Long-COVID is Associated with Impaired Red Blood Cell Function

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Keywords
long-COVID, oxygen binding, COHb

received 15.08.2023
accepted after revision 29.09.2023
published online 27.10.2023

Bibliography
Horm Metab Res 2024; 56: 318–323
DOI 10.1055/a-2186-8108
ISSN 0018-5043

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ABSTRACT

COVID-19 disease, caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2), induces a broad spectrum of clinical symptoms ranging from asymptomatic cases to fatal outcomes. About 10–35 % of all COVID-19 patients, even those with mild COVID-19 symptoms, continue to show symptoms, i. e., fatigue, shortness of breath, cough, and cognitive dysfunction, after initial recovery. Previously, we and others identified red blood cell precursors as a direct target of SARS-CoV-2 and suggested that SARS-CoV-2 induces dysregulation in hemoglobin- and iron-metabolism contributing to the severe systemic course of COVID-19. Here, we put particular emphasis on differences in parameters of clinical blood gas analysis and hematological parameters of more than 20 healthy and Long-COVID patients, respectively. Long-COVID patients showed impaired oxygen binding to hemoglobin with concomitant increase in carbon monoxide binding. Hand in hand with decreased plasma iron concentration and transferrin saturation, mean corpuscular hemoglobin was elevated in Long-COVID patients compared to healthy donors suggesting a potential compensatory mechanism. Although blood pH was within the physiological range in both groups, base excess- and bicarbonate values were significantly lower in Long-COVID patients. Furthermore, Long-COVID patients displayed reduced lymphocyte levels. The clinical relevance of these findings, e. g., as a cause of chronic immunodeficiency, remains to be investigated in future studies. In conclusion, our data suggest impaired erythrocyte functionality in Long-COVID patients, leading to diminished oxygen supply. This in turn could be an explanation for the CFS, dyspnea and anemia. Further investigations are necessary to identify the underlying pathomechanisms.

Introduction

COVID-19, caused by the SARS-CoV-2 virus, is primarily a respiratory disease but can also affect other organ systems, such as the hematological compartment. Several studies reported an increase in white blood cell count, a decrease in red blood cell (RBCs) count and hemoglobin level, an increase in ferritin and D-dimer levels and other clotting markers [1–4]. Symptoms of COVID-19 vary from mild to severe and may include fever, cough, shortness of breath, fatigue, diffuse body pain, loss of taste or smell, and sore throat [2, 3]. In approximately 6–35 % of all COVID-19 patients, these

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symptoms can persist for months after the initial infection with SARS-CoV-2 [5]. This symptomatic persistence has been termed Long-COVID or Post-COVID and can occur even in individuals who have had mild or asymptomatic infections [3]. Symptomatic constellations comprise chronic fatigue, shortness of breath, chest pain, and cognitive dysfunction ("brain fog") [6]. There is evidence that sex may have an impact on the development of Long-COVID, as some studies report women at higher risk [7, 8].

The pathophysiological mechanisms of Long-COVID are still under discussion and include the effects of viral persistence, inflammation, excessive blood clotting, and autoimmunity [9]. It was suggested that the hematological system is altered in Long-COVID as lower hemoglobin levels, increased D-dimers, anemia, thrombocytopenia, and lymphopenia have been reported in Long-COVID patients [10–12]. In addition, changes in RBCs size and morphology have been demonstrated in Long-COVID, which may contribute to impaired oxygen diffusion [13].

Previously, we and others identified RBC precursors as a direct target of SARS-CoV-2 and suggested that SARS-CoV-2 induces dysregulation in hemoglobin- and iron-metabolism contributing to the severe systemic course of COVID-19 [14–16]. Therefore, in this study, we put particular emphasis on the analysis of hematological parameters and blood gas analysis of Long-COVID patients compared to healthy donors.

Material and Methods

Sample acquisition

Blood samples from healthy donors were provided by the German Red Cross Blood Donation Service North-East, Institute for Transfusion Medicine Dresden and by the Division of Pneumology, Medical Department I (University Hospital Carl Gustav Carus, Dresden, Germany). Blood samples from Long-COVID patients were provided by the Division of Pneumology, Medical Department I (University Hospital Carl Gustav Carus, Dresden, Germany). The diagnosis of Long-COVID was made according to the German national guideline for Long-COVID and included documentation of previous SARS-CoV-2 infection, standardized symptom and functional assessment and standardized exclusion of other causes [17]. Matching of Long-COVID patients and healthy donors was not performed.

Blood collection and sampling

Three ml whole blood from healthy donors and from Long-COVID patients were collected in S-Monovettes EDTA K3 (Sarstedt, Nümbrecht, Germany) by venipuncture using a sterile disposable Safety-Multifly-Needle 21 G (Sarstedt). Determination of RBCs, hemoglobin content and hematocrit were performed on a Sysmex XN 1000 (Sysmex Deutschland GmbH, Norderstedt, Germany). Measurement of pH value and blood gas analyzing were carried out with an ABL800 Flex (Radiometer Medical ApS, Brønshø, Denmark).

Plasma was collected by centrifugation of the blood at 2000 × *g* for 10 minutes. Measurement of iron metabolism parameters was performed in the Institute of Clinical Chemistry and Laboratory Medicine (Dresden, Germany).

Statistical analysis

All graphic results are presented as mean ± SEM. Graph Pad Prism v.6 (GraphPad Software, San Diego, USA) was used for statistical analysis and figure preparation. All datasets were tested for normality. Clinical parameters were analyzed using chi-square test. Two-sided p-values of less than 0.05 were considered statistically significant.

Ethics approval

Blood samples from all donors and Long-COVID patients were used in anonymized form and in accordance with the guidelines approved by the Ethics Committee of the Technical University of Dresden [BO-EK-49012022]. Informed consent was obtained from all donors and patients.

Results

Demographic data and clinical symptoms

Patient's demographics are presented in ▶ **Table 1**. The mean age of Long-COVID patients was significantly lower compared to healthy donors (46.1 vs. 35.3 years). However, there were no significant differences in terms of gender distribution, with twice as many women as men in both groups. Smoking status was also not statistically significant different between the groups. The cohort of Long-COVID patients was selected based on their clinical symptoms, including chronic fatigue syndrome, cough, shortness of breath and cognitive dysfunction (▶ **Table 2**). Furthermore, most of the patients had only a mild course of COVID-19 disease and were treated in an outpatient setting. Only 2 patients required inpatient treatment.

▶ **Table 1** Patient's demographics.

	Healthy donors	Long-COVID patients	p-Value
Number of samples	**24**	**40**	
Age, years			
Mean (SD)	35.3 ± 11.5	46.1 ± 13.2	0.0018 **
Range	18–59	17–69	
Sex			0.630
Female	17 (70.8 %)	26 (65.0 %)	
Male	7 (29.2 %)	14 (35.0 %)	
Number of smokers			0.320
Never	6 (25 %)	12 (30.0 %)	
Non-smoker	10 (41.7 %)	12 (30.0 %)	
Former	2 (8.3 %)	7 (17.5 %)	
Current	4 (16.7 %) (0.45/22/38/36PY)	2 (5.0 %) (5/32PY)	
Unknown	2 (8.3 %)	7 (17.5 %)	

Data are presented as mean and SD. **p<0.01.

▶ **Table 2** Reported clinical symptoms of Long-COVID.

Symptom	Number of Long-COVID patients
Chronic fatigue	28 (70.0 %)
Shortness of breath	31 (77.5 %)
Cough	25 (62.5 %)
Cognitive dysfunction	7 (17.5 %)
Hospitalization	2 (5.0 %)
Total number of patients with reported symptoms	**40**

▶ **Table 3** Hematological and iron metabolism parameters in Long-COVID-19 patients compared to healthy donors.

	Healthy donors	Long-COVID patients	p-Value
Blood parameters	**n = 24**	**n = 40**	
Hemoglobin [mmol/l]	8.44 ± 0.16	8.70 ± 0.18	0.647
Red blood cells [10^{12}/l]	4.74 ± 0.08	4.70 ± 0.08	0.631
Hematocrit	0.412 ± 0.01	0.416 ± 0.01	0.723
MCV [fl]	87.2 ± 1.47	88.2 ± 0.80	0.948
Lymphocytes [10^9/l]	**2.25 ± 0.12**	**1.88 ± 0.09**	**0.007****
Thrombocytes [10^9/l]	257.4 ± 9.15	264.8 ± 9.81	0.938
Monocytes [10^9/l]	0.53 ± 0.03	0.55 ± 0.04	0.876
White blood cells [10^9/l]	6.57 ± 0.26	7.02 ± 0.35	0.944
Iron metabolism	**n = 21**	**n = 31**	
Plasma ferritin [µg/l]	84.8 ± 12.4	135.4 ± 24.1	0.236
Plasma iron [µmol/l]	11.94 ± 1.01	9.22 ± 0.72	0.05
Plasma transferrin [g/l]	2.40 ± 0.08	2.35 ± 0.07	0.72
Transferrin saturation [%]	**20.2 ± 1.78**	**15.6 ± 1.34**	**0.04***

Data are presented as mean ± standard error of the mean (SEM). Tests were performed two-sided. Mann–Whitney U-test was used for statistical analyses. The bold entries represent significant differences between the sample groups. * $p < 0.05$. ** $p < 0.01$.

Lymphocyte count and plasma iron levels are significantly reduced in Long-COVID

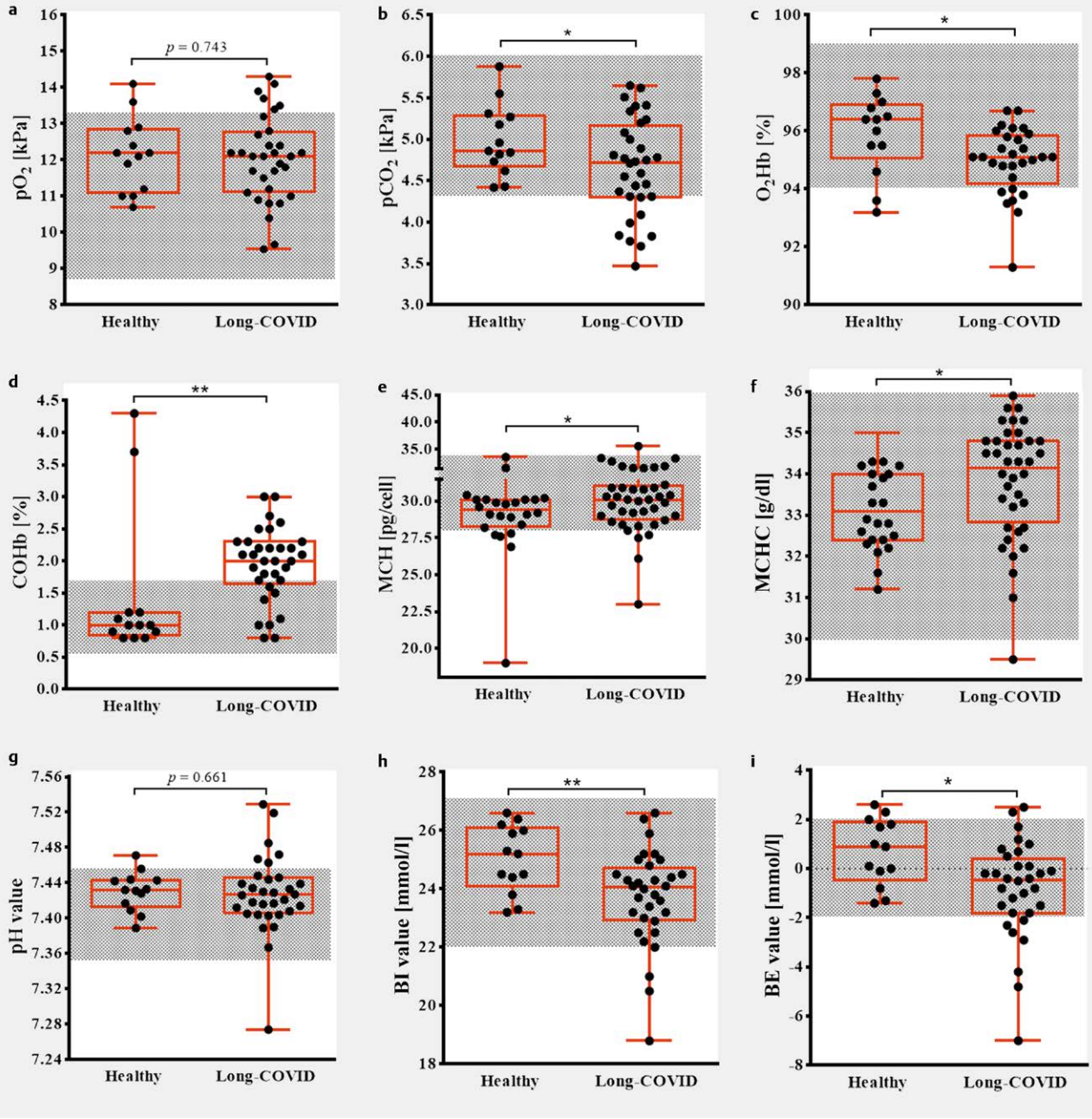
First, we analyzed the heme and iron metabolism in blood samples from Long-COVID patients and healthy donors. We found no significant differences in hemoglobin content, the amounts of RBCs and the hematocrit values in the blood samples of Long-COVID patients compared to healthy donors (▶ **Table 3**). However, the mean corpuscular hemoglobin (MCH) as well as the mean corpuscular hemoglobin concentration (MCHC) were significantly higher in Long-COVID patients compared to healthy donors (▶ **Fig. 1a, b**). In contrast, the peripheral lymphocyte count was significantly decreased in Long-COVID, albeit still within the physiological range. Regarding the iron metabolism, plasma iron levels were marginally reduced, whereas transferrin saturation was significantly lower in samples from Long-COVID patients compared to healthy donors.

Oxygen binding to hemoglobin is impaired in Long-COVID patients

Next, we performed clinical blood gas analysis to identify alterations in oxygen binding to hemoglobin and the acid-base balance in Long-COVID patients compared to healthy donors. The percentage of oxygen bound hemoglobin was significantly lower in Long-COVID patients (▶ **Fig. 1c**). Interestingly, this was accompanied by a concomitant increase in carbon monoxide binding (▶ **Fig. 1d**). No differences were observed regarding pO_2 (▶ **Fig. 1e**), but the pCO_2 was significantly lower in the arterial blood of Long-COVID patients compared to healthy donors (▶ **Fig. 1f**). Despite the fact that blood pH was within physiological limits in both groups (▶ **Fig. 1g**), the values for base excess and bicarbonate were significantly lower in Long-COVID patients compared to healthy donors (▶ **Fig. 1h, i**).

Discussion

Long-COVID is associated with a plethora of symptoms and can impact nearly all organ systems, including the hematological compartment. Here, we show that Long-COVID patients suffer from impaired oxygen binding to hemoglobin with concomitant increase in carbon monoxide (CO) binding. Elevated carboxyhemoglobin (COHb) levels are common in sepsis, hemolysis, and severe inflammatory conditions, and can cause profound hypoxia and, ultimately, lead to neurocognitive deficits and myocardial depression (reviewed in [18]). Furthermore, it was proposed that the cell's redox state and metabolic demands are regulated by the hemoglobin oxygen saturation and deoxyhemoglobin binding to the cytosolic N-terminus of band 3 (AE1) [19, 20]. AE1 is known to be the most abundant membrane protein in mature RBCs, with a role in chloride shift (bicarbonate/chloride homeostasis) and as a docking site for several structural proteins contributing to membrane integrity [20, 21]. Elevated levels of COHb may affect the erythrocyte integrity by down-regulation of oxygen saturation. This is in line with observations from Kubankova et al., who reported changes in deformability, and heterogeneity of erythrocyte deformation and size in COVID-19 patients that persisted for months after hospital discharge [22]. At low oxygen saturation, deoxyhemoglobin outcompetes the glycolytic enzymes to bind to the AE1 N-terminus, thereby favoring glycolysis and the generation of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (DPG) to promote further oxygen release and tissue oxygenation, thus relieving hypoxia. Long-COVID patients regularly suffer from shortness of breath, which in turn leads to a compensatory increase in respiratory rate, which then could cause respiratory alkalosis. This is in part compensated by kidney-dependent removal of circulating bicarbonate [23], which could explain lower bicarbonate levels and base excess in the arterial blood of Long-COVID patients compared to healthy donors. This is further supported by the observed lower pCO_2 in Long-COVID patients, albeit pH remained unchanged compared to healthy donors. Although, arterial plasma [H^+] changes have no effect on the O_2 flow from the lungs to peripheral tissues,



▶ **Fig. 1** Blood gas analysis of arterial blood from Long-COVID patients and healthy donors: (**a**) MCH, (**b**) MCHC, (**c**) O_2Hb, (**d**) COHb, (**e**) pO_2, (**f**) pCO_2, (**g**) pH value, (**h**) bicarbonate value, and (**i**) base excess value. Grey doted boxes indicate the physiological range. Data are presented as boxes with Min and Max including single values. Tests were performed two-sided. Mann–Whitney U-test was used for statistical analyses. *$p<0.05$, **$p<0.01$.

they are important indicators of the actual degree of a systemic acid-base disturbance [24]. Since MCH and MCHC were also elevated in Long-COVID patients, we suggest a potential compensatory mechanism. Elevation of these hematological parameters were also reported by other researchers focusing on this subject [25]. Higher MCHC can have multiple causes, including autoimmune hemolytic anemia (AIHA), which is common during (chronic) viral infections [26, 27]. In case of AIHA, a rare autoimmune disorder, the immune system creates autoantibodies to destroy red blood cells before they can be replaced, leading to anemia and hemoglobin being present outside of the red blood cells, which in turn results in higher MCHC values [28]. Thus, the moderate plasma iron deficiency and transferrin saturation found in this study could indicate a certain degree of hemolysis. Under hemolytic conditions, referring to an uncontrolled RBC breakdown, iron is released and lost via the urine and thus transferrin saturation can be low due to

the resulting iron deficiency [29]. In order to refine these hypotheses, it is important to measure DPG levels in Long-COVID patients in future studies.

The lymphocyte count was significantly lower in Long-COVID patients compared to healthy donors. Lymphocytes are crucial in regulating cellular immunity. Especially in patients with severe COVID-19 disease, reduced numbers of all lymphocyte types (T-, B- and natural killer cells) were measured [14, 30], which has been shown to be a direct effect of the coronavirus disease [31]. The decreased lymphocyte count in Long-COVID patients may be explained by immune exhaustion, which is a phenomenon that is frequently associated with chronic viral infections [32]. In both lung-resident and circulating T cells from COVID-19 patients an escalation in the expression of exhaustion markers, including PD-1, CTLA-4, TIGIT and Tim-3, was observed [33, 34]. There is evidence that SARS-CoV-2, similar to other chronic viral infections, appears to severely impair the functional subsets of CD4 + and CD8 + T cells [32, 35]. Thus, weakening of the immune system could favor the spread of SARS-CoV-2, which in turn could have yet unknown long-term implications and could be a driver of Long-COVID. Moreover, the reactivation of latent pathogens, including herpesviruses and others, may contribute to Long-COVID [36]. Nevertheless, further investigation is required to clarify the clinical relevance of reduced lymphocyte counts in Long-COVID patients.

Potential limitations

There are certain limitations to this study, which have to be addressed in future research on this topic. As healthy donors and Long-COVID patients were not matched with regard to age, sex, comorbidities and co-medication a putative confounding effect cannot be ruled out. In addition, no correlation with regard to type and severity of symptomatic and functional impairment in Long-COVID patients was performed. Furthermore, larger cohorts with complete information on medical history will be necessary to validate our findings and to shed light on disease-driving mechanisms.

Conclusions

Our study demonstrates for the first time, that Long-COVID patients show impaired oxygen binding to hemoglobin potentially caused by elevated COHb concentration in the arterial blood. Although the underlying pathomechanisms still need to be determined in clinical as well as experimental studies, a potential immunodeficiency and impaired erythrocyte function leading to disturbances of the acid-base balance, could be plausible causes of Long-COVID. In conclusion, our study identified novel facets of Long-COVID pathophysiology, which in turn could open up innovative therapeutic avenues in the future.

Author contributions

R.K. designed, performed and analyzed experiments, interpreted data and wrote the manuscript. K. T. recruited patients, recorded the medical history and interpreted clinical data. M.C., M.T., and J.T. helped with performance of experiments. D.K. helped with interpretation of data and contributed to manuscript writing. T.T. initiated the study, acquired funding, contributed to data interpretation and edited the manuscript. S.K. analyzed and interpreted data, oversaw statistical analysis and wrote the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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