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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Increased mortality among hypertensive COVID-19 patients: Pay a closer look on diuretics in mechanically ventilated patients

Early data on Covid-19 from Wuhan, China, have emphasized that hypertension is a potential risk factor for severe Covid-19 and increased mortality. Accordingly, in the two largest reports on Covid-19 patients receiving mechanical ventilation, one from Lombardy, Italy, and the other from New York, USA, reported high mortality rates; hypertension was the most common comorbidity.[1,2] However, there is a lack of data concerning the exact mortality in hypertensive mechanically ventilated patients. Moreover, the specific antihypertensive classes that these patients were receiving, are not known; only data on renin-angiotensin-aldosterone system (RAAS) inhibitors are reported.[3]

Initially, concerns had been raised on the relation between drugs affecting RAAS inhibitors and Covid-19 outcomes. Angiotensin converting enzyme (ACE) 2 acts as the receptor for SARS-COV-2 to enter into the cells, therefore, ACE-2 expressing cells present increased susceptibility to Covid-19 infection. As a result, angiotensin receptor blockers (ARBs) and ACE 2 inhibitors have been the center of attention during the present epidemic. Data arising from large series of patients receiving RAAS inhibitors begin to support the lack of association between their daily prescription and increased mortality.[2,3] Reynolds et al, assessed the relationship between previous treatment with ACE inhibitors (and other antihypertensive classes) and the likelihood of severe Covid-19. Of 2573 infected patients with hypertension, 634 had severe Covid-19 (i.e., intensive care unit admission (ICU), mechanical ventilation (MV), or death). There were no differences concerning medication use (ACE inhibitors, beta-blockers, calcium channel blockers, diuretics) and the incidence of severe disease development.[3] However in this study, MV patients accounted for only 43% of all ICU admissions, while the number of deaths significantly exceeded the number of MV patients.[3] Therefore, no conclusion can be drawn, neither on the mortality in the subgroup of MV patients, and especially the hypertensive MV subgroup, nor on the possible contribution of specific antihypertensive classes (i.e. diuretics). Moreover, in New York the mortality rate of the patients receiving mechanical ventilation (320 patients) was 76.4% for those younger than 65 years and 97.2% for those over 65, but, actually, the mortality in the proportion of MV patients with hypertension, and even more the possible contribution of the specific antihypertensive classes, can not be estimated.[2]

In MV hypertensive patients, other factors may contribute to an unfavorable outcome; regarding antihypertensive treatment, standard therapy with a diuretic, until just before ICU admission may play a crucial role. Reynolds et al, are the first to report on diuretic use (even if only referring on hydrochlorothiazide).[3] Yet, the proportion of MV patients receiving diuretics is not mentioned. Heart-lung interactions play a significant role in MV patients which can be exaggerated in hypovolemic patients.[4] Under this perspective, diuretic use may be of great importance. Currently, diuretics are used in hypertension, usually in combination with other classes of drugs; thus, in the more severe forms. Covid-19 patients with respiratory failure, just before intubation, are hypovolemic per se (fever in the preceding days and respiratory distress compromising adequate fluid intake). Moreover, a restricted fluid resuscitation is indicated in patients with ARDS, trying to keep the lung “dry”, a strategy helpful to avoid intubation, or later for a successful weanin;g[5] decreasing redundant fluids improves lung function and oxygenation. Therefore, diuretics are continued or even increased in such cases. Meanwhile, when the patients are in distress, endogenous catecholamines are increased, preserving blood pressure levels. Sedation, used for intubation, releases the sympathetic tone inducing vasodilation and shock; in a report from Seattle, USA, 82% of the patients presented persistent hypotension 12 hours after intubation. Although possible, it is not reported whether hypertensive patients on previous diuretic treatment needed increased vasopressor doses when intubated.

Heart-lung interactions may, indeed, be more pronounced in hypertensive patients on diuretics, and account for a proportion of the reported fatalities when MV is initiated. Increased Positive End Expiratory Pressure (PEEP) levels, in a hypovolemic patient on vasopressors, may induce right heart dysfunction through compression of the pulmonary vasculature. This may be exacerbated in Covid-19 lung with widespread vascular thrombosis with microangiopathy and alveolar capillary thrombosis; these findings have been recently reported in lung autopsy findings from patients dying from Covid-19.[6] In addition, when lung compliance is relatively normal, as it has been recorded in Covid-19 lung injury, substantial amount of the alveolar pressure is transmitted to the pleural pressure.[5] Therefore, relatively high PEEP, as indicated by the ARDSnet and the most recent surviving sepsis campaign guidelines, in a non-recruitable lung with almost normal compliance may significantly increase pleural pressure and have a detrimental impact on hemodynamics by deteriorating venous return.[4] Both conditions (right ventricular dysfunction and decreased venous return) reduce the cardiac output.

Moreover, maintaining an arterial blood pressure of 60 to 65 mmHg, as proposed, may have a detrimental impact on hypertensive patients on MV.[5] Relative hypotension in these patients, along with the decreased cardiac output resulting from mechanical ventilation onset, as analyzed previously, may significantly affect the course of the disease. At the tissue level, hypovolemia and vasoconstriction induce hypoperfusion and end-organ damage which can lead to multiorgan dysfunction syndrome (MODS) and an unfavorable outcome. Renal hypoperfusion may be one of the main mechanisms explaining the acute kidney injury (AKI) observed (5% of the ICU Covid-19

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patients required renal replacement therapy).[5] It is well known that renal function is primarily affected in MODS.

In conclusion, increased mortality among hypertensive patients is probably a fact. On the other hand, RAAS inhibitors don't seem to contribute to the increased mortality. Probably other factors or concomitant medication may explain the unfavorable outcome, especially among MV patients. Diuretics, commonly used in hypertensive patients, may be detrimental exacerbating heart-lung interactions upon mechanical ventilation initiation, especially when a strategy of increased PEEP is applied. Certainly, this is a hypothesis, as there is a complete lack of evidence concerning the diuretic use among MV patients; yet, there is a sound pathophysiologic mechanism that could contribute to the increased reported mortality. Hemodynamic and fluid status consideration, along with lower airway pressures during the respiratory cycle (Plateau Pressure, PEEP) among hypertensive Covid-19 MV patients could probably improve their outcomes.

Ethical statement

The article doesn't contain the participation of any human being and animal.

Verification

All authors have seen the manuscript and agree to the content and data. All the authors played a significant role in the paper.

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Declaration of Competing Interest

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