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.

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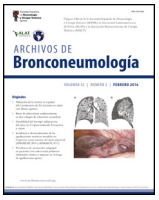

Scientific Letter

The Role of Blood Gas Analysis in the Post-Acute Phase of COVID-19 Pneumonia

To the Director,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) pandemic represents a clinical and public health emergency and the national healthcare systems suffers from the high incidence of difficult-to-treat cases.[1,2] While the infection can be asymptomatic, the disease can cause multi-organ dysfunction.[2]

Occurrence of acute respiratory failure is the most important cause for immediate hospitalization.[2–4] Up to 20% of COVID-19 patients need intensive care unit (ICU) care, with 30%–100% treated with mechanical ventilation.[5] Mortality of ICU patients ranged from 26% to 61.5%.[6] Among critically ill patients, severe acute hypoxemic respiratory failure is the dominant finding, whereas hypercapnia is rare.

According to the Berlin definition,[7] the severity of hypoxaemia defines the severity of acute respiratory distress syndrome (ARDS), based on ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2). Until now, the clinical features of COVID-19-related ARDS (CARDS) are still unclear.[8] An important question is whether (or not) CARDS is a distinct form of ARDS that requires a different treatment strategy.

It seems that patients affected from COVID-19 respiratory failure meet criteria for moderate to severe ARDS.[9,10] Baseline respiratory mechanics are not different in CARDS patients who eventually die from those who survive being extubated or remaining intubated.

After the acute phase, differences are observed suggesting differential trajectories of respiratory failure.[11]

However, the current knowledge on pulmonary pathogenesis and lung function impairment in the post-acute phase is still limited[12,13] due to the recommendations on lung function tests during the pandemic phase published by the European Respiratory Society.[14] In this regards a good alternative to gather information about the ability of the lung to exchange gases could be the arterial blood gases analysis (ABG).

Knowing PaO_2, $PaCO_2$ and FiO_2, the alveolar-to-arterial oxygen ($AaDO_2$) gradient can be calculated; $AaDO_2$ gradient enables indeed a more precise evaluation of the pathophysiological basis of hypoxemia than the more widely used PaO_2/FiO_2 (P/F).[15]

Published data about gas exchange impairment of patients surviving the acute phase of COVID-19 are lacking.

Aim of this study is to assess the role of $AaDO_2$ gradient and P/F in the post-acute phase of COVID-19 pneumonia.

COVID-19 survivors discharged from medical wards after a negative molecular test for SARS-CoV-2 were admitted to four clinical centres of the Istituti Clinici Scientifici Maugeri, Italy, and enrolled between April 1st and September 1st, 2020 to undergo clinical evaluation and multidisciplinary rehabilitation. The rehabilitation programme was implemented following the Italian position paper[16]: interventions were chosen considering age, clinical severity, length of immobilization, and comorbidities.[16]

The study was approved by the central ethical committee (CEC2279).

Clinical, radiological, and functional data were collected (Tables 1 and 2).

Quantitative variables were described with means (standard deviations, SD) or medians (Interquartile ranges, IQR) in case of parametric or non-parametric distribution, respectively. Absolute and relative (percentage) frequencies were used to describe qualitative variables. Student *t* or Mann–Whitney test was computed to assess differences for parametric and non-parametric quantitative variables. A *p*-value less than 0.05 was considered statistically

Table 1
Baseline characteristics of 145 patients recovered from COVID-19.

Variable	All patients with ABG at admission and/or discharge (*N* = 145)
Age	69.7 (10.8)
Males	99/145 (68.3)
BMI, kg/m²	25.3 (23.4–29.3)
LoS for rehabilitation, days	22.5 (17–31)
Current or former smoker	34/75 (45.3)[a]
Comorbidities	
TB	1/145[b] (0.7)
Asthma	7/145 (4.8)
COPD	13/144 (9.0)[a]
Diabetes mellitus	15/82 (18.3)[a]
Pulmonary embolism	3/82 (3.7)[a]
Blood hypertension	35/56 (62.5)[a]
Acute respiratory failure treatment	
ICU admission	59/145 (40.7)
NIV	84/145 (57.9)
Oxygen therapy	134/145 (92.4)
Radiological involvement	
Emphysema	46/109 (42.2)[a]
Pulmonary consolidation	43/109 (39.4)[a]
Ground glass	65/109 (59.6)[a]
Bronchiectasis	34/109 (31.2%)[a]
Pulmonary fibrosis	46/109 (42.2)[a]

Data are expressed as number (%) and Mean ± SD or median interquartile range (IQR).

[a] Denominator corresponds to total number of patients for whom data are available.

[b] Previous history of TB.

BMI: body max index; LoS: length of stay; TB: tuberculosis; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit: NIV: non-invasive ventilation.

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Table 2
Blood gas analysis and clinical characteristics of 145 patients recovered from COVID-19.

	Patients with ABG at admission (n = 137/145)			Patients with ABG at discharge (n = 66/145)		
Variable	No-ICU (n = 80/137)	ICU (n = 57/137)	p-Value	No-ICU (n = 39/66)	ICU (n = 27/66)	p-Value
FiO_2	21 (21–24)	21 (21–21)	0.32	21 (21–21)	21 (21–21)	0.07
PaO_2	72.2 (67–88)	74.8 (68–87.9)	0.71	81 (72.6–90.7)	75.6 (70.7–86.3)	0.22
$PaCO_2$	37.6 (34–42.5)	36.4 (32.5–41.5)	0.12	36.8 ± 4.6	35.6 ± 3.3	0.24
pH	7.4 (7.4–7.5)	7.4 (7.4–7.5)	0.49	7.42 ± 0.03	7.43 ± 0.03	0.69
saO_2	96.3 (95–98)	96.9 (95.1–98.3)	0.42	96.3 (95.1–97.4)	96 (95–97.6)	0.83
P/F	341 ± 71.5)	353 ± 63.1	0.27	379.1 (343.8–418.6)	360 (336.7–410.7)	0.45
$AaDO_2$	33.1 (23.7–47)	30 (22.9–40.3)	0.34	24.4 (16.8–35.9)	27.8 (22.8–34)	0.29
D-Dimer	580 (2.3–880)	380 (270–535)	0.43	565 (445–780)	365 (270–450)	0.39
Resp. rate	20 (18–20)	18 (17–20)	0.12	18 (16–18)	18 (17–18)	0.51
Hearth rate	82 ± 11.5	82.2 ± 13.7	0.93	70.6 ± 9.4	77.5 ± 10.6	0.02

	Patients with ABG both at admission and discharge (n = 58/145)								
	All 58 patients			No ICU (N = 33/58)			ICU (N = 25/58)		
	ABG admission	ABG discharge	p-Value	ABG admission	ABG discharge	p-Value	ABG admission	ABG discharge	p-Value
FiO_2	21 (21–25.5)	21 (21–21)	<0.0001	21 (21–28)	21 (21–21)	0.002	21 (21–24)	21 (21–21)	0.004
PaO_2	85.8 ± 19	80.2 ± 12	0.06	86.6 ± 18.9	81.9 ± 11.4	0.25	84.5 ± 19.6	77.6 ± 12.8	0.11
$PaCO_2$	34.7 (33.0–39.8)	36.3 (33.1–39.5)	0.44	35.5 (33.4–41.0)	37 (33.8–39.6)	0.21	34.2 (31.5–37.8)	35.7 (32.9–37.1)	0.76
pH	7.44 (7.41–7.46)	7.42 (7.40–7.45)	0.004	7.43 (7.40–7.45)	7.42 (7.40–7.44)	0.33	7.44 (7.42–7.47)	7.43 (7.40–7.45)	0.004
SaO_2	96.9 (95.4–98.1)	96.2 (95.1–97.5)	0.29	96.7 (95.6–98.0)	96.3 (95.1–97.5)	0.41	96.9 (94.9–98.4)	96 (95–97.6)	0.52
P/F	359.3 ± 77.4	377.4 ± 60.3	0.12	358.6 ± 75.7	382.6 ± 60.3	0.09	360 ± 81.4	369.5 ± 60.8	0.67
$AaDO_2$	33.0 (19.2–49.8)	24.4 (18.1–32.7)	0.004	33.4 (16.8–49.5)	22.8 (15.0–32.7)	0.01	32.6 (21.8–54.6)	27.1 (22.1–32.4)	0.19
D-Dimer	630 (380–890)	525 (365–760)	0.0003	685 (560–1225)	580 (460–800)	0.0004	390 (330–490)	365 (270–450)	0.25
Resp. rate	18 (17–20)	18 (16–18)	0.003	18 (17–20)	18 (16–18)	0.02	18 (17.5–19.5)	18 (17–18)	0.12
Heart rate	83.6 ± 12	73.5 ± 10.5	<0.0001	82.9 ± 11.5	70.8 ± 9.7	<0.0001	84.7 ± 13.0	77.5 ± 10.6	0.01

Data are expressed as Mean ± SD or median interquartile range (IQR).
ABG: arterial blood gas; ICU: intensive care unit: FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of arterial oxygen; $PaCO_2$: partial pressure of arterial carbon dioxide; pH: potential of hydrogen; SaO_2: Oxygen saturation in arterial blood; P/F: PaO_2/FiO_2; $AaDO_2$: alveolar-to-arterial oxygen; Resp: respiratory.

significant. The statistical software STATA version 16 (StataCorp, Texas, USA) was used to perform all statistical computations.

One-hundred and forty-five consecutive patients were recruited. The mean (SD) age was 70 (10.8) years and 99 (68.3%) patients were male; 21 (14.5%) had preexisting pulmonary disease (1 TB sequelae, 13 COPD, 7 asthma) and 34 (45%) were current or former smokers. Overall, 59 (40.7%) CARDS patients were originally discharged from ICU and 86 patients from non-ICU departments; among patients from non-ICU departments 30 (34.9%) underwent both non-invasive ventilation (NIV) and supplemental oxygen, 47 (56.7%) supplemental oxygen only, and 9 (10.5%) did not receive any therapies (Table 1).

Blood gases analysis was performed at admission or discharge in 137 (94.5%) and 66 (45.5%) patients, respectively (Table 2); blood gases analysis was carried out both at admission and at discharge only in 58 (40%) patients (Table 2).

No statistically significant differences were observed for intrapulmonary gases exchanges (SaO_2, PaO2, PaCO2, P/F, $AaDO_2$) respiratory rate D-dimer between patients originally intubated when compared with those non-intubated during the acute COVID-19 phase (Table 2).

A statistically significant post-rehabilitation improvement was observed in 58 patients evaluated with ABG both at admission and at discharge, for the following parameters: $AaDO_2$ (p: 0.004), D-dimer (p: 0.0003), respiratory (p: 0.003) and heart rate ($p < 0.0001$) but not for P/F (Table 1). These findings are confirmed among the 33/58 patients not ICU-admitted ($AaDO_2$ (p: 0.01), D-dimer (p: 0.0004), respiratory (p: 0.02) and heart rate ($p < 0.0001$) and not on P/F), while among the 25/58 patients originally admitted at ICU the $AaDO_2$, D-dimer and respiratory rate lose the statistical significance (Table 2).

Stratifying further these 58 patients by gender, age, length of stay (LoS) of hospital rehabilitation, BMI, smoking history and hypertension, $AaDO_2$ retains statistical significance in males (p: 0.002), aged > 70 years (p: 0.03), LoS < 24 days (p: 0.002), obese (p: 0.007), smokers (p: 0.02) and those affected by hypertension (p: 0.002).

Our preliminary data on patients admitted for rehabilitation after recovery from COVID-19 suggest the following:

a) The finding that intrapulmonary gases exchanges between originally intubated vs non-intubated patients during the acute COVID-19 phase do not differ significantly may suggest an atypical ARDS, although the effect of both the selection process and the small sample size cannot be excluded.
b) The D-dimer as well presents no differences between the two groups of patients described above, potentially suggesting a multifactorial damage (alveolar damage, parenchymal damage and vascular damage): more damage would be expected among the previously intubated patients, likely to have suffered a more severe acute COVID-19 phase.
c) In patients with ABG both at admission and discharge ($n = 58$), a statistically significant improvement was observed at discharge for $AaDO_2$ gradient and the same results were confirmed for 33/58 patients not ICU-admitted. By contrast, $AaDO_2$ gradient lost the statistical significance among the 25/58 CARDS patients originally admitted at ICU. This might suggest that $AaDO_2$ is more sensitive than P/F in the COVID-19 post-acute phase to monitor the lung damage in those not admitted to the ICU.
d) Stratifying further these 58 patients $AaDO_2$ gradient retains statistical significance in males, aged > 70 years, LoS < 24 days, obese, smokers and those affected by hypertension suggesting it may be a sensitive marker in severe patients.
e) Alveolar-to arterial oxygen, which can be calculated knowing PaO_2, $PaCO_2$ and FiO_2, can provide a more accurate evaluation of hypoxemia than P/F, because this could mirror changes in PaO_2, FiO_2 or both.[12] More evidence is needed to understand the role of the $AaDO_2$ gradient as a marker of lung function impairment. Case reports from post-mortem findings and biopsies showed mononuclear inflammation and frequently diffuse alveolar damage, with necrosis of alveolar epithelial cells, hyaline membrane formation, and hyperplasia of type II pneumocytes. In addition, consolidations due to fibroblastic proliferation with extracellular matrix and fibrin forming clusters in airspaces, as well as vascular damages, were described.[8] All together alveolar, epithelial and vascular impairment could justify either ventilation-perfusion mismatch or intra-pulmonary shunting with an increase in $AaDO_2$. In our study, the $AaDO_2$ gradient might improve in the medium-term among the patients previously admitted at ICU (or remained unchanged due to irreversible damage of the lungs).

Additional studies are needed to ideally plan a longer follow-up ABG in monitoring the COVID-19 post-acute phase.

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Conflict of interest

The authors declare to have no conflict of interest directly or indirectly related to the manuscript contents.

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Dina Visca[a,b,*,1], Giovanni Battista Migliori[c,1], Anh-Tuan Dinh-Xuan[d], Rosella Centis[c], Stefano Belli[e], Michele Vitacca[f], Maria Aliani[g], Elisabetta Zampogna[a], Davide Feci[b], Patrizia Pignatti[h], Martina Zappa[b], Laura Saderi[i], Giovanni Sotgiu[i], Antonio Spanevello[a,b]

[a] *Division of Pulmonary Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS, 21049 Tradate, Italy*
[b] *Department of Medicine and Surgery, Respiratory Diseases, University of Insubria, 21100 Varese-Como, Italy*
[c] *Respiratory Diseases Clinical Epidemiology Unit, Istituti Clinici Scientifici Maugeri, IRCCS, 21049 Tradate, Italy*
[d] *Respiratory Physiology Unit, Department of Respiratory Medicine, Cochin Hospital, Université de Paris, 75013 Paris, France*
[e] *Istituti Clinici Scientifici Maugeri, IRCCS, Respiratory Rehabilitation Unit of the Institute of 28010 Veruno, Novara, Italy*
[f] *Istituti Clinici Scientifici Maugeri, IRCCS, Respiratory Rehabilitation of the Institute of Lumezzane, 25065 Brescia, Italy*
[g] *Istituti Clinici Scientifici Maugeri, IRCCS, Respiratory Rehabilitation Unit of the Institute of Cassano Delle Murge, 70124 Bari, Italy*
[h] *Allergy and Immunology Unit, Istituti Clinici Scientifici Maugeri, IRCCS, 27100 Pavia, Italy*
[i] *Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, 07100 Sassari, Italy*

[*] Corresponding author.
E-mail address: dina.visca@icsmaugeri.it (D. Visca).
[1] These authors (D. Visca and G.B. Migliori) contributed equally to this manuscript.