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VIEWPOINT

Sympathetic activation: a potential link between comorbidities and COVID-19

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In coronavirus disease 2019 (COVID-19), higher morbidity and mortality are associated with age, male gender, and comorbidities, such as chronic lung diseases, cardiovascular pathologies, hypertension, kidney diseases, diabetes mellitus, and obesity. All of the above conditions are characterized by increased sympathetic discharge, which may exert significant detrimental effects on COVID-19 patients, through actions on the lungs, heart, blood vessels, kidneys, metabolism, and/or immune system. Furthermore, COVID-19 may also increase sympathetic discharge, through changes in blood gases (chronic intermittent hypoxia, hyperpnea), angiotensin-converting enzyme (ACE)1/ACE2 imbalance, immune/inflammatory factors, or emotional distress. Nevertheless, the potential role of the sympathetic nervous system has not yet been considered in the pathophysiology of COVID-19. In our opinion, sympathetic overactivation could represent a so-far undervalued mechanism for a vicious circle between COVID-19 and comorbidities.

Introduction

In coronavirus disease 2019 (COVID-19), higher morbidity and mortality are associated with comorbidities, such as chronic lung disease, cardiovascular pathologies, hypertension, kidney diseases, diabetes mellitus, and obesity [1–3]. Conversely, COVID-19 deaths are frequently caused by a final homeostasis dysregulation caused not only by pulmonary damage but also by cardiac, circulatory, renal, and/or metabolic effects. Attention has been focused on the mechanisms involved in the comorbidity-induced increase in morbidity/mortality but the potential role of the sympathetic nervous system has not yet been considered, despite sympathetic activation represents one of the specific characteristics of most above comorbidities and it could play a detrimental effect on COVID-19 patients.

All comorbidities associated with increased morbidity/mortality in COVID-19 are characterized by sympathetic overactivation

It is widely known that increased sympathetic discharge is associated with chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, cardiovascular diseases (hypertension, heart failure), renal pathologies, and metabolic disturbances (diabetes, obesity, metabolic syndrome). Increase in

Abbreviations
ACE1, angiotensin-converting enzyme type 1; ACE2, angiotensin-converting enzyme type 2; AngI, angiotensin I; AngII, angiotensin II; ARDS, acute respiratory distress syndrome; AT_1-R, angiotensin II type 1 receptor; COVID-19, coronavirus disease 2019; IL, interleukin; MasR, Mas receptor; MSNA, muscle sympathetic nerve activity; SARS-CoV, severe acute respiratory syndrome–coronavirus; TNF-α, tumor necrosis factor-α.

peripheral hypoxic chemosensitivity is a common mechanism stimulating sympathetic activation in the above conditions [4–9], but other stimulatory mechanisms are present.

Chronic obstructive pulmonary disease and obstructive sleep apnea syndrome increase sympathetic activation mainly through chronic intermittent hypoxia, which acts by increasing the peripheral chemosensory response [10,11].

In heart failure, the increased sympathetic outflow correlates with disease progression and poor prognosis [12,13]. It has been ascribed to decreased arterial/cardiopulmonary baroreflex, increased chemosensitivity, increased metabolic reflexes, or progression of correlated renal insufficiency or sleep apnea syndrome [14–16].

Renal damage (for instance, experimental models of renal ischemia–reperfusion) is also associated with sympathetic activation, due to the activation of the renal afferents and brain renin–angiotensin system. Conversely, in a positive feedback loop, sympathetic overactivity stimulates tubular Na^+/H_2O reabsorption, decreases renal blood flow, and stimulates renin–angiotensin system. It also aggravates ischemia/reperfusion-induced renal damage through pro-inflammatory mechanisms (reviewed in Ref. [17]).

In obesity, diabetes, and metabolic syndrome, sympathetic overactivity has been ascribed to high levels of circulating insulin and leptin, which stimulate the sympathetic outflow both centrally and peripherally, and/or to chronic intermittent hypoxia due to obstructive sleep apnea [18,19]. Sympathetic overactivation in turn increases insulin resistance, maintaining a positive feedback loop [20].

The effects of smoking on COVID-19 are still highly controversial, and conflicting data are present in the literature. Epidemiological studies and meta-analyses report unexpectedly low prevalence of smoking among COVID-19 hospitalized patients [21]. Conversely, other authors observed significant associations of smoking with clinical progression and mortality of hospitalized COVID-19 patients, consistently with the well-known detrimental effects of smoking on lung function [22,23]. The potential role of autonomic effects could also warrant an evaluation, as cigarette smoking results in increased sympathetic discharge and decreased baroreflex activity [24–28].

Sympathetic overactivity may exert significant detrimental effects on COVID-19 patients

In COVID-19, the comorbidity-induced increase in sympathetic activity may show negative effects on pulmonary, cardiovascular, renal, metabolic, and immune/inflammatory homeostasis.

In COVID-19, cardiovascular complications frequently occur, including arrhythmias, myocarditis, heart failure, and myocardial infarction [29]. All these conditions are negatively affected by sympathetic overactivation and could represent a way through which comorbidity-induced sympathoactivation may increase COVID-19 morbidity/mortality. In some reports, myocardial injury has been reported in 20–40% of hospitalized cases [30–33]. Cases of Takotsubo syndrome have also been reported in COVID-19 [34–37]. In this kind of stress-related cardiomyopathy, myocardial injury is probably mediated by catecholamine-induced vascular spasm and/or direct catecholamine action on myocytes. In particular, catecholamine release in response to cytokine storm, or metabolic and emotional distress has been proposed to play a role in COVID-19-related Takotsubo syndromes [34–37], consistently with our hypothesis.

Acute kidney injury has been reported in > 20% of severe or deceased COVID-19 patients, and chronic kidney diseases are also significantly associated with severe COVID-19 [2]. Moreover, the above mechanisms involved in the vicious cycle between sympathetic overactivity and renal function also show detrimental effects on the cardiocirculatory [38,39] and lung [40] functions. Thus, it appears reasonable that sympathetic activation in comorbidities may exert negative homeostasis effects in COVID-19 also through renal effects. Moreover, liver injuries have also been reported in COVID-19 patients [41] and sympathetic activation may also be detrimental for liver function [42].

The autonomic system also exerts a modulatory role on the immune system, and its potential role in the complex immunological situation of COVID-19 is all to be studied. Sympathetic nerve fibers innervate most lymphoid organs, including bone marrow [43] and adrenergic receptors are present in many different immune cell types [44]. The effects of sympathetic system on immune system are quite complex and depend on the differentiation state of the immune cells. However, the evidence is available about a pro-inflammatory effect at least in some tissues and experimental or pathological conditions. For instance, in a mouse model of angiotensin (Ang)II-mediated hypertension, sympathetic stimulation produces noradrenaline-mediated T-cell activation and vascular inflammation [45]. Bilateral ablation of renal sympathetic nerves prevents immune activation and renal inflammation in a murine model of AngII-induced hypertension [46]. Catheter-based renal denervation has been demonstrated to reduce monocyte activation and inflammation markers

in hypertensive patients [47]. In an experimental mouse model of chronic stress, hematopoietic stem cell proliferation and increased output of neutrophils and inflammatory monocytes have been reported, in response to noradrenaline release by sympathetic nerve fibers [48]. Increased sympathetic discharge through the splenic nerve has also been reported to increase cytokine release by splenocytes [49]. Conversely, the vagal nerve has an inhibitory effect on tumor necrosis factor-α (TNF-α) release by macrophages [50,51]. The anti-inflammatory effects of the parasympathetic vagal system have been observed also with reference to intestinal diseases [52–54] and arthritis [55]. These potential immune/inflammatory effects of a sympathetic/parasympathetic imbalance seem particularly intriguing in the pathophysiology of COVID-19, which led to homeostasis derangement also through a 'cytokine storm'.

Apart from the above effects on systemic homeostasis, increased sympathetic activity may have specific detrimental effects on the respiratory system. Sympathetic overactivation and the correlated renin–angiotensin system overflow play a pivotal role in progression of pulmonary hypertension [56–58]. It has been pointed out that angiotensin-converting enzyme (ACE)1/ACE2 imbalance may contribute to progression to acute respiratory distress syndrome (ARDS) in COVID-19 patients through pulmonary vasoconstriction, inflammation, and oxidative and fibrotic damage [29]. Sympathetic innervation is known to increase pulmonary capillary leakage and favor ARDS [59–62]. Restrictive lung function has been associated with increased sympathetic nerve activity in heart failure, possibly due to interstitial pulmonary edema or changes in alveolar capillary units [63].

Aging and male gender are also associated with sympathoactivation

Risks of severe COVID-19 and related mortality increase with advancing age and male gender, as also sympathetic activation. In fact, muscle sympathetic nerve activity (MSNA) has been reported to increase with age in nonobese normotensive men and women, the latter showing lower values for age < 50 years [64]. Conversely, children are known to be protect by severe disease; various mechanisms are probably involved (developmental changes in immunity, lower prevalence of comorbidities, higher lung regenerative potential), but a possible role of the quite complex maturation of the sympathetic/parasympathetic balance may not be excluded. For instance, plasma norepinephrine, which is mainly derived from sympathetic nerve endings, increases with advancing puberty in males [65]. Relevant gender differences are present in obesity-induced increase in sympathetic activity. For instance, resting MSNA is positively correlated with body mass index in men but not in women [66,67]. This gender-based difference is partly explained by correlation of sympathetic overactivation with abdominal fat, more than subcutaneous one [68]. Thus, increased sympathetic activation could (at least partially) contribute to the pathophysiologic association of aging and male gender with COVID-19 morbidity/mortality.

COVID-19 may furtherly increase sympathetic output in a vicious circle

The sympathetic nervous system is activated by the hypoxic and hypercapnic stimuli which characterize respiratory dysfunctions. In particular, a large amount of studies has stressed that chronic intermittent hypoxia increases sympathetic output through increased carotid body sensitivity. Thus, COVID-19-induced alterations of the respiratory function may furtherly aggravate sympathetic overactivity (Fig. 1).

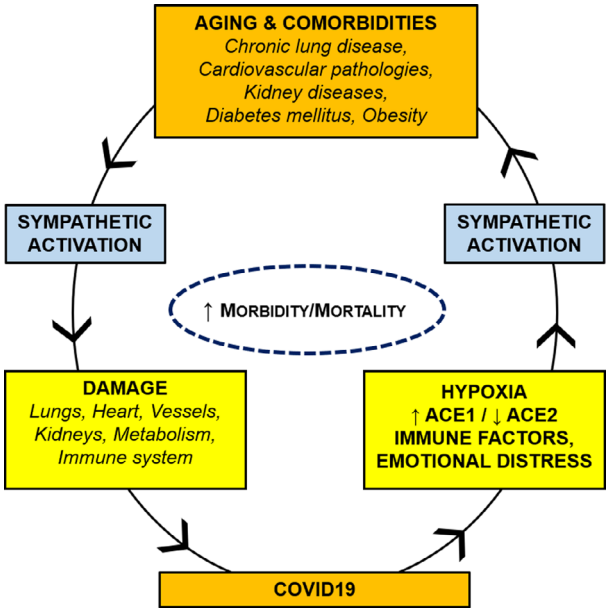

Fig. 1. Vicious circle between COVID-19 and comorbidities. Aging and comorbidities (lung, cardiovascular, kidney, and metabolic diseases) are characterized by sympathetic overactivity, which may exert detrimental effects on lungs, heart, vessels, kidney, metabolism, and/or immune system of COVID-19 patients. COVID-19 may furtherly increase sympathetic discharge, through hypoxia, ACE1/ACE2 imbalance, immune/inflammatory factors, and emotional distress.

COVID-19 may also activate the sympathetic system through increased production and release of AngII. The cellular receptor for severe acute respiratory syndrome–coronavirus (SARS-CoV) and SARS-CoV-2 is ACE2, a usually membrane-bound homologue of angiotensin-converting enzyme. ACE2 is widely expressed not only in lungs but also in other organs, such as heart, brain, kidney, and intestine. ACE1 and ACE2 have different enzymatic functions and produce different effects: ACE1 converts AngI in AngII; ACE2 converts AngI in Ang(1–9), which is then converted in Ang(1–7), and may also convert AngII in Ang(1–7). Thus, in the different tissues, a balance between the two pathways [ACE1/AngII/angiotensin II type 1 receptor (AT1-R) and ACE2/Ang(1–7)/Mas receptor (MasR)] is present, which can be affected in various clinical conditions. As a consequence, ACE2 decreases the production of AngII in favor of Ang(1–7). AngII mediates vasoconstriction, fibrosis, hypertrophy, and inflammation through AT1-R binding; Ang(1–7) mediates vasodilation, antifibrosis, antigrowth, and anti-inflammation through MasR binding [4]. Apart from the above effects, AngII mediates sympathoexcitation, whereas Ang(1–7) mediates sympathoinhibition. Internalization of SARS-CoV-2 causes inhibition of ACE2 activity and progressive depletion of membrane-bound ACE2 [69–73], with ACE1/ACE2 imbalance and increase in AngII.

Circulating AngII may increase the sympathetic output both centrally, at the level of the circumventricular organs (area postrema and subfornical organ) [58], and peripherally, by acting on the carotid body [58,74]. Thus, COVID-19-induced increase in AngII (proportional to the viral load) [75] may represent an additional way to furtherly worsen sympathoactivation in comorbidities.

Moreover, the brainstem, and particularly the solitary tract nucleus, is directly invaded by different types of coronaviruses, so that neuroinvasion by SARS-CoV-2 has also been hypothesized [76]. ACE2 is also expressed in the solitary tract nucleus and carotid body so that sympathetic activation may be furtherly increased by local ACE1/ACE2 imbalance and AngII stimulation.

In the COVID-19 severe patients, the occurrence of a 'cytokine storm' [interleukin (IL)-6, IL-10, and TNF-α] has been reported [77]. AngII may also activate macrophages and other immune cells to produce inflammatory cytokines, such as IL-6, TNF-α, and others [78–80]. Circulating cytokines mainly activate the parasympathetic system, through the so-called inflammatory reflex pathway, but in certain conditions stimulation of the sympathetic output has also been reported [81].

In the discussion of cardiovascular implications of COVID-19, Guzik *et al.* [82] have recently recalled that the activation of the sympathetic nervous system is associated with viral infections themselves and even with social isolation [83,84].

Conclusions

In conclusion, all comorbidities associated with increased morbidity/mortality in COVID-19 are characterized by sympathetic overactivation, similarly to aging and male gender. Sympathetic overactivity may exert significant detrimental effect on COVID-19 patients through its actions on lungs, heart, vessels, kidney, metabolism, and/or immune system. In turn, COVID-19 may also furtherly increase sympathetic discharge through change in blood gases (chronic intermittent hypoxia, hyperpnea), ACE1/ACE2 imbalance, or cytokine release. Thus, sympathetic overactivation could represent a so-far undervalued mechanism at the basis of the vicious circle between COVID-19 and comorbidities. Finally, it must be kept in mind that the clinical course of COVID-19 is characterized by different evolutionary phases and heterogeneous individual responses, so that the potential role of the sympathetic nervous system will have to be investigated consistently with this pathophysiological and clinical complexity.

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Conflicts of interest

The authors declare no conflict of interest.

Author contributions

AP, AE, and RDC conceptualized the data; AP, AE, SB, RB-B, CS, ES, VM, and RDC curated the data; AP wrote the original draft preparation; AP, AE, SB, RB-B, CS, ES, VM, and RDC wrote, reviewed, and edited the manuscript; and AP and RDC supervised the data.

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