

Arterial Carboxyhemoglobin Levels In Covid-19 Critically Ill Patients

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Research

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Abstract

Background : Oxidative stress conditions may be responsible for an up-regulation of the expression of heme oxygenase, the enzyme synthesizing carbon monoxide (CO) in cells. Elevated levels of arterial carboxyhemoglobin (CO-Hb) have been found in critically ill patients, including those suffering from acute lung injury. We aimed to investigate the changes of arterial CO-Hb levels in COVID-19 critically ill patients.

Methods : A retrospective cohort study was conducted on the medical charts of 63 patients admitted in the ICU for severe COVID-19 infection over the period March 1 – May 31, 2020.

Results : The overall ICU mortality rate was 39%. Non-survivors had a significantly higher profile of arterial CO-Hb levels than survivors ($p < 0.001$), but arterial CO-Hb increased significantly from admission to day 30 in both groups ($p < 0.001$). Mortality could not be predicted by the changes in arterial CO-Hb, but there was a correlation between the maximal arterial CO-Hb value and SOFA score on admission. No correlation could be demonstrated between arterial CO-Hb and serum C-reactive protein (CRP) as a marker of the inflammatory response.

Conclusions : A greater increase of arterial CO-Hb levels over time may represent another marker of severity of COVID-19 infection in ICU patients.

Background

Elevated carbon monoxide (CO) concentration has been found in exhaled breath of patients suffering from various pulmonary inflammatory disorders. In hemodynamically stable patients, and provided that ventilatory conditions remain constant, expired CO is reflecting endogenous CO production. Carbon monoxide is mainly derived from heme catabolism, with heme oxygenase being the step-limiting enzyme of the heme degradation. Heme oxygenase exists under three isoforms, one inducible (HO-1) and two constitutives (HO-2 and HO-3). HO-1 isoform is induced within cells mainly during oxidative stress [1]. In the absence of exogenous source of CO, arterial carboxyhemoglobin (CO-Hb) levels are reflecting the endogenous CO production. We aimed to investigate in patients admitted to the intensive care unit (ICU) for severe COVID-19 infection the profile of arterial CO-Hb levels and its relationship with outcome.

Material & Methods

Study population

This retrospective observational cohort study was performed in a single center, university hospital (900 beds) with a 48 ICU-beds facility. Inclusion criteria were patients older than 18 years admitted to the ICU for COVID-19 infection over the period ranging from March 1, 2020 to May 31, 2020. The diagnosis of COVID-19 infection was made by the combination of RT-PCR analysis of a nasopharyngeal swab and lung computed tomography (CT). The local ethics committee approved the study. Specific treatment for

COVID-19 varied according to the update of international recommendations. For the patients with mechanical ventilation, a lung protective strategy was applied in the volume-control mode. Adaptation of ventilator settings including inspired fraction of oxygen (FiO₂) was made according to the results of arterial blood gas analysis. All the patients were ventilated alternating prone with supine position. Inhaled nitric oxide (NO) therapy was applied for refractory hypoxemia or pulmonary hypertension.

Data collection

Investigators collected demographics, medical history, vital signs, physical examination, laboratory investigations, pharmacological treatment, ventilator settings and scores from a dedicated data collection program (Qcare, C3, Germany). Data analysis was performed until day 30.

Laboratory investigations

For each patient, the determination of arterial CO-Hb was performed at least four times a day simultaneously to arterial blood gas analysis by a co-oximeter Radiometer ABL800 (Copenhagen, Denmark). Calibration was performed every day. A mean daily value of arterial CO-Hb was recorded for each patient. Serum bilirubin and C-reactive protein (CRP) levels were measured routinely at the hospital laboratory.

Severity of illness and outcome

Severity of the illness was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score. Scoring was based on the worst variables recorded in the 24 hrs following ICU admission. The outcome was expressed as mortality and duration of mechanical ventilation in the ICU.

Statistical analysis

Continuous variables were reported as means and standard deviations and categorical variables as counts and percentages. Means were compared between groups using Student t test. Time trends were compared between groups using generalized linear mixed models with the group (survivor or non survivor) as a fixed factor and time as a random repeated factor. The null hypothesis was rejected at p-values < 0.05. Analyses were performed using SPSS software, version 25 (IBM, Chicago, IL, USA and graphed with Graphpad Prism 8.0 (GraphPad Software, La Jolla, CA, USA).

Results

Sixty-three patients were admitted in the ICU for COVID-19 infection during the study period. At the peak of the epidemic, 26/48 of the available beds were occupied by COVID-19 patients. Demographics of the population are detailed in Table I. Smokers represented a very small percentage of the population and were weaned from tobacco smoking since several days before ICU admission. Forty-one patients were mechanically ventilated. All the patients who deceased had required mechanical ventilation immediately after ICU admission. The duration of mechanical ventilation was not different between survivors and non-

survivors ($p = 0.92$). The overall mortality in the ICU was 35%. The SOFA score on admission was significantly higher in the non-survivors group, but not the APACHE II score. The arterial CO-Hb level on admission was similar in both groups. The difference between the peak and admission arterial CO-Hb level was significant for both groups ($p < 0.001$). The non-survivors had a higher arterial CO-Hb profile than the survivors ($p < 0.001$) (Fig. 1). As expected, the profile of the PaO₂/FiO₂ ratio, arterial PCO₂ and serum CRP was also different among survivors and non-survivors. The relationship between arterial CO-Hb, PaO₂/FiO₂ ratio, arterial PCO₂ and serum CRP was investigated at different time points (admission, day 5, 10, 15, 20, 25, 30), but no correlation was found (Table II). A correlation was found between peak arterial CO-Hb and SOFA ($p = 0.01$). Mortality could not be predicted by minimal or maximal bilirubin, admission, minimal, maximal, or [maximal – admission] arterial CO-Hb.

Discussion

The majority of ICU hospitalized COVID-19 patients not only experienced ARDS, but also vascular inflammation, thrombosis, and ultimately multi-organ damage. The triggering factors are likely multiple. Among them, excess of free heme is a potential offending agent as it has been shown to exacerbate and contribute to the pathogenesis of numerous inflammatory diseases [2]. Therefore, it may be postulated that accumulated free heme and Hb could be involved in the mechanisms mediating pulmonary permeability and inflammation in COVID-19 patients [3]. Protective mechanisms against free heme include HO-effector molecules biliverdin/bilirubin, CO and ferritin.

Our data clearly show a different profile of arterial CO-Hb levels among non-survivors of COVID-19 infection in the ICU. In the group of survivors, arterial CO-Hb also significantly increased from baseline at 30 days. Maximal arterial CO-Hb levels were in correlation with disease severity as expressed by SOFA score. But no values of arterial CO-Hb were predictive of mortality; however, the cohort was very small. The number of smokers was surprisingly limited in the present study and there was no difference at baseline in arterial CO-Hb levels among smokers and non-smokers. Therefore, it was assumed that exogenous CO did not play a significant role. It is also documented that CO-Hb may vary following hemorrhage or hemolysis but these conditions were not encountered in our patients.

The main source of endogenous CO results from the metabolism of heme by heme oxygenase. There is a direct relationship between the arterial CO-Hb and the endogenous production of CO either in healthy volunteers or in clinical studies [4–6]. Changes in ventilator variables may also affect arterial CO-Hb concentration [7]. Several factors may affect the elimination of the endogenously produced CO: CO lung diffusing capacity, alveolar ventilation, lung capillary oxygen pressure, carboxyhemoglobin concentration, endogenous CO production and CO catabolism. The increase of the inspired fraction of oxygen will logically result in a transient increase in CO lung elimination as a result of a competition of CO and O₂ for the same binding sites.

In the present study, changes in inspired oxygen fraction or ventilator settings occurred in almost all of the patients, particularly at the acute initial stage. As arterial CO-Hb was a mean of 4 to 8 daily values for

each patient, we can estimate that these changes would have a minimal impact on CO lung excretion. On the other hand, arterial CO-Hb represents a balance between endogenous CO production and CO elimination. It remains difficult to establish if the increase in arterial CO-Hb has to be ascribed to an increase of CO production or to an impaired CO elimination through the alveolo-capillary membrane. There was no correlation between arterial CO-Hb and PCO₂, and a strict parallelism between CO and CO₂ pulmonary elimination is not expected.

Previous investigations have shown that carboxyhemoglobin levels may be elevated in trauma and surgical patients [8–9], and in patients with inflammatory lung disease [10, 11] and critical illness [4, 12, 13]. We failed to demonstrate a correlation between arterial CO-Hb and serum CRP. The kinetics of both factors appear different, as high CRP levels are likely present at the early phase during the so-called “cytokine storm”, while increase of arterial CO-Hb is slower as reflecting heme catabolism and impairment of the alveolo-capillary membrane.

The heme-catabolizing enzyme heme oxygenase (HO)-1 is highly inducible in oxidative stress. Patients with acute respiratory distress syndrome are reported to have an increased expression of (HO)-1 [14]. Arterial carboxyhemoglobin level was measured in a cohort of 1267 ICU patients mainly admitted after cardiovascular surgery. Both low minimum and high maximum levels of arterial carboxyhemoglobin were associated with increased intensive care mortality [15]. Arterial carboxyhemoglobin levels also correlated with biomarkers of the inflammatory response. These data suggested that the failure to up-regulate the activity of the HO system in the presence of a pro-inflammatory stress may be associated with a worse prognosis, while excessive (HO)-1 induction may also affect negatively the outcome. In patients from a medical ICU, survivors had slightly higher minimal and marginally higher average CO-Hb levels when compared to non-survivors [16].

Carbon monoxide signaling could have lung protective effects by modulating autophagy, mitochondrial biogenesis, apoptosis, and cellular proliferation [17].

The administration of exogenous CO has been proposed as therapeutic intervention in various conditions including acute lung injury [18–20]. Contrasting results have been published as some *in vivo* studies suggested that the endogenous production of CO or its exogenous administration was protective, while other studies were negative [21]. In a human model of sepsis-related ARDS, inhalation of low doses of CO was associated with an increase in arterial CO-Hb ranging from 3.48 to 4.9%. No serious adverse events occurred in the CO-treated group, while circulating mitochondrial DNA levels were reduced [22].

Carbon monoxide can confer anti-inflammatory protection in rodent models of ventilator-induced lung injury (VILI). This modulation could be partly due to an increased expression of caveolin-1 [19].

Among the drugs recently proposed to treat COVID-19 infection, dexamethasone seems able to reduce hemolysis and induce HO-1 in macrophages in other conditions [23]. Induction of HO-1 can also be achieved by a large variety of agents, including aspirin, statins, probucol, valsartan, niacin, resveratrol, and curcumin.

Conclusions

In conclusion, non-survivors of severe COVID-19 infection had a profile with higher arterial CO-Hb levels than survivors. This could be in relationship with the intensity of inflammatory response, oxidative stress and heme degradation. In patients with a favorable outcome, the slight increase of arterial CO-Hb over time could be explained by the induction of HO-1, but also by a mildly disturbed pulmonary CO elimination through a less severely damaged alveolo-capillary barrier.

Abbreviations

ARDS

acute respiratory distress syndrome; CO:carbon monoxide; CO-Hb:arterial carboxyhemoglobin; COVID-19:disease caused by coronavirus 2; HO:heme oxygenase

Declarations

Availability of data and materials

The datasets are available from the corresponding author on reasonable request

Ethics approval and consent to participate

The trial was conducted with the guiding principles of the Declaration of Helsinki and was approved by the local institutional ethics committee.

Consent for publication

Not applicable

Competing interests

The authors have no competing interests to declare

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Author's contributions

PC, LG, VM, XW, CC and PFL participated to the clinical management of the patients. DCZ, PH were involved in the study design and protocol development. PC reviewed the medical charts and encoded the

data. DCZ conducted the statistical analysis. All authors reviewed, revised and approved the final version of the manuscript.

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Tables

Variable	Survivors (n = 41)		Non-survivors (n = 22)		p-value
	mean	SD or percentage	mean	SD or percentage	
Age (years)	57.1	10.9	65.4	11.1	0.006
% men	33	80%	17	77%	
Smokers	3	7.3%	2	9.1%	0.85
APACHE II score	11.4	5.2	16.2	8.5	0.008
SOFA score	5.0	2.2	7.2	3.2	0.003
Bilirubin min (mg/dl)	0.54	1.16	0.39	0.22	0.55
Bilirubin max (mg/dl)	1.24	1.61	2.46	6.18	0.24
CO-Hb on admission (%)	1.10	0.50	0.95	0.24	0.19
Ventilatory mode					
-mechanical ventilation	19	46%	22	100%	< 0.001
-high flow nasal canula	8	19.5%	0	0%	< 0.001
-oxygen mask	14	34.1%	0	0%	< 0.001
Duration of mechanical ventilation (hours)	365	618	351	308	0.92

Table I. Demographics of the population (survivors, non-survivors)

CO-Hb	PaO ₂ /FiO ₂	PCO ₂	CRP
admission			
ρ=	-0.052	0.12	-0.056
p-value	0.71	0.35	0.66
day 5			
ρ=	0.028	0.063	0.049
p-value	0.82	0.69	0.76
day 10			
ρ=	-0.06	0.19	-0.23
p-value	0.73	0.25	0.89
day 15			
ρ=	-0.24	-0.04	0.25
p-value	0.21	0.82	0.18
day 20			
ρ=	-0.54	0.11	0.01
p-value	0.007	0.61	0.64
day 25			
ρ=	-0.47	0.41	0.34
p-value	0.032	0.064	0.13
day 30			
ρ=	-0.092	0.23	-0.1
p-value	0.29	0.43	0.74
Table II. Spearman's correlation coefficient (ρ) between arterial carboxyhemoglobin (CO-Hb), PaO ₂ /FiO ₂ ratio, arterial partial pressure of CO ₂ (PCO ₂) and serum C-reactive protein (CRP) at different time points.			

Figures

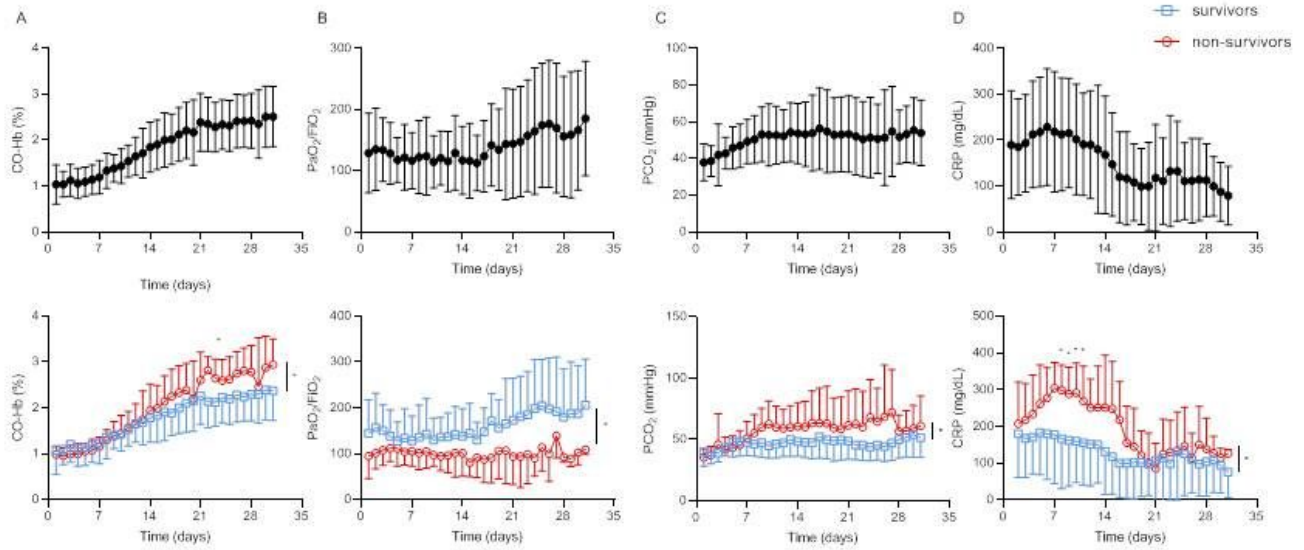


Figure 1

Profile of arterial carboxyhemoglobin (CO-Hb) (A), PaO₂/FiO₂ ratio (B), arterial partial pressure of CO₂ (PCO₂) (C) and serum C-reactive protein (CRP) (D) over time in the whole cohort (upper part) and comparison between survivors and non-survivors (lower part). *: statistically significant difference of trend between survivors and non-survivors.