



Dyspnea perception and neurological symptoms in non-severe COVID-19 patients

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Abstract

Introduction The relationship between dyspnea and COVID-19 is unknown. In COVID-19 patients, the higher prevalence of neurological symptoms and the lack of dyspnea may suggest common underlying pathogenetic mechanisms. The aim of this preliminary study is to address whether there is a lack of dyspnea in COVID-19 patients and if there is a relationship between neurological symptoms and the perception of dyspnea.

Methods A structured interview regarding the occurrence of subjective neurological symptoms was performed and coupled with a questionnaire about the intensity and qualities of dyspnea. Respiratory rate (RR) and an arterial blood gas on room air were concurrently evaluated.

Results Twenty-two patients (age 68.4 ± 13.9 years, 13 males and 9 females) were included and divided into two groups according to the Borg dyspnea scale: dyspneic patients $BU \geq 1$ (DYSP) and non-dyspneic patients $BU < 1$ (NDYSP). The prevalence of dyspnea overall was 31.8%. The prevalence of neurological symptoms, dyspnea descriptors, RR, pH, $PaCO_2$, PaO_2 , or lactate was similar between groups.

Conclusion This study confirms that the prevalence of dyspnea is low in non-severe COVID-19 patients, but contrary to our hypothesis of a relationship between shortness of breath and neurological symptoms, we have not been able to find any evidence of an impairment in dyspnea perception, either in the DYSP or NDYSP group.

Keywords Dyspnea · COVID-19 · dyspnea descriptors · arterial blood gas

Introduction

Recently, Bertrand Recansens et al. have observed that patients with COVID-19 perceive less breathlessness than would be expected in their condition, and the lack of dyspnea perception despite the severe respiratory failure leads to intubation [1]. Two main mechanisms have been hypothesized:

either a damage of C-pulmonary fibers due to the cytokine storm caused by inflammation or a direct neurotoxic effect of the virus [1]. In COVID-19 patients, the high prevalence of neurological symptoms (36.4%) [2] and the low prevalence of dyspnea (between 19 and 55% according to the studies) [3–5] may suggest an involvement of the neurological pathways involved in dyspnea perception.

Dyspnea is a complex symptom defined as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity” [6]. Work/effort to breathe, difficult inspiration/air hunger, and tight chest are three different well-studied qualities of dyspnea and underpin distinct neurological pathways [6]. However, the evaluation of dyspnea needs to be anchored to physiological parameters and mostly to the central respiratory neural drive or to mechanical loads such as ventilation or respiratory rate (RR) [7].

The aim of this preliminary study is to address whether there is a lack of dyspnea in COVID-19 patients and if there is a relationship between neurological symptoms and the perception of dyspnea.

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Table 1 Characteristics of the study patients

Characteristics	Total (n = 22)	Dyspnea (n = 7)	No dyspnea (n = 15)	p value
Age, yrs. (SD)	68.4 (13.9)	71.2 (15.8)	67.1 (13.2)	n.s.
Male, n (%)	13 (59)	4 (57)	9 (60)	
BMI, kg/m ² (SD)	25.6 (4.0)	25.0 (4.2)	25.9 (3.7)	n.s.
Dyspnea, BU (SD)	1.4 (2.1)	4.1 (2.2)	0.1 (0.2)	< 0.01
Exertional dyspnea, MRC (SD)	2.5 (1.4)	3.4 (1.4)	2.0 (1.1)	< 0.05
Any neurological symptom, %	81.8	85.7	80.0	
Ageusia, %	27.3	42.9	20.0	
Anosmia, %	13.6	14.3	13.3	
Headache, %	22.7	57.1	6.7	
Sleepiness, %	50.0	85.7	33.3	
Respiratory rate, bpm (SD)	17.1 (3.7)	15.1 (4.0)	18.1(3.0)	n.s.
pH, log (SD)	7.45 (0.04)	7.45 (0.04)	7.45 (0.04)	n.s.
PaO ₂ , mmHg (SD)	78.5 (13.0)	78.6 (14.2)	78.4 (13.8)	n.s.
PaCO ₂ , mmHg (SD)	36.3 (2.6)	36.4 (2.8)	36.2 (2.9)	n.s.
Lactate, mmol (SD)	1.57 (0.78)	1.36 (0.82)	1.67 (0.89)	n.s.
Work/effort to breath, %	22.7	14.3	26.7	
Air hunger, %	22.7	14.3	26.7	
Inspiratory difficulties, %	36.4	28.6	40.0	
Expiratory difficulties, %	4.5	0	6.7	
Tight chest, %	22.7	57.1	6.7	
Anxiety/fear of breathing, %	13.6	14.3	13.3	

Yrs, years; SD, standard deviation; n, number; BU, Borg Unit; MRC, Medical Research Council; bpm, breaths per minute; PaO₂, partial arterial oxygen pressure; PaCO₂, partial arterial carbon oxide pressure

Methods

We conducted a preliminary prospective study in non-severe hospitalized COVID-19 patients admitted to the respiratory ward of “Tor Vergata Hospital” and able to answer the questionnaires, in the period between April 15 and May 10, 2020 (protocol no. 48.20, version 2020 of the local ethics committee at University Hospital of Rome Tor Vergata). All the patients signed informed consent [8]. Patients were classified as non-severe COVID-19 in the absence of respiratory distress and the need of non-invasive or invasive mechanical ventilation.

A structured interview about the occurrence of subjective neurological symptoms was performed and coupled with a questionnaire about breathlessness. RR and partial arterial pressure of carbon dioxide and oxygen (PaCO₂, PaO₂), pH, and lactate on room air (RA) were evaluated. The neurological interview consisted of 13 items, each related to a specific symptom, requiring a dichotomized answer (YES/NO): (1) hyposmia, (2) dysgeusia, (3) auditory dysfunction, (4) headache, (5) confusion, (6) dizziness, (7) numbness/paresthesia, (8) fatigue, (9) daytime sleepiness, (10) sleep impairment, (11) muscle ache, (12) depression, and (13) anxiety [8]. The intensity of dyspnea was evaluated with the modified Borg scale (Borg unit, BU); a single item (0–10) rating of intensity activity limitation due to dyspnea the days before hospital

admission was evaluated with the modified Medical Research Council (mMRC) scale, a unidimensional (0–4) rating of activity limitation. The qualities of dyspnea were asked with a 6-item questionnaire requiring a dichotomized answer (YES/NO): (1) work/effort to breathe, (2) hunger of breathing, (3) difficult inspiration, (4) difficult expiration, (5) tight chest, and (6) anxiety or fear to breathe [6].

Results

Twenty-two patients (age 68.4 ± 13.9 years, 13 males and 9 females) were included and divided into two groups according to the Borg dyspnea scale: dyspneic patients BU ≥ 1 (DYSP) and non-dyspneic patients BU < 1 (NDYSP). Of these patients, 21 (95.5%) had at least 1 of the following underlying disorders: hypertension (17 [77.3%]), diabetes (6 [27.3%]), cardiac or cerebrovascular disease (14 [63.6%]), and malignancy (1 [4.3%]). The results are shown in Table 1.

The prevalence of neurological symptoms was similar between groups, and there was no difference in the distribution of neurological symptoms, even if the prevalence of dysgeusia, headache, and daytime sleepiness was higher in the DYSP group vs the NDYSP group. There was no difference in RR, pH, PaCO₂, PaO₂, or lactate. The only significant difference was a greater exertional dyspnea at the time of

hospital admission (MRC DYSP vs NDYSP: 3.4 vs 2, $p < 0.05$). Moreover, there was no difference in the dyspnea descriptors' distribution, even if the prevalence of "tight chest" was higher in the dyspneic patients.

Discussion

These preliminary data confirm that the prevalence of dyspnea is low in non-severe COVID-19 patients, but there is no relationship between the lack of dyspnea and the presence of neurological symptoms.

The prevalence of dyspnea in our group was 31.8% and this is in line with other reports [3–5]. In the Guan et al. study, the prevalence of dyspnea was 18.7%, but it was higher in more severe patients (37.6% vs 15.1% in non-severe patients) [3]. In the Young et al. study [5], 2 out of 18 patients reported shortness of breath, but the RR was 18 breaths per minute (16–21) and the saturation was between 95 and 100%, suggesting that most patients do not have any increase in the mechanical or metabolic loads which could cause an increase in dyspnea perception. Conversely, in the Huang study [4], the prevalence of dyspnea was 55% (92% in the ICU patients vs 37% of non-ICU patients), but 62% of patients in the ICU had a RR higher than 24 breaths per minute (bpm) compared with just 14% of patients not in the ICU who had a RR greater than 24 ($p = 0.0023$). Most of our patients had a PaO_2 within the normal range (60–100 mmHg) and a PaCO_2 around 36 mmHg, suggesting a low metabolic stimulus to the central respiratory drive, and the RR was lower than 24 bpm in all patients, confirming a low mechanical load of respiratory muscles; therefore, our results could not be extended to more severe patients. It is possible that some patients may have a reduced chemosensitivity to hypoxia and a reduced perception of dyspnea as demonstrated in other conditions [9], but a blunted response to hypoxemia has not been demonstrated in COVID-19 patients.

Interestingly, some patients described their dyspnea as "tight chest" and this form of dyspnea is relatively specific to stimulation of airway receptors and can be indirectly associated to stimulation of the C-pulmonary fibers by the virus or the cytokine storm [10], but since this symptom was more common in the DYSP group (57.1%) than in the NDYSP group (6.7%), we believe that the damage of the fibers would be perceived as an increase in dyspnea sensation, although with a different quality, and not as a suppression of dyspnea.

Conclusion

Even if the hypothesis of a lower dyspnea perception due to a neurological involvement of the nervous system is intriguing, there is no evidence of it yet and our findings do not support

this hypothesis. Furthermore, the available data on COVID-19 patients seem to confirm that dyspnea is more frequent in more severe patients and its low prevalence is probably due to the fact that patients are admitted to the hospital for other causes. Though it is not possible to exclude that the lack of dyspnea perception could be the cause of a severe clinical presentation in some COVID-19 patients, it does not seem to be the main feature in COVID-19. The small size of the sample does not allow to draw conclusive results and further studies are needed.

Authors' contribution 1) Drafting the article or critically revising it for important intellectual content: JO, CL, AC, EP, MM, MP, NBM, and PR

2) Final approval of the version to be published: JO, CL, AC, MM, MP, NBM, and PR

3) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any of its parts are appropriately investigated and resolved: JO, CL, AC, MM, PDM, MP, NBM, and PR

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All participants gave written informed consent after receiving an extensive disclosure of study purposes. The local ethics committee at University Hospital of Rome Tor Vergata approved the procedures (protocol no. 48.20, version 2020).

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