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Short Communication

Silent hypoxia in patients with SARS CoV-2 infection before hospital discharge

Natascha Josephine Ulstrand Fuglebjerg, Tomas Oestergaard Jensen, Nils Hoyer, Camilla Koch Ryrsø, Birgitte Lindegaard, Zitta Barrella Harboe*

Department of Infectious Diseases and Pulmonary Medicine, Nordsjællands University Hospital, Denmark

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ABSTRACT

Objective: To assess the degree of hypoxia and subjective dyspnea elicited by a 6-minute walking test (6MWT) in COVID-19 patients prior to discharge.
Methods: A 6MWT was performed in 26 discharge-ready COVID-19 patients without chronic pulmonary disease or cardiac failure. Heart rate, oxyhemoglobin saturation (SpO_2), respiratory rate, and subjective dyspnea measured on the Borg CR-10 scale were measured before and immediately after the 6MWT, with continuous monitoring of SpO_2 and heart rate during the 6MWT. The 6MWT was terminated if SpO_2 dropped below 90%. A historical cohort of 204 patients with idiopathic pulmonary fibrosis (IPF) was used for comparison.
Results: 13 (50%) of the COVID-19 patients developed exercise-induced hypoxia ($SpO_2 < 90\%$) during the 6MWT, of which one third had pulmonary embolism. COVID-19 patients experienced less hypoxia-related dyspnea during the 6MWT compared with patients with IPF.
Conclusion: The 6MWT is a potential tool in the diagnosis of asymptomatic exercise-induced hypoxia in hospitalized COVID-19 patients prior to discharge. Due to important methodological limitations, further studies are needed to confirm our findings and to investigate their clinical consequences.
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Manuscript

Anecdotal evidence is emerging that patients with COVID-19 may present with 'silent hypoxia', which refers to a discrepancy between the level of hypoxia and subjective dyspnea experienced by the patient (Couzin-Frankel, 2020). This phenomenon is of potential concern among patients with chronically compromised end-organ perfusion, for example in ischemic heart disease, where the absence of dyspnea may permit an acute ischemic event to progress to a critical level without the usual early warning symptoms. We aimed to investigate whether silent hypoxia in adult COVID-19 patients ready for discharge can be elicited by a 6-minute walking test (6MWT).

Patients hospitalized with COVID-19 confirmed by polymerase chain reaction (PCR) testing at the University Hospital of Copenhagen, North Zealand, Denmark were eligible for inclusion at the time of planned discharge, which required resolution of fever and an oxyhemoglobin saturation (SpO_2) of 94% or above at rest, without supplementary oxygen. Patients with chronic lung diseases and New York Heart Association (NYHA) class II and above were excluded. The 6MWT was carried out according to the American Thoracic Society (ATS) statement from 2002 by trained pulmonary physiotherapists (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002). Patients were instructed to walk the greatest distance possible in 6 min, at a self-determined pace, pausing to rest if needed. Heart rate (HR), SpO_2, respiratory rate (RR), and dyspnoea rated between 1 and 10 on the Borg CR-10 dyspnea scale (Borg and Kaijser, 2006; Borg, 1982) were recorded before and immediately after the 6MWT. A PaO_2 below 80 mmHg (10.6 kPa) is generally considered pathological, while a PaO_2 of at least 60 mmHg (8 kPa), which correlates to an SpO_2 of 90%, is required to maintain sufficient tissue oxygenation (Hansen et al., 1984). SpO_2 and HR were continuously monitored during the 6MWT. We assumed that patients with no history of chronic lung disease should be able to maintain an SpO_2 of 96% or above, even during physical activity

* Corresponding author: Deparment of Infectious Diseases and Pulmonary Medicine, University Hospital of Copenhagen, North Zealand, Denmark, Dureha-vevej 29, 3400 Denmark.
E-mail address: zitta.barrella.harboe@regionh.dk (Z.B. Harboe).

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Table 1
Baseline characteristics of 26 patients with COVID-19 undergoing the 6-minute walking test (6MWT) at hospital discharge and a historical cohort of 204 patients with idiopathic pulmonary fibrosis who underwent the same test.

	COVID-19 patients			IPF patients (n = 204)
	Total number of patients (n = 26)	6-MWT completed (n = 13)	6-MWT terminated early due to SpO2 < 90% (n = 13)	
Age in years, median (range)	63 (29–85)	62 (29–85)	64 (38–76)	74 (42–92)
Male sex, n (%)	16	8 (62)	8 (62)	158 (77)
Number of comorbidities per patient, median (range)	1 (1–5)	1 (1–5)	1 (1–4)	Unknown
Need for ICU during admission, n (%)	8 (31)	2 (15)	6 (46)	Unknown
Need for mechanical ventilation during admission, n (%)	2 (15)	0 (0)	2 (15)	Unknown
Infiltrate on chest X-ray during admission, n (%)	21 (81)	8 (62)	13 (100)	Unknown

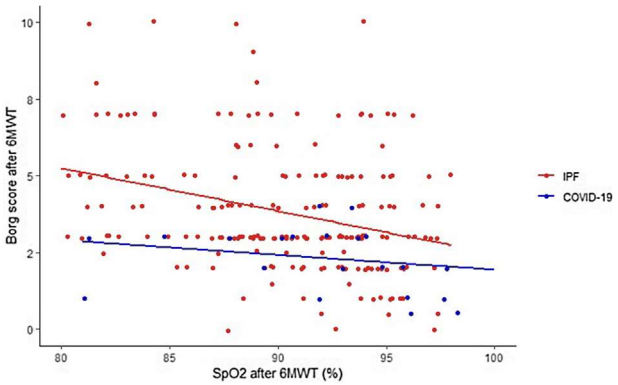

Figure 1. Decline in oxygen saturation (SpO_2) and Borg CR-10 dyspnea scale rating after 6MWT in patients with COVID-19 (blue) and idiopathic pulmonary fibrosis (red). Each dot represents one patient. The lines are based on univariate linear regression.

(Casanova et al., 2011). A previous prospective cohort of 204 patients with idiopathic pulmonary fibrosis (IPF), who also underwent the 6MWT according to the ATS guidelines, was used for comparison (Hoyer et al., 2019).

Forty-seven consecutive patients were screened between April 16 and April 28, 2020, and all 26 eligible patients without exclusion criteria were included. The 6MWT was terminated early in 13 patients (50%) due to an SpO_2 below 90%. Baseline characteristics in patients who terminated the 6MWT early compared with those who completed the 6MWT, as well as baseline characteristics for the comparison group, are presented in Table 1. COVID-19 patients with an SpO_2 below 90% during the 6MWT had only discrete increase in perceived dyspnea (Figure 1). Six patients who terminated the 6MWT early due to hypoxia were investigated with CT angiography and/or ventilation-perfusion scintigraphy in order to exclude pulmonary embolism (PE), which was confirmed in four patients. As a comparison group, IPF patients had a similar decline in SpO_2, but they developed more pronounced concomitant worsening in the level of subjective dyspnea measured by the Borg scale (Figure 1). COVID-19 patients had a mean peak score of 2.5 on Borg CR-10 (range 0–5) during the 6MWT, compared with 4.1 (range 0–10) in IPF patients.

In summary, nearly half of hospitalized COVID-19 patients without chronic pulmonary disease developed marked exercise-induced hypoxia without accompanying subjective dyspnea at the time of discharge, and one third of patients who terminated the 6MWT early had PE. We interpret this as evidence of silent hypoxia.

Our study had several limitations. No previous studies have examined the role of the 6MWT in otherwise healthy adults with COVID-19 or other acute respiratory tract infections, although exercise-induced hypoxia has been used in the diagnosis and severity assessment of *Pneumocystis jirovecii* pneumonia in HIV-positive adults (Sauleda et al., 1994). Clinical implications of this hypoxia are thus not well described, and we therefore decided to routinely terminate the 6MWT early if SpO_2 dropped below 90% for safety reasons. This could have led to underestimation of the relative degree of dyspnea in COVID-19 patients, since they were compared with a control group of IPF patients, who were all allowed to complete the 6MWT unless they developed chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, or pale or ashen appearance, in accordance with the ATS guidelines. Furthermore, patients in our control group all had IPF, a condition resulting in hypoxic respiratory failure, and therefore increased tolerance to lower SpO_2 without subjective dyspnea was a possibility in this group.

We propose further, larger studies to confirm our findings using a more accurately matched prospective group of controls, and to investigate the clinical consequences of silent hypoxia in particular among patients at elevated risk of serious end-organ ischemic events after discharge to the community.

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Ethical approval

The study was approved by the Danish Health and Medicines Authority (ID: 31–1521-264) and by the Danish Data Protection Agency (P-2020-375).

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