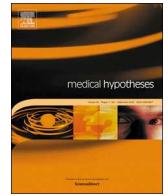




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Letter to Editors

Endothelial dysfunction in Coronavirus disease 2019 (COVID-19): Gender and age influences



A B S T R A C T

Several risk factors are associated with a worse outcome for COVID-19 patients; the most recognized are demographic characteristics such as older age and male gender, and pre-existing cardiovascular conditions. About the latter, hypertension and coronary heart disease are among the most common comorbidities recorded in infected patients, together with type 2 diabetes mellitus (T2DM). Data from Istituto Superiore di Sanità (ISS, Italy) show that more than 68.3% of patients had hypertension, 28.2% ischemic heart disease, 22.5% atrial fibrillation, while 30.1% T2DM. Several authors suggested that cardiovascular diseases and diabetes mellitus are linked to endothelial dysfunction, and all of them are strictly related to aging.

Considering the impact of the gender on the COVID-19 epidemic, even if confirmed cases from each nation are changing every day, epidemiological data clearly evidence that in men the infection causes worse outcomes compared to women. In Italy, up to 21 May, in the age range of 60–89 years, male deaths were 63.9% of total cases. The reason behind this difference between genders appears not clear; however, the diversity in sex-hormones and styles of life are believed to play a role in the patient's susceptibility to severe SARS-CoV-2 outcomes. It is known that the activation of endothelial estrogen receptors increases NO and decreases ROS, protecting the vascular system from angiotensin II-mediated vasoconstriction, inflammation, and ROS production.

During the pandemic, joining forces is vital; thus, as people help doctors by limiting their displacements out of their houses avoiding hence the spread of the infection, doctors help patients to overcome severe SARS-CoV-2 infections by using multiple pharmacological approaches. In this context, the preservation of endothelial function and the mitigation of vascular inflammation are prominent targets, essential to reduce severe outcomes also in male older patients.

Introduction

Several types of drugs are available to treat Coronavirus Disease 2019 (COVID-19) patients, but no specific clinical trial confirmed their safety and efficacy [1]. Therefore, the patient's spontaneous immune response is still essential for healing. Consequently, elderly patients, frequently affected by many comorbidities, may incur in the worst outcome. To 27 May 2020 there have been more than 5.59 million confirmed cases of COVID-19 and 350.531 deaths all around the world, while recovered patients have been more than 2.28 million [2]. In Italy, up to 25 May 2020 the median age of the 230.414 confirmed cases of COVID-19 is 62 years [3]. The case fatality rate of older patients in the ranges of 60–69, 70–79, and 80–89 years is 10.5%, 25.8% and 31.9%, respectively [3], while the median age of death is 81 years [4].

Even if there is no real evidence about the drugs used to prevent and cure the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5], several pharmacological agents are employed off-label as supportive treatment for patients; among these, antivirals (e.g., remdesivir), immunomodulators (e.g., tocilizumab), antibiotics (e.g., azithromycin), together with respiratory assistance if needed [6]. The generally accepted approach against COVID-19 infections can be distinguish in two steps: 1) contrast the spread using social distancing and community containment, and 2) pharmacological treatment of patients, discerning mild and severe infections. All this, while waiting to discover the vaccine.

Ever since the pandemic started, pulmonary impairment has been held to account for the high morbidity and mortality [7,8]. This is in accordance with the coronavirus dissemination through respiratory system, including mouth and nose mucosae [9]; these tissues are rich in angiotensin converting enzyme 2 (ACE2) which is the main binding site for the entry of the virus into host cells [10]. About this, it should be underlined that ectoenzyme ACE2 is expressed also in several other

human organs, such as small intestine (jejunum) and kidneys, and in the cardiovascular and central nervous systems [11]. Among these tissues, ACE2 is highly expressed in human vascular and cardiac pericytes suggesting the vulnerability of cardiovascular system to SARS-CoV-2 infection [12–15]. This observation may explain the multi-organ damage arising from COVID-19 infections which has been reported by frontline doctors during the treatment of this disease [16]. Several cases of cardiac complications are reported in these patients [17–19]. An exemplificative case report concerns an healthy 53-years-old patient who developed an acute myopericarditis with systolic dysfunction, a week after the onset of fever and dry cough due to COVID-19 infection [20].

Several risk factors are associated with a worse outcome for COVID-19 patients; the most recognized are demographic characteristics such as older age and male gender, and pre-existing cardiovascular conditions [16,21–24]. About the latter, hypertension and coronary heart disease are among the most common comorbidities recorded in infected patients, together with type 2 diabetes mellitus (T2DM) [17,18,24]. Data from Istituto Superiore di Sanità (ISS, Italy) show that more than 68.3% of patients had hypertension, 28.2% ischemic heart disease, 22.5% atrial fibrillation, while 30.1% T2DM [4]. Furthermore, authors demonstrated that cardiac injury is independently related to increased mortality in COVID-19 patients [17]; unfortunately, the cardiac injury mechanisms in these patients are still not well understood.

Several authors suggested that cardiovascular diseases and diabetes mellitus are linked to endothelial dysfunction [25–28], and all of them are strictly related to aging (Fig. 1). In general, the vasoconstriction induced by vascular modulators is increased in elderly, while agonist-mediated endothelial vasodilation is attenuated [29–31]. Furthermore, a reduced chronic adaptive capacity of older heart and vessels has been reported in animal models and in humans [31]. It can be speculated that the cause-effect relation between COVID-19 and cardiovascular

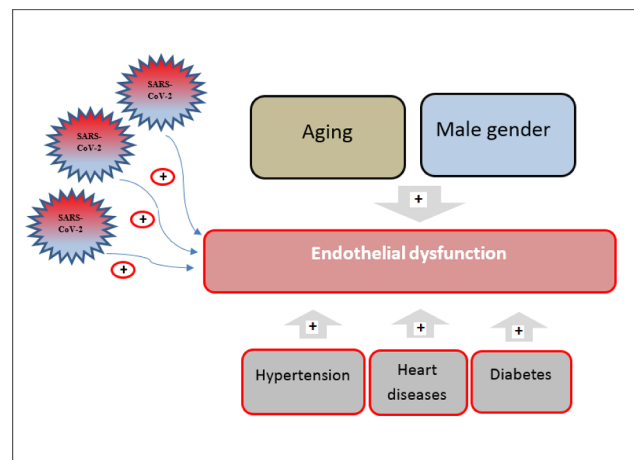


Fig. 1. Graphical representation of aggravating factors of the endothelial dysfunction. SARS-Cov-2 infection should be considered an additional risk for cardiovascular diseases.

impairment is bidirectional. On the one hand, patients with cardiovascular diseases and persistent endothelial dysfunction can be more susceptible to SARS-Cov-2 infection, having an higher ACE2 exposure in vascular and heart pericytes, as recently suggested [12]; on the other hand, the infection itself can cause endothelial damage through heavy inflammatory changes (Fig. 1). Besides, authors showed that patients with pneumonia have various alterations of vascular responses to endothelin 1, adrenomedullin, nitric oxide (NO), etc [32]. In addition they observed that the vascular changes are age-related, evidencing a decrease in peripheral vascular resistance during acute phase of pneumonia in younger patients, but an increased resistance in elderly patients [32].

Overall, for the multi-organ damage arising from the COVID-19 infections a common basis could be the status of endothelial dysfunction in each patient. In support of this idea, several clinical evidences have been reported [15]. The endothelial dysfunction highlighted by post-mortem examinations is also supported by data reporting an evident increase of thromboembolic complications in COVID-19 patients and suggesting to treat them with low-molecular-weight heparin (LWMH) [33,34]. It is well-known that endothelial cell injury can strongly activate the coagulation system via exposure of tissue factor and other pathways. Therefore, COVID-19 infection, aggravating the endothelial dysfunction of patients, generates a detrimental hypercoagulable state [35].

In general, the main causes of endothelial dysfunction are: 1) aging, 2) sex hormones and their decline during aging, 3) ROS, 4) increased circulating endothelial microparticles and progenitor cells (EMPs/PCs) ratio, and 5) a pro-inflammatory status [36,37].

Considering the impact of the gender on the COVID-19 epidemic, even if confirmed cases from each nation are changing every day, epidemiological data clearly evidence that in men the infection causes worse outcomes compared to women [21–24]. In Italy, up to 21 May, in the age range of 60–89 years, male deaths were 63.9% of total cases [4]. The reason behind this difference between genders appears not clear; however, the diversity in sex-hormones and styles of life are believed to play a role in the patient's susceptibility to severe SARS-CoV-2 outcomes. It is known that the activation of endothelial estrogen receptors increases NO and decreases ROS, protecting the vascular system from angiotensin II-mediated vasoconstriction, inflammation, and ROS production [38,39]. Interestingly, Hudson and co-workers have suggested that women with congestive heart failure respond more favourably to angiotensin receptor blockers (ARBs) than men who had a more effective survival with angiotensin converting enzyme inhibitors (ACEI) [40]. In the China STATUS II study, women showed a greater antihypertensive response to treatment with the ARB valsartan

combined with amlodipine compared to men on the same treatment [41]. Recently, it has been suggested that ARBs could be preferred over ACE inhibitors in COVID-19 patients since the former preserve the function of ACE2 enzyme, which counterbalance renin angiotensin system activation [42]. However, this topic still remains controversial [43]. Overall, estrogens improve endothelial function through several mechanisms: 1) reduction of oxidative stress, 2) modulation of the renin-angiotensin system, and 3) attenuation of the cellular endothelin-1 system [44].

Could not we use protective agents to preserve cardiac and vascular functions during COVID-19 treatments?

During the pandemic, joining forces is vital; thus, as people help doctors by limiting their displacements out of their houses avoiding hence the spread of the infection, doctors help patients to overcome severe SARS-CoV-2 infections by using multiple pharmacological approaches. In this context, the preservation of endothelial function and the mitigation of vascular inflammation are prominent targets, essential to reduce severe outcomes also in male older patients.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110015>.

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