Ventilation Is Not Depressed in Patients with Hypoxemia and Acute COVID-19 Infection

To the Editor:

Early reports of patients with hypoxemia and coronavirus disease (COVID-19) pneumonia exhibiting little respiratory distress have prompted the suggestion that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection results in a unique respiratory pathophysiology (1). One hypothesis to explain the apparent disconnect between severe hypoxemia and the reported absence of dyspnea is a blunted hypoxic ventilatory response (HVR).

We therefore sought to test the hypothesis that patients with hypoxemia and COVID-19 have reduced ventilation compared with healthy control subjects. As part of a cross-sectional study of gas exchange in patients with early COVID-19 pneumonia on presentation to the hospital, we measured mean alveolar partial pressure of CO_2 ($P_{A_{CO_2}}$), which represents the inverse of alveolar ventilation ($\dot{V}_A$), and related it to the severity of hypoxemia as measured by Pa_{O_2}. Published healthy subject data relating $P_{A_{CO_2}}$ to Pa_{O_2} under normoxic and acute hypoxic conditions (2–4) were used to assess whether $\dot{V}_A$ levels of patients with COVID-19 were in the expected range for the severity of hypoxemia, thus inferring the ventilatory response of these patients.

Methods

The protocol was approved by the Swedish Ethical Review Authority (diary no. 2020-02966).

Subjects. Thirty spontaneously breathing symptomatic patients admitted to Danderyd Hospital, Stockholm, Sweden, who were ⩾18 years of age, had a positive PCR result for COVID-19, and had Sa_{O_2} levels of <96% were included. Patients unable to maintain constant V_T and breathing frequency over the data collection period (of several breaths) were excluded. All patients gave written informed consent.

Protocol. Pa_{O_2} and Pa_{CO_2} were measured from an arterial blood sample collected over two or three steady-state breaths while the patient was breathing ambient air. Immediately before collecting the blood sample, exhaled CO_2 concentrations and gas flow were measured at 100 Hz at the mouth (Oxycon Pro; Vyaire Medical [5]), and, after adjustment for analyzer lag, mean $P_{A_{CO_2}}$ was determined as the average of three separate breaths. Measured Pa_{O_2} and Pa_{CO_2} were corrected to body temperature (6), and exhaled gas measurements were also temperature adjusted using the Antoine equation.

Data analysis. We calculated the term $40/P_{A_{CO_2}}$ (indicating the $\dot{V}_A$ relative to that which would be present in the same patient had $P_{A_{CO_2}}$ been normal at 40 mm Hg). This term, abbreviated to $\dot{V}_A$rel, was plotted against Pa_{O_2}.

Results

Data were collected from 22 males and 8 females, aged 23–85 years (mean ± SD, 50.7 ± 15.0 yr). All subjects had mildly symptomatic COVID-19 pneumonia; the majority were tachypneic (respiratory rate, 21.8 ± 7.2 breaths/min; range, 9–38), 22 had dyspnea, and most were febrile at the time of testing (body temperature, 38.0 ± 1.0°C; range, 36.5–40°C). No patient required ICU admission. Exhaled CO_2 was collected between 2 and 100 seconds (mean ± SD, 35 ± 10 s) before the arterial blood gas sample. Pa_{O_2} ranged from 52.9 to 107.5 mm Hg (mean ± SD, 72.0 ± 12.7 mm Hg), arterial oxygen saturation ranged from 89% to 99% (mean ± SD, 94 ± 2%), Pa_{CO_2} ranged from 27.8 to 46.8 mm Hg (mean ± SD, 36.3 ± 4.6 mm Hg), and $\dot{V}_A$rel ranged from 1.1 to 1.7 (mean ± SD, 1.3 ± 0.2). Approximately 50% of patients had $\dot{V}_A$rel values that were in broad agreement with normal values (Figure 1). For all remaining patients, $\dot{V}_A$rel was greater than expected from the normal data. Most importantly, in no patient was $\dot{V}_A$rel lower than that seen in healthy subjects at any Pa_{O_2}.

Discussion

Our findings demonstrate that in this group of 30 patients with acute symptomatic COVID-19, $\dot{V}_A$ was normal or increased at any Pa_{O_2} as compared with that in healthy subjects exposed to acute hypoxia. Contrary to our hypothesis, no patient had evidence of reduced or blunted ventilation. Notably, all patients had $Pa_{O_2} > 50$ mm Hg, the nominal level below which hypoxia-driven dyspnea and ventilation increase rapidly in healthy subjects (Figure 1) (7). To our knowledge, these findings represent the first report with data showing that ventilatory responsiveness in spontaneously ambient air–breathing patients with COVID-19 is normal or increased and not decreased. A strength of our study is that our patient data are based on a direct, noninvasive measurement of $P_{A_{CO_2}}$ from exhaled gas analysis, thus providing a surrogate measurement of $\dot{V}_A$ that is obtainable at the bedside in a clinical infectious disease setting.

Limitations. This is an observational cross-sectional study, and we are unable to determine the mechanism contributing to the observed $\dot{V}_A$rel data. Potential mechanisms influencing ventilatory drive in COVID-19 pneumonia include the following: *1*) genetically determined differences in HVR (8, 9); *2*) sustained hypoxemia over a period of hours to days, resulting in an increase in HVR (via the hypoxia-inducible factor hydroxylase system) (10); *3*) SARS-CoV-2 invasion of the carotid body or central nervous system, resulting in direct changes in ventilatory response (8); and *4*) other disease-related but not COVID-19–specific factors affecting ventilatory control (e.g., sensory receptor inputs, fever, anxiety, pain, inflammation) or respiratory mechanics. Additional studies would be required to establish the roles of these contributing factors.

We recruited spontaneously breathing, symptomatic, hospitalized patients with COVID-19 who were judged by their caregivers to be safe while breathing ambient air for the few minutes of the study, and our findings may not be generalizable to other COVID-19 disease stages or severities. We did not perform classical HVR protocols, with control of inhaled gases and direct

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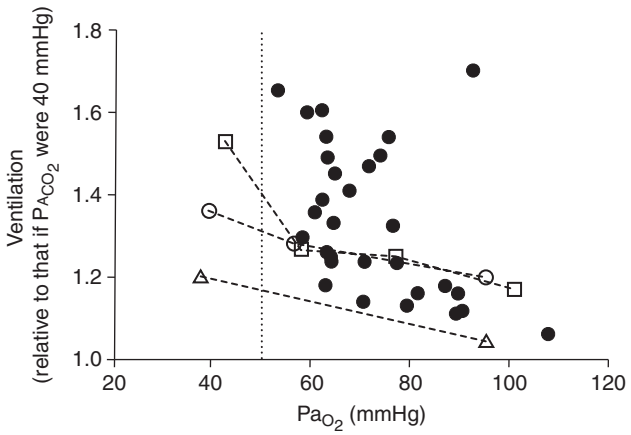

Figure 1. Pa_{O_2} plotted against 40/alveolar partial pressure of CO_2 ($P_{A_{CO_2}}$), indicating alveolar ventilation ($\dot{V}_A$) relative to that which would be present in the same patient had $P_{A_{CO_2}}$ been normal at 40 mm Hg ($n = 30$; solid circles). In no patient was relative $\dot{V}_A$ less than 1.0 or less than that calculated for healthy young adult subjects from Wagner and colleagues (2) (open circles, dashed lines representing 7 males and 1 female; mean ± SD age, 29.8 ± 6.1 yr), Hammond and colleagues (3) (open triangles, dashed lines representing 10 males; mean ± SD age, 22.0 ± 1.2 yr), and Torre-Bueno and colleagues (4) (open squares, dashed lines representing 9 males; mean ± SD age, 26.0 ± 6.0 yr). Pa_{CO_2} for historical control subjects was calculated using measured Pa_{CO_2}, and the multiple inert gas elimination technique was used to measure $\dot{V}_A/\dot{Q}$ inequality to estimate the arterial–alveolar difference. Vertical dotted line represents $Pa_{O_2} = 50$ mm Hg.

measurement of ventilation in each individual, because of logistical challenges in a highly infectious acute disease setting. Our data consist of a single sample for each patient, and we do not know where each subject is operating in their intrinsic HVR relationship. We also have not included concurrent healthy or non–COVID-19 pneumonia control subjects and have used historical control subjects from three prior physiological studies in which healthy young subjects were studied over the same range of Pa_{O_2} levels as encountered in our patients with COVID-19.

Conclusions

Patients with acute COVID-19 (spontaneously breathing ambient air) do not have depressed $\dot{V}_A$ relative to their degree of hypoxemia. Indeed, some patients have relatively high ventilatory levels. These findings do not support the concept of impaired HVR in COVID-19 pneumonia. ■

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

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