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Title: The liaison between respiratory failure and high blood pressure: evidence from COVID-19 patients

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Introduction

Expanding from China around the World, COVID-19 is the disease caused by the Severe Acute Respiratory Syndrome Related Coronavirus 2 (SARS-CoV-2). COVID-19 primarily manifests by hypoxic normo-hypocapnia with preserved lung compliance [1]. In the absence of targeted treatment, sub-intensive clinicians support patients with non-invasive ventilation and anti-inflammatory/anti-viral agents waiting for status improvement. Angiotensin-converting enzyme 2 (ACE2), highly expressed on the external membrane of lungs, heart, kidney and gastrointestinal tract cells, displays the binding site for the spike protein of SARS-CoV-2 [2]. ACE2, identified as counterpart of the Renin-Angiotensin-Aldosterone System (RAAS), converts Angiotensin (Ang) II to Ang-(1-7) and Ang I to Ang-(1-9). ACE2 activity induces vasodilatation and reduces cell growth and inflammatory response. In experimental models that mimic the viral acute respiratory distress syndrome (ARDS), the absence of *Ace2* led to inflammation, vascular permeability and lung injury via activation of Ang II pathway [3, 4]. The decrease in ACE2 activity by SARS-CoV-2 can unleash a cascade of injurious effects through a heightened imbalance in the actions of the products of ACE vs ACE2. Moving to a clinical setting, the ACE2 downregulation may be one of the pathways sustaining arterial hypertension [5] and pulmonary arterial hypertension [6]. Therefore, it is conceivable that in COVID-19 a cleavage of membrane ACE2 along with its circulatory levels could impact on the disease progression and clinical worsening [7]. Thus, to support a pathophysiological role of ACE2, the present report shares clinical data from an observational study conducted on 40 patients with a diagnosis of COVID-19, hospitalized in the Cardiorespiratory Sub-Intensive COVID-19 Unit at the Fondazione IRCCS Ca' Granda Policlinico Hospital of Milan.

Methods

Forty consecutive patients with COVID-19 were recruited. At that time, standardized treatment was hydroxychloroquine and lopinavir/ritonavir. Blood pressure (BP), partial pressure of oxygen and inspiratory fraction of oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) and alveolar-arterial oxygen gradient ($\Delta\text{A-aO}_2$) were measured 2 to 4 times/day according to standard clinical protocol. Median value of plasma potassium concentration ($[\text{K}^+]_{\text{plasma}}$) was also evaluated. In the case of any supplementation of potassium, or administration of mineralcorticoid receptor antagonists or diuretic stimulators, the $[\text{K}^+]_{\text{plasma}}$ we considered was referred prior to the pharmacological intervention. The relationship between respiratory and hemodynamic variables, *i.e.* $\Delta\text{A-aO}_2$ vs meanBP was evaluated by Poon's analysis which allows to normalize the inter-individual variability [8]. The composite of death and invasive ventilation were evaluated after 28 days of hospitalization.

Results

Mean age was 64 ± 11 years and twenty-nine out of forty patients were male. All patients had normal heart function, but one had stable heart failure with reduced ejection fraction. Despite only 23 patients presented with a pre-existing history of hypertension (preHT), all patients, although under optimized non-invasive ventilatory treatment (optimal FiO_2 and positive end-respiratory pressure), showed a degradation of $\text{PaO}_2/\text{FiO}_2$ and $\Delta\text{A-aO}_2$ concomitant with a raised BP and average drop in $[\text{K}^+]_{\text{plasma}}$ (figure, Panel A-B-C-D). $[\text{K}^+]_{\text{plasma}}$ median was 3.8 mmol/L. The median time period leading to a negative clinical picture was 4.25 days. According to hemodynamic and respiratory changes, patients were grouped as follows: group 1 (8/40 patients, 4/8 with preHT) and group 2 (32/40

patients, 15/32 with preHT). Group 1 showed temporary oscillations towards high BP with contrary changes in lung function (best vs worst status: $\text{PaO}_2/\text{FiO}_2=311$ vs 130 mmHg; $\Delta\text{A-aO}_2=107$ vs 312 mmHg; meanBP= 83 vs 89 mmHg). After 28 days, these patients showed better outcomes, *i.e.* no deaths and clinical improvement, even after the need of invasive ventilatory support (2 cases). Patients in group 2 were in critical disease (best status: $\text{PaO}_2/\text{FiO}_2=286$ mmHg; $\Delta\text{A-aO}_2=158$ mmHg; meanBP= 88 mmHg). They experienced a rapid deterioration of clinical conditions with linear increasing of BP and progressive worsening in gas exchange (worst status: $\text{PaO}_2/\text{FiO}_2=122$ mmHg; $\Delta\text{A-aO}_2=364$ mmHg; meanBP= 111 mmHg). Panel E shows a positive correlation between $\Delta\text{A-aO}_2$ and meanBP as assessed by Poon's analysis (slope= 6.666 , $R^2=0.757$; $p < 0.0001$). According to our hypothesis, $[\text{K}^+]_{\text{plasma}}$ was considered as marker of RAAS activation and in group 2 the median value of 3.8 mmol/L was used to stratify the patients. The slope of $\Delta\text{A-aO}_2/\text{meanBP}$ relationship was significantly (U Test, $p < 0.001$) steeper in those with $[\text{K}^+]_{\text{plasma}} < 3.8$ mmol/L (see grey dots of panel F). After 28 days, compared to group 1, those in group 2 had a greater prevalence of intensive care need (6/32) and a higher mortality (16/32) in a very short period time (6.1 days). At the date of April 12th, the remaining 10 patients were still alive or discharged at home.

Discussion

Our findings showed that in COVID-19 a degradation of lung function may be associated with a rise in BP. Though COVID-19 is primarily known as a respiratory disease, it seems to move progressively to a vascular disease resulting in a hemodynamic instability. In line with the evidence that SARS-CoV-2 knocks out the vasodilatory modulation driven by ACE2 [7, 9], we indirectly documented the RAAS activation by monitoring $[\text{K}^+]_{\text{plasma}}$ changes. Indeed, there is particular concern about hypokalemia in COVID-19, due to interaction of SARS-CoV-2 with RAAS [10]. According to $[\text{K}^+]_{\text{plasma}}$ and BP variability, an up-regulation of aldosterone might be one of the fatal mechanisms leading to a negative prognosis. Aldosterone which is a potent arteriolar vasoconstrictor directly acts on salt and water retention as well as on inflammation [6]. Considering that a raising BP could mirror the systemic vasoconstriction due to ACE2 depletion, the increased ventilatory dead space ($\Delta\text{A-aO}_2$) may be an expression of changes in pulmonary vessels tone leading to blood flow redistribution. Indeed, in stable condition, hypoxic pulmonary vasoconstriction is physiologically protective allowing a perfusion steering blood flow toward functionally preserved lung regions [11]. When COVID-19 reaches a certain stage, there is a disproportionate endothelial damage that disrupts pulmonary vasoregulation, promotes ventilation-perfusion mismatch (the primary cause of initial hypoxemia), and fosters thrombogenesis [12]. Overall, our evidence, that has to be further verified suggests that COVID-19 patients are less capable to counteract the progressive activation of the RAAS, then the Ang II/AT1R axis, via downregulation of ACE2. In group 1 a sort of physiological or pharmacological counterbalance restored the best possible status. In group 2, the extreme severity of the disease has led to worst outcome. The quicker the hemodynamic changes, the greater the severity of COVID-19 syndrome. While the results of the trial on recombinant-human-ACE2 are still awaited (NCT04335136), COVID-19 patients may benefit from known endothelial active agents, *i.e.* ACE-inhibitors, angiotensin II type-I receptor blockers or mineralcorticoid-receptor antagonists.

Figure legend:

Box plots of oxygen and inspiratory fraction of oxygen ratio ($\text{PaO}_2/\text{FiO}_2$; panel A), Alveolar-arterial oxygen gradient ($\Delta\text{A-aO}_2$; panel B), meanBP (BP_{mean} ; panel C), plasma potassium levels ($[\text{K}^+]_{\text{plasma}}$; panel D). Statistical significance was obtained through Mann-Whitney U Test comparing “Best status” with “Worst status”. * $p < 0.001$.

Poon’s analysis of $\Delta\text{A-aO}_2/\text{meanBP}$ (panel E; $n = 137$; slope = 6.666, $R^2 = 0.757$; $p < 0.0001$) and Poon’s analysis of $\Delta\text{A-aO}_2/\text{meanBP}$ according to $[\text{K}^+]_{\text{plasma}}$ stratum (panel F). In panel F grey dots represent the group with $[\text{K}^+]_{\text{plasma}} \leq 3.8 \text{ mmol/L}$ ($n = 78$; slope = 6.686, $R^2 = 0.774$; $p < 0.0001$); white dots represent the group with $[\text{K}^+]_{\text{plasma}} > 3.8 \text{ mmol/L}$ ($n = 59$; slope = 4.491, $R^2 = 0.670$; $p < 0.0001$).

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