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

To the Editor:

Expanding from China around the world, coronavirus 2019 (COVID-19) is the disease caused by severe acute respiratory syndrome-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 noninvasive ventilation and anti-inflammatory/anti-viral agents waiting for status improvement. Angiotensin-converting enzyme (ACE)2, 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 a 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 viral acute respiratory distress syndrome, the absence of *Ace2* led to inflammation, vascular permeability and lung injury *via* activation of the 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 *versus* 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, hospitalised in the Cardiorespiratory Sub-Intensive COVID-19 Unit at the Fondazione IRCCS Ca' Granda Policlinico Hospital (Milan, Italy).

40 consecutive patients with COVID-19 were recruited. At that time, standardised treatment was hydroxychloroquine and lopinavir/ritonavir. Blood pressure (BP), arterial oxygen tension/ inspiratory oxygen fraction (P_{aO_2}/F_{IO_2}) and alveolar–arterial oxygen tension difference (P_A–a_{O_2}) were measured two to four times per day according to standard clinical protocol. Median value of plasma potassium concentration ($[K^+]_{plasma}$) was also evaluated. In the case of any supplementation of potassium, or administration of mineral corticoid receptor antagonists or diuretic stimulators, the $[K^+]_{plasma}$ we considered was referred prior to the pharmacological intervention. The relationship between respiratory and haemodynamic variables, *i.e.* P_A–a_{O_2} *versus* mean BP was evaluated by Poon's analysis which allows us to normalise the inter-individual variability [8]. The composite of death and invasive ventilation were evaluated after 28 days of hospitalisation.

Mean age was 64±11 years and 29 out of 40 patients were male. All patients had normal heart function, but one had stable heart failure with reduced ejection fraction. Despite only 23 patients presenting with a pre-existing history of hypertension (preHT), all patients, although under optimised noninvasive ventilatory treatment (optimal F_{IO_2} and positive end-respiratory pressure), showed a degradation of P_{aO_2}/F_{IO_2} and P_A–a_{O_2} concomitant with a raised BP and average drop in $[K+]_{plasma}$ (figure 1a–d). Median $[K+]_{plasma}$ was 3.8 mmol·L^{-1}. The median time-period leading to a negative clinical picture was 4.25 days. According to haemodynamic 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
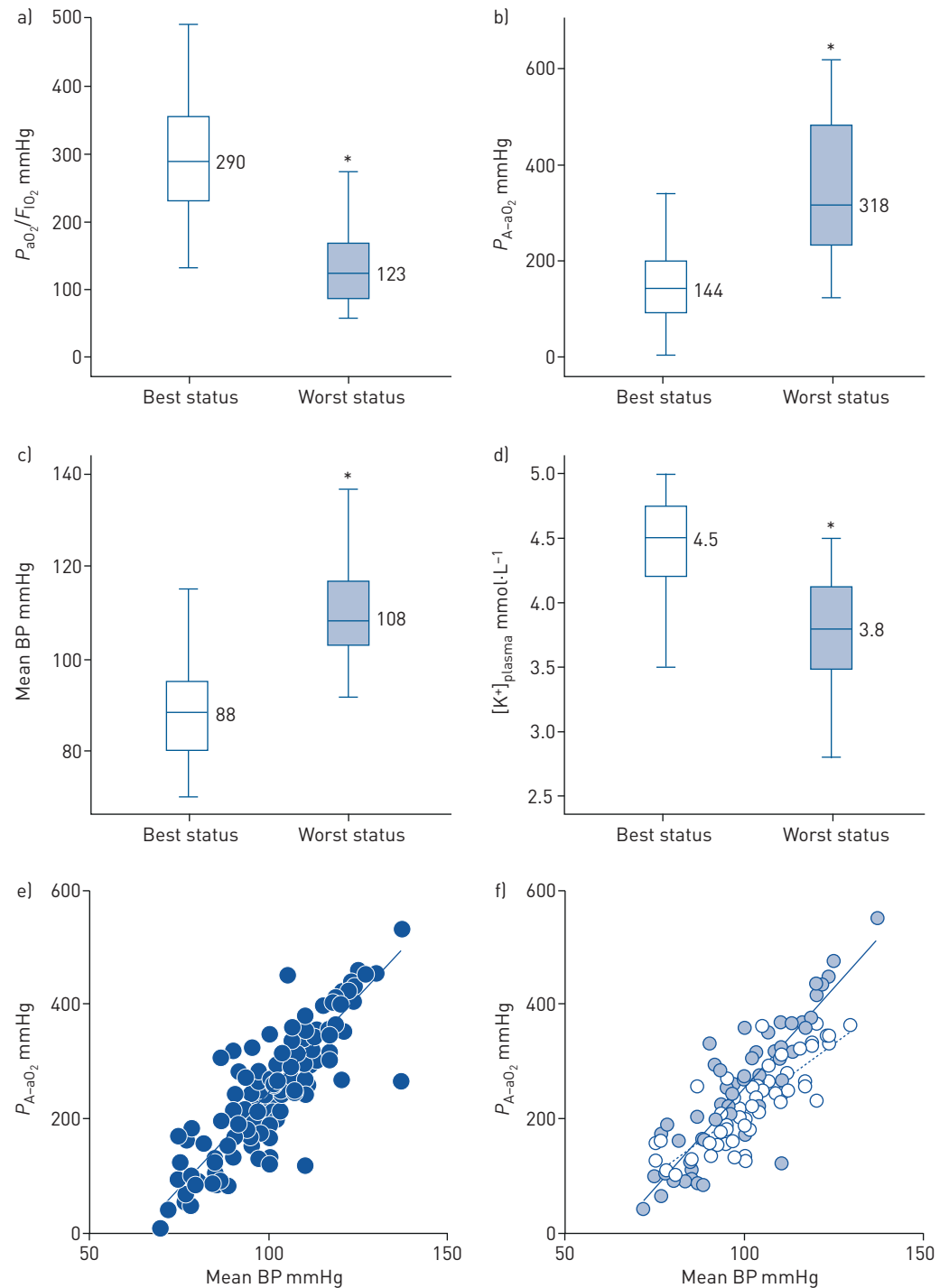
FIGURE 1 Box plots of a) oxygen and inspiratory fraction of oxygen ratio, b) alveolar–arterial oxygen gradient, c) mean blood pressure (BP) and d) plasma potassium levels ($[K+]_{plasma}$). Statistical significance was obtained through Mann–Whitney U-test comparing best status with worst status. *: p<0.001. e) Poon's analysis of P_A–a_{O_2}/mean BP: n=137, slope=6.666, R^2=0.757; p<0.0001. f) Poon's analysis of P_A–a_{O_2}/mean BP according to $[K+]_{plasma}$ stratum. In (f) pale blue dots represent the group with $[K+]_{plasma} \leqslant 3.8$ mmol·L^{-1} (n=78; slope=6.686, R^2=0.774; p<0.0001) and white dots represent the group with $[K+]_{plasma}$ >3.8 mmol·L^{-1} (n=59; slope=4.491, R^2=0.670; p<0.0001). P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; P_A–a_{O_2}: alveolar–arterial oxygen tension difference.

oscillations towards high BP with contrary changes in lung function (best *versus* worst status: P_{aO_2}/F_{IO_2}=311 *versus* 130 mmHg; P_A–a_{O_2}=107 *versus* 312 mmHg; mean BP=83 *versus* 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 (two cases). Patients in group 2 were in critical disease (best status:

P_{aO_2}/F_{IO_2}=286 mmHg; P_A–a_{O_2}=158 mmHg; mean BP=88 mmHg). They experienced a rapid deterioration of clinical conditions with linear increasing of BP and progressive worsening in gas exchange (worst status: P_{aO_2}/F_{IO_2}=122 mmHg; P_A–a_{O_2}=364 mmHg; mean BP=111 mmHg). Figure 1e shows a positive correlation between P_A–a_{O_2} and mean BP as assessed by Poon's analysis (slope=6.666, R^2=0.757; p<0.0001). According to our hypothesis, [K+]$_{plasma}$ was considered a marker of RAAS activation and in group 2 the median value of 3.8 mmol·L^{-1} was used to stratify the patients. The slope of P_A–a_{O_2}/mean BP relationship was significantly (U-test p<0.001) steeper in those with [K+]$_{plasma}$ <3.8 mmol·L^{-1} (figure 1f). After 28 days, compared to group 1, those in group 2 had a greater prevalence of intensive care need (six out of 32) and a higher mortality (16 out of 32) in a very short period time (6.1 days). As of 12 April 2020, the remaining 10 patients were still alive or discharged at home.

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 haemodynamic 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 [K$^+$]$_{plasma}$ changes. Indeed, there is particular concern about hypokalemia in COVID-19, due to interaction of SARS-CoV-2 with RAAS [10]. According to [K$^+$]$_{plasma}$ and BP variability, an upregulation 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 an increased BP could mirror the systemic vasoconstriction due to ACE2 depletion, the increased ventilatory dead space (P_A–a_{O_2}) may be an expression of changes in pulmonary vessel 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 disproportionate endothelial damage that disrupts pulmonary vasoregulation, promotes ventilation–perfusion mismatch (the primary cause of initial hypoxaemia), 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. The disequilibrium of AngII/ATR1 balance may be effective on the cardiovascular system once COVID-19 progresses and ACE2 reduces. 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 haemodynamic changes, the greater the severity of COVID-19 syndrome. While the results of the trial on recombinant-human-ACE2 are still awaited (clinicaltrials.gov identifier NCT04335136), COVID-19 patients may benefit from known endothelial active agents, *i.e.* ACE-inhibitors, angiotensin II type-I receptor blockers or mineral corticoid-receptor antagonists.

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