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REVIEW ARTICLE

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COVID-19 and cardiovascular problems in elderly patients: Food for thought

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Abstract

The global number of COVID-19 infections, as of December 23, 2020, stood at approximately 79 million, with over 1.7 million deaths. The development of vascular inflammation may also contribute to a hypercoagulable state and endothelial dysfunction in such patients. It is known that multi-organ damage is more likely in patients with sepsis if they develop coagulopathy and that inhibition of thrombin synthesis can have a positive impact in reducing mortality. In this review, we will focus on the protection of the most fragile groups of the population, such as the elderly. This segment of the population will be a key issue and probably of primary interest to all. Biomarkers appear to be extremely useful as an indicator of what is happening from a pathophysiological point of view in the heart, allowing us to better stratify the prognosis of our patients affected by COVID-19, especially in the most severe cases and those with comorbidities.

KEYWORDS

cardiovascular patients, COVID-19, elderly

1 | INTRODUCTION

COVID-19 has been declared a global pandemic by the World Health Organization.[1] The global number of infections, as of December 23, 2020, stood at approximately 79 million, with over 1.7 million deaths. The level of contagiousness of SARS-CoV-2 appears to be higher than that of other coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). This contagiousness may explain the rapid spread of the virus and the danger it poses, especially to the weakest groups of the population, such as the elderly. In Italy, as of December 9, 2020, there had been more than 60 000 deaths, with a lethality rate of 3.5%, second only to that of Mexico and Iran, and on a par with Great Britain. A high risk of death is present in patients with comorbidities; and age is emerging as the strongest predictor of death related to COVID-19,[2] which highlights the vulnerability of elderly patients to emerging diseases. The demographic projections of the United Nations indicate that in three decades, the number of people over 65 years will more than double that of children younger than 5 years.[3] In Italy, the lethality rate according to age group, as described by the Istituto Superiore di Sanità (ISS) document, "Cumulative Data of the Integrated Surveillance of the Istituto Superiore di Sanità," goes from 0.19% in those aged 40-49 years, to 2.97% in those aged 50-59 years, 10.23% in those aged 60-69 years, 16.17% in those aged 70-79 years, 19.03% in those aged 80-89 years, and about 25% in those aged ≥90 years. According to the ISS infographic, "Characteristics of Patients Who Died Positive for SARS-CoV-2 Infection in Italy," updated on December 2, 2020, the average age of patients who have died with a positive result for SARS-CoV-2 is approximately 80 years and is 30 years higher than the average age of patients who have contracted the infection. With aging, age-associated health conditions, particularly non-communicable diseases (such as

cardiovascular disease, neoplasms, and metabolic and autoimmune diseases) combined with treatments for these diseases and immune senescence, can substantially influence responses to infectious diseases and vaccines.[4] It is therefore essential to identify these patients to ensure their protection through effective prevention, treatment, and monitoring procedures. Initially, COVID-19 disease was identified as a disease involving the respiratory tract, with the possibility of progressing to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS) (R. Costa, A. Castagna, & G. Ruotolo, Personal Considerations). Ever increasing data highlight the possibility that in addition to the lungs, the heart is also a possible target of the coronavirus. In fact, the complications of COVID-19 that lead to death are mainly respiratory failure (94.1%), acute kidney damage (23.6%), superinfections (19.3%), and acute myocardial damage (10.8%) and cardiovascular diseases seem to represent a multiplier of the risk of death in case of infection with COVID-19.[2,5,6]

2 | COVID-19, ARTERIAL HYPERTENSION, AND THE AGED

The COVID-19 pandemic and earlier coronavirus outbreaks have been associated with ARDS as well as worse outcomes in older patients.[7,8] Cardiovascular disease and the presence of hypertension are consistently reported as more common factors among patients with COVID-19 who have had severe disease, been hospitalized in intensive care, received mechanical ventilation, and/or died compared to COVID-19 patients who have had mild disease.[9] Acute respiratory infections are associated with an elevated risk of cardiovascular death, especially in the weeks immediately following infection, and particularly in elderly patients and those with preexisting cardiovascular disease. The severity of pneumonia in these patients is linked with an increased risk of death. COVID-19 and other coronaviruses show tropism for angiotensin-converting enzyme 2 (ACE2) on type II pneumocytes. This tropism, the close anatomical juxtaposition of type II pneumocytes and the pulmonary vascular network, and a severe multifaceted inflammatory reaction, is likely to drive the generalized pulmonary hypercoagulable state seen in patients with COVID-19.[10,11] SARS-CoV-2 as well as other coronaviruses can utilize angiotensin-converting enzyme 2 (ACE2) protein for entry into cells.[12–15] ACE2 is a type I integral membrane protein that performs many important physiological functions: it is a counter-regulator to the angiotensin II activity generated through ACE1 and is protective against the harmful activation of the renin-angiotensin-aldosterone system; and it degrades angiotensin II into angiotensin (1-7), which exerts vasodilatory, anti-inflammatory, antifibrotic, and antigrowth effects.[16] In studies performed in humans, tissue samples from 15 organs showed that ACE2 is widely expressed, including in the heart and kidneys, as well as in the lung, where it plays a protective role; the lung is also the main site of entry for SARS-CoV-2 in the human host,[12–16] that is, the lung alveolar epithelial cells.[17,18] It has also been shown that the binding of glycoprotein with viral peaks to the ACE2 receptor leads to its downregulation with compromise of a pulmonary protective pathway and consequent lung damage during SARS-CoV infection, contributing to viral pathogenicity.[18] Downregulation of ACE2 causes excessive angiotensin (ANG) II production by the ACE enzyme correlated with ANG receptor type 1a (AT1R) stimulation and increased pulmonary vascular permeability, facilitates initial infiltration of neutrophils in response to bacterial endotoxin,[19,20] and can cause an uncontested accumulation of angiotensin II and local activation of the renin-angiotensin-aldosterone system (RAAS). Experimental data on rats showed that ACE2 expression decreases dramatically with aging[21]; this could provide an explanation for how the differential levels of ACE2 in the heart and lung tissues of the elderly versus the young, together with comorbidities and an impaired immune system, may favor the different spectrums of disease virulence observed among patients with COVID-19. The interaction between SARS viruses and ACE2 has led to a debate on the potential use of RAAS blockers in the context of the pandemic, as these drugs are able to influence the expression of ACE2, being able to promote the virulence of the disease.[22–24] Contrary to available animal models, there are few human studies regarding the effects of RAAS inhibition on ACE2 expression. Data on the effects of RAAS inhibitors on lung-specific ACE2 expression are lacking, and further mechanistic studies in humans are also lacking. It is necessary to better define the unique interaction between SARS-CoV-2 and the RAAS network.[25] Moreover, to date, no meta-analysis of randomized and controlled studies has ever shown an excess of infectious and/or inflammatory pathologies, or mortality, with ACE inhibitors or with sartans.[26–29] Therefore, in relation to their respective positions, the European Society of Cardiology (https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News), the American Heart Association (https:/www.heart.org/en/about-us/coronavirus-covid-19-resources), the Italian Society of Cardiology (https://www.sicardiologia.it/public/Documento-SIC-COVID-19.pdf), the Italian Society of Arterial Hypertension (https://siia.it/), and the Italian Society of Pharmacology (https://www.sifweb.org) believe that the suspension, albeit temporary, of ACE inhibitors or sartans in all patients who are taking them in order to prevent future SARS-CoV-2 infection is not supported by convincing scientific evidence. In patients with active infection, in whom there are clear indications for the continuation or initiation of treatment with ACE inhibitors or sartans, no definitive epidemiological data are available, nor that derived from animal models or from controlled clinical studies to support the decision to renounce, even temporarily, the use of these drugs, an event that could cause clinical instability and adverse health events.[23]

3 | COVID-19, COMORBIDITIES, CARDIOVASCULAR DISEASE, AND COAGULOPATHIES IN THE ELDERLY

Italian data also indicate a high risk of death in COVID-19 patients with comorbidities.[30] The development of vascular inflammation may also contribute to a hypercoagulable state and endothelial

dysfunction in such patients. It is known that multi-organ damage is more likely in patients with sepsis if they develop coagulopathy and that inhibition of thrombin synthesis can have a positive impact in reducing mortality. The International Society on Thrombosis and Haemostasis has provided recommendations[31] based only on some evidence indicating that a markedly increased D-dimer value, particularly in patients who develop D-D with thrombotic phenotype, is associated with high mortality in SARS-CoV-2-infected patients. Chronic cardiovascular disease may become unstable in the setting of viral infection as a consequence of imbalance between infection-induced increase in metabolic demand and reduced cardiac reserve. The clinical manifestations of COVID-19 can range from the asymptomatic positive subject to subjects with mild symptoms (such as fever, altered taste or smell, and dry cough), or to more severe forms, such as bilateral pneumonia, systemic inflammation, altered endothelial function, coagulopathy, activation platelet, ARDS, and multi-organ failure. The troponin increase can be present in up to 25% of hospitalized patients,[32] in some cases secondary to myocardial infarction, in others to myocarditis, venous thromboembolism, disseminated intravascular coagulation, specifically referred to as COVID-19 Induced Coagulopathy (CIC).[33] Thrombo-embolic episodes can in turn be caused by hypoxia secondary to SARS-Cov19 infection, through the triggering of circulating immune complexes. In some patients with aberrantly activated hemocoagulation cascade, positivity was found for antibodies of the IgG and IgA class anticardiolipin and anti-B2-glycoprotein, suggesting that these antibodies may play a role in the abnormal activation of the hemocoagulation cascade.[34] The most severe cases of COVID-19-associated interstitial pneumonia evolve with inflammatory alveolar edema (non-cardiogenic pulmonary edema), reduced lung compliance with reduced gas exchange, and severe hypoxemia, meeting the criteria for ARDS[35]; these are cases in which mechanical ventilation is necessary.[36] The development of ventilation-perfusion mismatch, with consequent intrapulmonary shunt (Qs/Qt), secondary to the presence of poorly ventilated lung regions, favors the severe hypoxemia found in these patients.[37] The advanced manifestations of SARS-Cov-2 infection have different characteristics from classical ARDS, which is particularly relevant for pulmonary circulation. These would consist of increased hypercoagulability, with phenomena of vascular thrombosis in situ, attenuated hypoxic pulmonary vasoconstriction, and pulmonary vascular remodeling.[38] The combination of diffuse pulmonary immunothrombosis related to SARS-Cov19 infection, a pathophysiological model of pulmonary intravascular coagulopathy, and age-related changes in immunity, may explain the cardiovascular mortality in these patients. In some deceased patients, an increased capillary neoangiogenesis due to vascular intussusception, different from angiogenesis by budding by marked increase in the capillary surface, observed in other forms of ARDS, such as that of H1N1,[39] would have been highlighted as an autopsy finding, and favored from the expression of pro-angiogenic genes and from the high local blood flow.[40] Direct viral damage at the endothelial level, both at the level of the pulmonary and peripheral circulation, is certainly decisive in the activation of coagulation.[41] Hypoxia can change the basal anti-inflammatory and antithrombotic phenotype of the endothelium towards a pro-inflammatory and pro-coagulant phenotype through the expression of pro-coagulating factors induced by hypoxia, as reported in other forms of ARDS.[42] Fever, diarrhea, and dehydration, often present in COVID-19, can aggravate the picture described above. These data suggest that their identification in critically ill patients, who already have several risk factors for thrombosis, may be important in recommending an early start of anticoagulation therapy. Moreover, the use of low molecular weight heparin in addition to protecting critically ill patients from thromboembolism has been shown to possess anti-inflammatory properties: based on the immunothrombosis model, which highlights a bidirectional relationship between the immune system and thrombin generation, blocking thrombin from heparin can dampen the inflammatory response.[43] During COVID-19, extrapulmonary complications have been highlighted, including cardiac involvement, which can reach affect 20% of cases.[32,44] An acute cardiovascular syndrome has recently been defined, with clinical pictures accumulated by the occurrence of acute myocardial damage. The prevalence rates of acute myocardial damage and troponin increase are far higher in COVID-19 patients admitted to intensive care[45,46] and in those who do not survive.[44] Furthermore, in patients with acute myocardial injury and troponin increase, the death rate is high, in the order of 50%-60%.[32,47] The increase in troponin is considered a marker of disease severity and poor prognosis, probably as it expresses the presence of systemic damage in the COVID-19 patient.[48] Therefore, the prognostic significance of a slight increase in this marker may be uncertain, especially in intubated and elderly patients. Some authors suggest extensively evaluating troponin to identify patients at greater risk early,[49] but there is no unanimous agreement on this aspect.[50] ProBNP and CK-MB were also considered markers of myocardial damage. NT-proBNP is postulated to increase the risk of heart failure in patients with COVID-19.[51] A meta-analysis also showed the possibility that NT-proBNP was independently associated with mortality after adjustment to troponin and creatine kinase myocardial band.[52] In cases with an infectious outcome, the median time to onset of acute myocardial damage is 14.5 days. A slight progressive increase in troponin was observed in these patients up to Day 16, after which it rapidly increased.[44]. In other circumstances, troponin, which is normal on admission, has been observed to increase in the week before death[53] Still other authors have shown an early increase in the marker of myocardial damage from the early stages of the disease[54] These data reinforce the hypothesis that the increase in troponin, while representing the presence of myocardial damage, would seem to be mainly evidence, in patients with COVID-19, of the severity of the generalized (systemic) disease.[48] The mechanisms of myocardial damage could be manifold. A possible mechanism could be direct heart damage secondary to the stimulation of the angiotensin 2 converting enzyme (ACE2), present on vascular endothelial cells and myocytes, which would act as a receptor for SARS-Cov-2.[6] A second mechanism could be macro- and microcirculatory thrombosis, which can also be correlated to a state of hypercoagulability observed in some patients.[55]

A further hypothesized mechanism is that related to the systemic inflammatory response mediated by the release of cytokines, the so-called "cytokine storm."[6] Cytokine storm and cytokine release syndrome are life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation that can be triggered by various therapies, pathogens, cancers, autoimmune conditions, and monogenic disorders.[56] A complex, interconnected network of cell types, signaling pathways, and cytokines is involved in cytokine storm disorders. Interferon-γ, interleukin (IL)-1, IL-6, tumor necrosis factor (TNF), and IL-18 are key cytokines that often have elevated levels in cytokine storm and are thought to have central immunopathologic roles. Serumcytokine levels that are elevated in patients with COVID-19-associated cytokine storm include those of IL-1β, IL-6, IP-10, TNF, interferon-γ, macrophage inflammatory protein 1α and 1β, and vascular endothelial growth factor.[45,57] Higher IL-6 levels are strongly associated with shorter survival.[58] Left ventricular dysfunction can present in different forms. Ventricular stress dysfunction, known as Takotsubo syndrome and so far highlighted in a few cases by SARS-Cov-2 infection, presents on echocardiography with the typical contraction of the left ventricle with systolic apical ballooning and was confirmed on coronary angiography, which did not highlight significant coronary stenosis. Several pathophysiological mechanisms involved in the genesis of myocardial damage in COVID-19 appear to be involved in the development of the syndrome in these patients, especially those related to microcirculatory dysfunction, excessive sympathetic stimulation, and cytokine storm.[59] Currently there are just over 10 clinical cases of myocarditis related to SARS-Cov-2 infection,[60] some with evidence of marked depression of contractility[60–65] and others with preserved function; one case has buffering pericardial effusion.[66] Myocardial dysfunction secondary to dysregulation of the cytokine system, also common to other serious pathological conditions, such as septic shock and myocardial infarction, could develop in patients with COVID-19. The mechanisms of cytokine-induced ventricular dysfunction are unknown; it is possible, however, that an excess of pro-inflammatory mediators, such as IL-6, interfere with the activity of calcium channels, resulting in a contractile depression of myocytes.[55] Also, nitric oxide and mitochondrial dysfunction could play a role in the development of myocardial contractile dysfunction,[55] which can be diffuse or regional and reversible. From a phenotypic point of view, left ventricular dysfunction due to dysregulation of the cytokine system does not have characteristic morphological elements, such as the apical ballooning of stress-induced ventricular dysfunction, but can lead to widespread or regional impairment of myocardial function and can be reversible. Furthermore, in a series on 105 consecutive patients,[67] 30% of whom were intubated and mechanically ventilated, it was observed that the right ventricle underwent dilation and hypokinesia in about 31% of cases; and some of them showed pulmonary embolism. In multivariate analysis, right ventricular dilation was the only variable significantly associated with mortality. Finally, in a recent series of patients with COVID-19 pneumonia, the independent predictors of in-hospital mortality were troponin I values, arterial oxygen saturation at the entrance, mean pulmonary arterial pressure, and tricuspid annular plane systolic excursion.[68] Further revealing information capable of predicting mortality risk independently and incrementally in these patients may also derive from the longitudinal strain of the right ventricle.[69]

4 | COVID-19 AND ARRHYTHMIAS

Although the data on the prevalence are scant and the exact contribution of COVID-19 to cardiac arrhythmias remains uncertain, heart rhythm disturbances and sudden cardiac death are among the manifestations of COVID-19. Patients with SARS-Cov-2 infection may have arrhythmias due to a variety of mechanisms, which are mutually interrelated and inter-facilitated. Palpitations were reported as a major symptom related to SARS-Cov-2 infection in patients without fever or cough. Abnormal heart rate has been described in approximately 6%-7% of hospitalized individuals with suspected COVID-19.[70] Sinus tachycardia is the most frequently encountered COVID-19-associated arrhythmia.[71] Prolonged QTc intervals have also been reported.[72] In an Italian multicentric, cross-sectional, retrospective analysis of 431 consecutive hospitalized COVID-19 patients who died or were treated with invasive mechanical ventilation, the electrocardiogram was abnormal in 93% of the patients and atrial fibrillation/flutter was detected in 22% of the patients. Electrocardiogram signs suggesting acute right ventricular pressure overload were detected in 30% of the patients.[73] High prevalence of arrhythmia might be, in part, attributable to metabolic disarray, hypoxia, or neurohormonal or inflammatory stress in the setting of viral infection in patients with or without prior CVD.[74,75] In addition to acquired arrhythmias, it is believed that patients with inherited arrhythmogenic cardiomyopathies, such as short QT and long QT syndrome, Brugada syndrome, and catecholaminergic polymorphism, are believed to be more susceptible to pro-arrhythmic effects of SARS-Cov-2, such as stress, fever, use of antiviral drugs, and electrolyte disturbance,[76] a condition that must be taken into account in the overall treatment of these patients.

5 | CONCLUSIONS

Diseases with pandemic potential, transmitted by vectors and favored by climate change, can put global health at risk, especially the health of the most fragile sections of the population, such as the elderly, who suffer from multimorbidity and who make up an increasing proportion of the population. The pandemic underway, at the root of an unprecedented crisis, forces us to think now about the best way to manage the care of the sick elderly, for the good of all, also in consideration of the costs and stresses for the health systems. Outlining the principles of effective immunity in the elderly will allow us to develop new strategies for wider disease prevention and control in older populations. The protection of this segment of the population will be a key issue, probably of primary interest to all.

Biomarkers appear to be extremely useful as an indication of what is happening from a pathophysiological point of view in the heart, allowing us to better stratify the prognosis of our patients affected by COVID-19, especially in the most severe cases and those with comorbidities.

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CONFLICT OF INTEREST

The authors report no competing interests.

AUTHOR CONTRIBUTIONS

Conceptualization: R.C., A.C., and G.R. Data curation: R.C., A.C., and G.R. Formal analysis: R.C., A.C., and G.R. Writing and original draft preparation: R.C., A.C., and G.R. Writing, review, and editing: R.C., A.C., and G.R. Supervision: G.R. All the authors agreed on the final text.

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