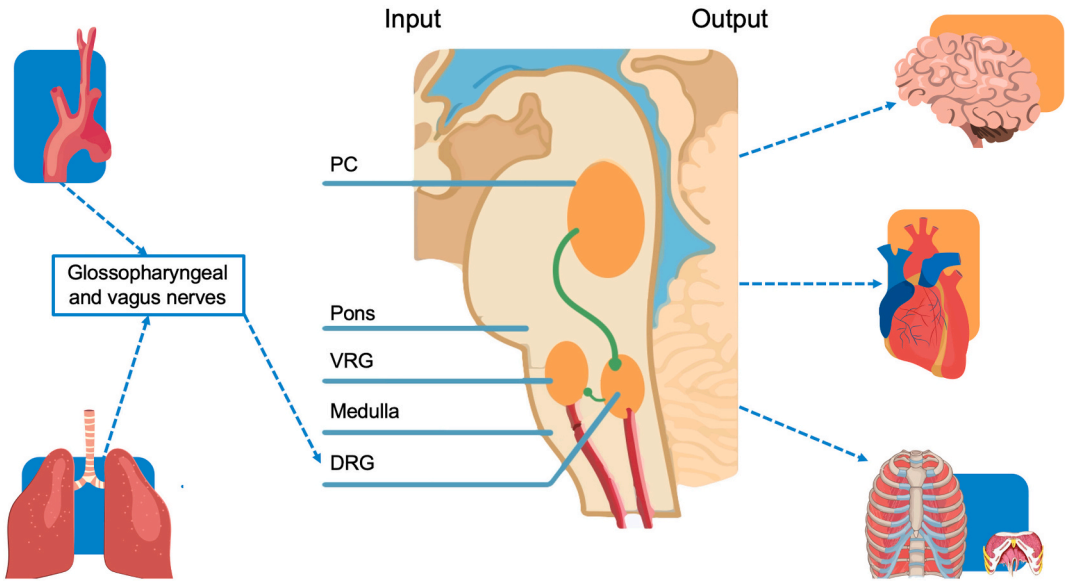

Fig. 3. Impaired neural regulation of breathing in COVID-19 patients with silent hypoxemia.
The dorsal respiratory group (DRG) is a subnucleus of the nucleus of the solitary tract (NTS). It contains a cluster of respiratory-modulated neurons. These neurons receive monosynaptic excitatory inputs from slowly adapting lung stretch receptors and peripheral chemoreceptors in the aortic and carotid bodies via the vagus and glossopharyngeal nerves. We hypothesize that in patients with silent hypoxemia, there is impaired sensing of low PaO_2 by the peripheral chemoreceptors, or decreased afferent nerve impulses from these receptors, resulting in the absence of compensatory tachycardia, tachypnea, and the sensation of "air hunger." Damage to the pulmonary parenchyma alone cannot explain the lack of hypoxemia sensing from the chemoreceptors of the carotid body, the principal mechanism by which mammals' sense lowered levels of oxygen. On the other hand, brainstem chemoreceptors are only sensitive to pH.
Abbreviations: PC, pneumotaxic center; VRG, ventral respiratory group; DRG, dorsal respiratory group.

et al., 2020); also, it participates in the control of the autonomic afferent functions coming from the carotid body, vagus, and glossopharyngeal nerves, causing a decreased sensation of dyspnea (González-Duarte and Norcliffe-Kaufmann, 2020). Therefore, we hypothesize that the presence of headache and silent hypoxia could have a clinical and pathophysiological relationship because of this common pathway, further inviting to investigate the neuroinvasive hypothesis for the development of silent hypoxemia.

A case series describing the characteristics of headache in 13 patients with confirmed COVID-19 found that it usually develops within the first days after illness onset (Toptan et al., 2020), and a different study, including 576 cases, found that headache is an independent predictor of lower mortality in hospitalized COVID-19 patients (Trigo et al., 2020); contrasting with our findings in which disease severity, requirements of IMV/ICU admissions, and in-hospital outcomes were similar between groups. Furthermore, in a series of 138 hospitalized patients, patients without dyspnea were admitted less frequently to the ICU than patients with dyspnea (19.6% vs. 63.9%) (Wang et al., 2020). Similarly, a study including 733 critically ill COVID-19 patients found that dyspnea was more frequent in patients who died (71.3% vs. 48.1%) (Xie et al., 2020). These findings are probably related to disease severity and to the fact that they were not explicitly studying the characteristics of patients with silent hypoxemia.

From those observations combined with our findings, we can partially conclude that neurologic involvement occurs early during the disease. Also, that silent hypoxemia may be neurogenic due to its association with new-onset headache and altered autonomic compensatory responses to hypoxemia. Surprisingly, we found that patients with silent hypoxemia seek medical attention earlier than patients with hypoxia and dyspnea, suggesting that headache may be the symptom that led patients to seek early medical attention.

There are several limitations in this study that should be discussed for the correct interpretation of these data. First, we classified the patients according to SpO_2, a method known to have variations of up to 10% with SpO_2 levels $\leq$80%, which may bias our results (Tobin et al., 2020). Also, as most patients were severely hypoxemic at admission, some arterial blood gases were measured after oxygen supplementation and PaO_2/FiO_2 ratio in non-IMV patients may not be a reliable measurement to assess disease severity. The latter, because the provided FiO_2 by oxygen delivery devices not solely depends on the oxygen flow rate but of additional factors that we were unable to control or measure, such as the respiratory pattern and minute ventilation, may influence its interpretation (Petersson and Glenny, 2014; Tobin et al., 2020). Also, the chest CT findings description was performed by the total percentage of lung damage and not by the type of radiological finding (ground-glass/consolidation).

Finally, a significant limitation is that dyspnea by itself is a symptom that may be either interpreted as the subjective perception of air hunger or as the objective presence of respiratory distress signs. For this analysis, we selected the clinical information defining dyspnea as the subjective symptom to avoid differences among physicians' criteria. Since the frequency of silent hypoxemia in our cohort was relatively limited, further studies are necessary to clarify whether silent hypoxemia is associated with relevant clinical outcomes in studies with larger sample sizes. Finally, it remains to be elucidated whether the high frequency of headache is due to decreased respiratory reflex sensibility or direct central nervous system viral invasion.

5. Conclusions

Silent hypoxemia is a phenomenon recently described in some COVID-19 patients. The physiopathology points toward a neurological dysfunction. Although this phenomenon may not be new in patients with other severe respiratory distress syndromes or chronic lung diseases, in the context of the COVID-19 pandemic, silent hypoxemia is relevant in the clinical practice since it may lead to an underestimation of the respiratory distress severity.

Data availability

De-identified data to replicate the results will be available to qualified researchers upon written request to the corresponding author.

Acknowledgements

We are in debt with all the medical and paramedical personnel of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán working extra shifts to provide optimal care for COVID-19 patients during the pandemic. Despite this difficult situation, they have made extraordinary efforts to produce objective information to understand this disease. Also, we would like to express our gratitude to Sandra Perez-Castañeda for helping us in creating Fig. 3.

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