Statement from Sudanese Society of Hypertension (SSH) on risks and management of hypertensive patients during COVID-19 pandemic

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Abstract

Hypertension is the single largest global contributor to disability-adjusted life years lost. The majority of the aged population have hypertension, and appear to be at increased risk of covid-19 infection. How hypertension modifies the risks and severity of covid-19 and the implications for hypertension treatment is less clear. Therefore, there is currently no reason to discontinue RAS blockers in stable patients facing the COVID-19 pandemic. In COVID-19 patients with severe symptoms, sepsis, or hemodynamic instability RAS blockers and other blood pressure lowering drugs should be used or discontinued on a case-by-case basis, taking into account current guidelines. Careful and continuous research is vital for an understanding of the mechanisms underlying any additional risk from hypertension with covid-19, and to determine the best and safest ways to treat those with severe manifestations of disease.

Introduction

In the last two decades, viral epidemics such as the severe acute respiratory syndrome coronavirus (SARS-COV) 2002-2003, H1N1 influenza in 2009 and the Middle East

respiratory syndrome coronavirus (MERS-COV) 2012 were recorded. On December 31, 2019, an epidemic in China, started; caused by the SARS-CoV-2 virus called "COVID-19.The WHO raised the threat to the COV-19 pandemic to the "very high" level, on February 2020.[1] Systematic reviews suggest that the key risk factors for hospital admissions include age, male sex, and other comorbidities [2] The most common comorbidities associated with increased risk of infection and worse outcomes were hypertension, diabetes and coronary heart disease 30%, 19%, 8% respectively[3]. Another

report showed that hypertensives are the most frequent patients with COVID-19 who developed acute respiratory distress syndrome (ARDS)[4]. Overall, it is confirmed by many studies that hypertension was associated with worse prognosis and death, about 58.3% of hypertensive patients with COVID-19 infection were admitted to ICU compared to 21.6% of individuals with normal blood pressure[5].

The frequency with which COVID-19 patients are hypertensive is not entirely surprising nor does it necessarily imply a causal relationship between hypertension and COVID-19 or its severity. This can be attributed to the fact that hypertension is exceedingly frequent in the elderly, and older people appear to be at particular risk of being infected with SARS-CoV-2 virus and of experiencing severe forms and complications of COVID-19.[6]

Pathogenicity

It is still unclear if uncontrolled hypertension is a risk factor for contracting COVID-19, also it is unproved that good blood pressure control would relieve the disease burden [7]

Owing to the interaction between COVID-19 and ACE2, it has been suggested that hypertension may be involved in the pathogenesis of COVID-19, by either playing a direct role as a pre-existing clinical predictor of disease severity, or by causing deterioration late during the disease course [8]

In hypertensive females, there is greater activity of Angiotensin II type 2 receptor (AT2R) than angiotensin II type I (AT1R) which translates into a decrease of harmful response of AT1R activation. More expression and activation of AT1R are seen in hypertensive males and hypothesized in causing vasoconstriction, pro-inflammatory response, increasing oxidative stress, leading to acute respiratory distress syndrome ARDS in severe COVID-19. This condition provides an explanation for the higher incidence of severe COVID-19 in males compared to females. Estrogen is also approved in bringing the tendency towards better RAS in females [9]

There is increasing understanding that severe COVID-19 causes considerable vascular abnormalities including widespread micro thrombotic and macro thrombotic events, renal and cardiac failure. The association of hypertension with its potential microvascular

disease, with more severe disease and poor outcomes from COVID-19, is therefore an important consideration.[10]

COVID-19 and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker paradox:

Whether the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) increase susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or protect against it is a subject of controversy.

The proposed mechanism by which ARBs and ACEIs aggravate COVID-19 illness is through the upregulation of angiotensin-converting enzyme 2 (ACE2) [11]. ACE2 physiologically counters the renin–angiotensin–aldosterone system (RAAS) activation and also serves as a receptor for SARS-CoV-2 [12]. ACE2 is expressed broadly in numerous tissues such as, lung alveolar epithelial cells, vasculature, intestine, and kidney. Once SARS-CoV-2 gains entry into the target cell, the host response is a major determinant of severity of the ensuing pathogenesis. Hence, the interaction of SARS-CoV-2 with ACE2 is a key factor for infectivity [13]. ACE2 exists primarily as a membrane-bound mono carboxyl peptidase. Interestingly, a soluble or circulating form of ACE2 (sACE2) was shown to block SARS viral entry into cells [14] and is now being considered as a potential therapy.

ACE2 is distinct and not directly related to the clinical use of ACEIs or ARBs, or to their mechanisms of action. ACEIs target ACE1to inhibit conversion of angiotensin I to angiotensin II, thereby reducing levels of angiotensin II available to bind and activate the type 1 angiotensin receptor (AT1), which mediates most of the vasopressor effects of angiotensin II [15]. On the other hand ARBs work by binding to AT1 receptors and directly blocking the actions of angiotensin II. In contrast to ACE, which acts to generate angiotensin II, ACE2 degrades angiotensin II into angiotensin [16] and is thus a negative regulator of the RAAS [17].

Paradoxically, mechanisms by which ACEIs and ARBs may be protective in SARS-CoV-2 infection are also being proposed [13,17]. Animal studies have found that direct angiotensin II suppression with ACEIs and AT1 receptor antagonism with ARBs may

promote and stabilize cell membrane complexes between ACE2 and AT1 receptors [18]. In theory, these complexes may reduce the ability of the virus to enter host cells [19]. Suppression of angiotensin II may also prevent virus-mediated acute lung injury [20] and other organ dysfunction, which is another proposed mechanism by which use of ACEIs and ARBs may be beneficial in COVID-19.

Recently, a living systematic review which included 14 observational studies (a total of 23 565 patients with COVID-19) [21] provided high-certainty evidence that a history of ACEI or ARB use was not associated with increased severity of COVID-19 illness. Moreover, the same review provided moderate-certainty evidence that there was no association between use of these medications and positive SARS-CoV-2 test results among symptomatic patients. Whether these medications are beneficial in COVID-19 treatment remains uncertain.

On the basis of the above mentioned studies, no indication exists to prophylactically stop ACEI or ARB treatment because of concerns about COVID-19. Indeed, withdrawal of long-term ACEIs or ARBs may be harmful, especially in patients with heart failure because observational studies and trials have suggested that discontinuation of ACEI or ARB therapy is associated with worse outcomes.

Immune response of COVID-19

The majority of COVID-19 cases (about 80%) are asymptomatic or exhibits mild to moderate symptoms, but approximately the 15% progresses to severe pneumonia and about 5% eventually develops ARDS, septic shock and/or multiple organ failure.[22,23]

Once CoV-2 gains entry into the target cell, mainly via the interaction with ACE2, the host response determines the severity of the ensuing pathogenesis. Notably, SARS-CoV-2 infection activates both innate and adaptive immune response, thus sustaining the resolution of COVID-19. It has been hypothesized that the acute lung injury (ALI) and ARDS observed in COVID-19 patients is mainly due to immune pathology induced by the excessive inflammatory innate response, so called cytokine storm[22]. Laboratory analysis of severe COVID-19 patients revealed increased levels of a number of proinflammatory cytokines in particular IL-6, IL-1, L-2, IL-8, IL-17, G-CSF, GMCSF,

IP-10, MCP-1, CCL3, and TNFα[22,24]. Evidence from literature indicates that the cytokine storm observed in COVID-19 resembles that occurring in Cytokines Release Syndrome (CRS), a form of systemic inflammatory response syndrome, and in secondary haemophagocytic lymphohistiocytosis (sHLH), an hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinemia with multi-organ failure, mainly induced by viral infections[25]. On the other hand, severe COVID-19 patients showed decreased levels of circulating CD4+ cells, CD8+ cells, B cells and natural killers (NK) cells as well as a decrease in monocytes, eosinophils and basophils. [23,26].

Regarding the adaptive immunity, it has been reported that SARS-CoV-2 reduces the percentage and count of CD3+, CD4+, and CD8+ lymphocytes populations[27]. In a retrospective, single-center study enrolling a cohort of 452 patients with COVID-19 in Wuhan, patients with severe COVID-19 displayed a significantly lower level of both helper T cells and suppressor T cells.[28]. In particular, among helper T cells, a decrease in regulatory T cells, with a more pronounced reduction according to the severity of the cases, and in memory T cells has been observed, whereas the percentage of naïve T cells was found increased [28] Notably, naïve and memory T cells are essential immune components, whose balance is crucial for maintaining a highly efficient defensive response. Overall, the lymphopenia observed in COVID-19 patients may depend on the fact that SARS-CoV-2 may directly infect lymphocytes minimally expressing ACE2, leading to lymphocyte death or, alternatively, may directly damage lymphatic organs since they express ACE2 receptors.[29]

As far as concerns B cells, by using single-cell RNA sequencing to characterize the transcriptome landscape of blood immune cell subsets during the recovery stage of COVID-19, significant changes in B cells has been found[30]. In particular, while the naïve B cells have been reported to be decreased, the plasma cells have been found remarkably increased in peripheral blood mononuclear cells. Moreover, several new B cell-receptor changes have been identified. In addition, isotypes, including IGHV3–15, IGHV3–30, and IGKV3–11, previously used for virus vaccine development have been confirmed.[30] The strongest pairing frequencies, IGHV3–23-IGHJ4, has been suggested to indicate a monoclonal state associated with SARS-CoV-2 specificity [30].

Moreover, given the pivotal role of B cells in the control of infections, tracking the antibody seroconversion response is an important process for the clinical evaluation of infections. In COVID-19 patients, while serum samples from patients with COVID-19 showed no cross-binding to the S1 subunit of the SARS-CoV spike antigen, some cross-reactivity of serum samples has been observed from patients with COVID-19 to nucleocapsid antigens of SARS-CoV. Interestingly, this study reports that 96.8%of tested patients achieved seroconversion of IgG or IgM within 20 days after symptom onset with a titer plateaued within 6 days after seroconversion. Moreover, 100% of patients had positive virus-specific IgG approximately 17–19 days after symptom onset. Instead, 94.1% patients showed positive virus-specific IgM approximately 20–22 days after symptom onset.[31]

Conclusions on management of Hypertensive Patients with COVID-19

There is no clear evidence that hypertension per se is associated with an increased risk of infection by COVID-19. Therefore, patients with hypertension should apply the same precautions as subjects of the same age category and with the same profile of comorbidities [31]

- In stable patients with COVID-19 infections or at risk for COVID-19 infections, treatment with ACEIs and ARBs should be executed according to the recommendations in the different guidelines

- The currently available data on COVID-19 infections do not support a differential use of RAS blockers (ACEI or ARBs) in COVID-19 patients.

- In COVID-19 patients with severe symptoms, sepsis, or hemodynamic instability RAS blockers and other blood pressure lowering drugs should be used or discontinued on a case-by-case basis, taking into account current guidelines.

- For Patients who may be anxious about taking antihypertensive medication and about their risks from infection during the covid-19 pandemic The evidence base is limited, so strong recommendations are difficult

- People with complications of hypertension, such as ischemic heart disease, are already regarded as being at high risk. It seems reasonable to advise those with poorly controlled hypertension (i.e. blood pressure above guideline targets), particularly if prolonged, to also consider themselves to be at high risk and, therefore, to follow appropriate social distancing advice. [32]

- Younger individuals with hypertension, with good control of blood pressure, risks of undiagnosed cardiovascular disease are low, and they could therefore be reassured

Future direction

Further research analyzing the continuously increasing data on the impact of hypertension and blood pressure lowering drugs, particularly RAS blockers, on the clinical course of COVID-19 infections is warranted.

Careful and continuous research is vital for an understanding of the mechanisms underlying any additional risk from hypertension with covid-19, and to determine the best and safest ways to treat those with severe manifestations of disease.

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