Double trouble: combined cardiovascular effects of particulate matter exposure and coronavirus disease 2019

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Abstract

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly grown into a pandemic. According to initial reports, the lungs were thought to be the primary target, but recent case studies have shown its reach can extend to other organs including the heart and blood vessels. The severity of cardiac complications of COVID-19 depends on multiple underlying factors, with air pollutant exposure being one of them, as reported by several recent studies. Airborne particulate matter (PM) attracts heightened attention due to its implication in various diseases, especially respiratory and cardiovascular diseases. Inhaled PM not only carries microorganisms inside the body but also elicits local and systemic inflammatory responses resulting in altering the host’s immunity and increasing susceptibility to infection. Previous and recent studies have documented that PM acts as a ‘carrier’ for the virus and aids in spreading viral infections. This review presents the mechanisms and effects of viral entry and how pollution can potentially modulate pathophysiological processes in the heart. We aimed to concisely summarize studies examining cardiovascular outcomes in COVID-19 patients and postulate on how PM can influence these outcomes. We have also reviewed evidence on the use of renin–angiotensin system inhibitors, namely angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, in patients with COVID-19. The interplay of pollution and SARS-CoV-2 is essential to understanding the effects of accentuated cardiovascular effects of COVID-19 and deserves in-depth experimental investigations.

Keywords

Aerosol • Airborne transmission • SARS-CoV-2 • COVID-19 • Particulate matter • Air pollution • Cardiovascular diseases

1. Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in the Hubei province of China in December 2019 and rapidly spread worldwide to pandemic levels. The World Health Organization (WHO) officially named the novel disease coronavirus disease 2019 (COVID-19) and declared the outbreak as a public health emergency of international concern.1 It has now been >6 months since the outbreak and, as of 31 August 2020, there have been 25 251 334 confirmed cases and 846 841 fatalities reported worldwide.2 The initial clinical reports of COVID-19 predominantly showed respiratory tract symptoms, characterized by fever, cough, fatigue, pneumonia, and acute respiratory distress syndrome.3 The lungs were initially thought to be the primary target of COVID-19; however, other clinical manifestations including cardiac complications, vascular impairment, and stroke are becoming increasingly evident.6,7 As the virus affects and damages other vital organs and tissues, COVID-19 is now regarded as a systemic disease.

In the February 2020 issue of the Lancet, Huang et al.3 reported that 12% of patients with COVID-19 were diagnosed with acute myocardial injury with elevated levels of troponin I (Tnl), a cardiac-specific biomarker of myocardial injury.5 In another study, severe and critical COVID-19 patients showed elevated Tnl levels and presence of arrhythmias. Other markers of cardiac inflammation, such as C-reactive protein and N-terminal probrain natriuretic peptide (NT-proBNP), were also found to be elevated7 and are probably associated with infection-
induced myocarditis and ischaemia.\(^8\) In addition, COVID-19 infections have been shown to be associated with heart failure and arrhythmias.\(^10\) Table 1 lists several cardiovascular complications of COVID-19 reported in recent clinical studies.

It remains arguable whether COVID-19 infection and cardiac complications are causally linked, directly associated, or if any externally modifiable factor is influencing this correlation. In a recent study by van Doremalen, it was shown that SARS-CoV-2 can remain viable and infectious in aerosols (particulate matter; PM) for hours and on surfaces for days.\(^20\) This could partially explain the reason behind the more severe fatality and transmission rates of COVID-19, unlike those observed with influenza viral infection.\(^6\) Fine PM may damage the respiratory system by inducing oxidative stress, leading to serious health problems including decreased resistance to respiratory viral infections.\(^21\) Recent literature clearly indicated that more polluted places are likely to have increased COVID-19 mortality.\(^22,23\) These are not the first studies to highlight a substantial link between air pollution levels and deaths from viral diseases. A study published in 2003 found that SARS patients were 84% more likely to die if they lived in areas with high levels of pollution, although these results were not adjusted for important confounders, such as age, gender, and other comorbid conditions.\(^24\)

A key determinant of the spread of COVID-19 has been identified as population density.\(^25\) As denser populations catalyse the spread of the virus,\(^26\) the possibility of the outbreak and transmission of the disease is higher in urban areas. However, there may be an effect from ambient air pollution as increased population density is associated with increased pollution.\(^27\) The direct or indirect correlation between COVID-19 infection, cardiovascular injury, and PM pollution is the main focus of this review, as we attempt to answer the question: does PM pollution act as a cofactor for viral entry into the heart and exacerbate the susceptibility and severity of cardiovascular disease (CVD) and deaths due to COVID-19?

2. Mechanisms and pathophysiological impact of viral entry into the heart

2.1 Mechanism of SARS-CoV-2 entry

The novel coronavirus SARS-CoV-2, which is closely related to SARS-CoV, has been found to infect cardiac tissue via a similar mechanism involving angiotensin-converting enzyme 2 (ACE2).\(^28\) ACE2 is found to be expressed in a wide variety of tissues, with some of the highest levels in the lungs and heart.\(^29,30\) ACE2 converts angiotensin I and angiotensin II into potent vasodilators angiotensin 1–9 and angiotensin 1–7, respectively.\(^31\) By counteracting the vasoconstrictive actions of angiotensin II, ACE2 negatively regulates the renin–angiotensin system (RAS) and plays a role in blood pressure homeostasis.\(^32\) The key player for viral entry into the host cells is the spike (S) protein, which is responsible for ACE2 binding and fusion to the host cell (Figure 1).\(^28\) Before the S protein can fuse, it must first be cleaved by a host cell protease known as transmembrane protease serine type 2 (TMPRSS2). This priming by TMPRSS2 is believed to be essential for cell entry by SARS-CoV-2, just as it was for SARS-CoV. In the absence of TMPRSS2, SARS-CoV was found to alternatively be primed by other host cell proteases, such as cathepsin B/L, which is also thought to be the case for SARS-CoV-2.\(^28\) Inhibition of cathepsin B/L significantly reduced SARS-CoV-2 entry, suggesting cathepsin B/L dependence. However, based on investigations of both the previous viral disease outbreaks SARS and Middle Eastern respiratory syndrome (MERS), cathepsin B/L is not believed to be essential for the viral spread and pathogenesis, unlike the priming by TMPRSS2.\(^28\)

2.2 Pathophysiological impact of SARS-CoV-2 on the myocardium

2.2.1 ACE2 regulation

Once SARS-CoV-2 binds to ACE2 and gains entry into the host cell, there is a subsequent down-regulation of ACE2 that results in reduced degradation of angiotensin II, a potent vasoconstrictor and culprit of endothelial damage and myocardial dysfunction.\(^33\) The resulting increased levels of circulating angiotensin II binds angiotensin II type 1 (AT1) receptors, along with sympathetic nervous system activation, are believed to contribute to the vasoconstriction and pulmonary damage that results in acute respiratory distress syndrome (ARDS).\(^32\) ACE2 can counteract the untoward effects of angiotensin II (by converting it to angiotensin 1–7) by exerting vasodilatory, anti-inflammatory, antioxidant, and anti-fibrotic effects.\(^33,34\) An important role for ACE2 in contributing to the cardioprotective effect was demonstrated by Loot et al.\(^35\) Their findings showed reversal of cardiac dysfunction and restoration of vascular endothelial response post-myocardial infarction (MI) after angiotensin 1–7 infusion. ACE2 gain-of-function studies revealed that it mediates favourable post-MI remodelling and recovery,\(^36\) and improved left ventricular diastolic function through reduction of oxidative stress, fibrosis, and myocardial hypertrophy.\(^37,38\) Alternatively, mice lacking ACE2 (loss of function) were more likely to develop left ventricular systolic dysfunction and heart failure with reduced ejection fraction.\(^29\)

Previous experimental and clinical studies demonstrated that SARS-CoV mediates myocardial inflammation associated with ACE2 down-regulation and is likely to be responsible for the adverse cardiac outcomes in SARS patients.\(^29\) Based on previous evidence, we speculate that binding of SARS-CoV-2 is likely to alter ACE2 function, resulting in adverse cardio-respiratory effects.

2.2.2 Exaggerated immune and inflammatory response

The overwhelming inflammatory response leading to production of large quantities of cytokines, known as the ‘cytokine storm’, is an indirect mechanism by which SARS-CoV-2 damages the myocardium.\(^39\) This ‘cytokine storm’ is usually seen in more critically ill patients, such as those with ARDS and multiple organ failure.\(^39\) It has been shown that severely ill COVID-19 patients had decreased expression of interferon (IFN)–γ in CD4+ cells, along with an exaggerated release of cytokines and chemokines, resulting in damage to the host cells and tissues.\(^40\) The magnitude of the ‘cytokine storm’ strongly correlates with infection severity, as severe COVID-19 cases were found to have significantly higher levels of interleukin (IL)–6, IL–10, and tumour necrosis factor (TNF)–α, along with more severe lymphopenia compared with moderate cases.\(^40\) IL-6 not only stimulates production of other cytokines, but also contributes to vascular leakage and interstitial oedema, and has been shown to cause myocardial dysfunction.\(^41\) Indeed, inflammation has been considered as an important risk factor for long QT-syndrome (LQTS) and Torsades de pointes (TdP), primarily via direct electrophysiological effects of cytokines on the myocardium.\(^42\) A recent study revealed an association between increased levels of IL-6 and high TnI levels, indicating a ‘cytokine storm’ as a contributor to myocardial injury.\(^13\)
2.2.3 Systemic effects: myocardial oxygen supply–demand mismatch

SARS-CoV-2 primarily causes pulmonary manifestations such as pneumonia and ARDS. The association between pneumonia and cardiac complications has been documented previously, and various studies also confirmed that extrapulmonary complications of acute respiratory infections serve as triggers of CVDs. Hypoxaemia and hypotension due to pulmonary dysfunction lead to insufficient oxygen supply to the myocardium. As a result of ongoing hypoxia, the cardiometabolic demand is increased in the wake of inadequate supply, further causing the imbalance between myocardial oxygen supply and demand. As the disease progresses, the oxygen supply–demand ratio becomes increasingly aggravated, ultimately leading to myocardial damage. Respiratory and metabolic acidosis and electrolyte and acid–base abnormalities are other systemic contributors leading to myocardial damage. Consequently (less cardiac output and ineffective circulating volume), the sympathetic nervous system is activated to maintain circulatory homeostasis and perfusion to vital organs by increasing inotropy and chronotropy of the failing myocardium. In the long term, these mechanisms turn maladaptive by further compromising coronary perfusion and are responsible

### Table 1 Cardiovascular complications/presentations of COVID-19

| Cardiovascular manifestation | Study | No. of patients | Clinical outcome |
|-----------------------------|-------|-----------------|-----------------|
| Acute cardiac injury, evidenced by elevated cardiac troponin I and/or electrocardiogram and echocardiogram changes | Huang et al. | 5 (out of 41 patients; 12%) | 4 out of 5 required ICU care |
|  | Wang et al. | 10 (out of 138 patients; 7.2%) | More likely to end up in ICU (exact data not provided) |
|  | Shi et al. | 82 (out of 416 patients; 19.7%) | 42 out of 82 experienced mortality (51.2%) |
|  | Zhou et al. | 33 (out of 191 patients; 17%) | 32 out of 33 experienced mortality |
| Arrhythmia | Wang et al. | 16 (out of 36 patients in the ICU; 44.4%) | Required ICU care |
| Myocarditis | Zeng et al. | 1 patient | Deceased |
|  | Sala et al. | 1 patient | Recovered and discharged |
|  | Kim et al. | 1 patient | Not reported |
| Heart failure | Zhou et al. | 44 (out of 191 patients; 23%) | 28 out of 44 experienced mortality |
|  | Fried et al. | 1 patient | Required mechanical ventilation |
| Cardiomyopathy | Arentz et al. | 7 (out of 21 patients; 33%) | Not reported specifically for cardiomyopathy |
|  | Fried et al. | 1 patient | Stable on mechanical ventilation |
| Venous thrombo-embolism | Wichmann et al. | 7 (out of 12 patients; 58%) had a DVT | 4 out of 12 patients died directly of PE |
|  | Lodigiani et al. | 28 (out of 362 patients; 7.7%) | 8 out of the 28 cases occurred in ICU patients |

ICU, intensive care unit. DVT, deep vein thrombosis.
for disease progression leading to myocardial stunning, arrhythmias, and sudden death.\textsuperscript{50} COVID-19 is associated extra-pulmonary complications may manifest as cardiomegaly and pericardial effusion on chest computed tomography (CT) imaging.\textsuperscript{51}

3. Pollution as a cofactor for increased myocardial damage in COVID-19

3.1 PM and SARS-CoV-2 interaction

Air pollution represents a serious public health issue as it ranks ninth in overall mortality worldwide,\textsuperscript{52} and hence is recognized as one of the top 10 global health burdens.\textsuperscript{53} Particularly through its impact on CVDs, it causes as many as 8.9 million premature deaths per year worldwide.\textsuperscript{54} Besides nitrogen dioxide (NO\textsubscript{2}) and ozone (O\textsubscript{3}), the current focus of research is mainly on PM (PM\textsubscript{2.5} and PM\textsubscript{10}) as these occur frequently at elevated concentrations in large metropolitan areas. PM is comprised of solid particles and liquid droplets from various sources and are classified according to their aerodynamic diameters: coarse (PM\textsubscript{10}), fine (PM\textsubscript{2.5}), and ultrafine (PM\textsubscript{0.1}). The size, surface area, and chemical composition determine the toxicity of PM.\textsuperscript{55} According to various particle size deposition models,\textsuperscript{56,57} particles with aerodynamic diameter >10 μm deposit in the nose or extrathoracic airway, while inhaled particles of the size range 3–6 μm reach and deposit in the lower respiratory tract. Particles between 2.5 and 0.1 μm can penetrate deep into the alveolar region. In particular, PM\textsubscript{2.5} and PM\textsubscript{10} have been shown to act as carriers for viral spread and facilitate the prolonged survival of microorganisms,\textsuperscript{58} including viruses,\textsuperscript{59} which could partly explain the association of air pollution with the increased spread of respiratory viral infections.\textsuperscript{59} Ye et al.\textsuperscript{60} demonstrated a positive correlation between the infection rate due to respiratory syncytial virus and PM fractions (PM\textsubscript{2.5}, $r = 0.446$, $P < 0.001$; and PM\textsubscript{10}, $r = 0.397$, $P < 0.001$). Other similar studies provided evidence on the interaction between PM and viruses,\textsuperscript{61} and highlighted that an increase in PM\textsubscript{2.5} concentration by 10 μg/m\textsuperscript{3} was associated with a higher incidence of viral infection.\textsuperscript{62}

With recent studies specifically exploring the PM–SARS-CoV-2 interaction, data are now available confirming this lethal association. Experiments conducted by van Doremalen et al.\textsuperscript{20} indicated that the transmission of SARS-CoV-2 by aerosols is plausible, since it remains via respiratory syncytial virus and PM fractions (PM\textsubscript{2.5}, $r = 0.446$, $P < 0.001$; and PM\textsubscript{10}, $r = 0.397$, $P < 0.001$). Other similar studies provided evidence on the interaction between PM and viruses,\textsuperscript{61} and highlighted that an increase in PM\textsubscript{2.5} concentration by 10 μg/m\textsuperscript{3} was associated with a higher incidence of viral infection.\textsuperscript{62} Several recent studies have now documented that PM acts as a medium for the aerial transport of SARS-CoV-2\textsuperscript{20,26} and plays a role in exacerbating morbidity and mortality of COVID-19 patients. The Italian Society of Environmental Medicine (SIMA) was the first to hypothesize a possible link between the high COVID-19 mortality rates observed in Northern Italian regions and PM concentrations. A specific Position Paper published in March 2020 demonstrated a significant correlation between daily PM\textsubscript{10} levels exceeding the legal limit (50 μg/m\textsuperscript{3}) in the northern regions (Lombardy and in cities located in the Po valley) compared with southern regions (Rome and Southern Italy), where the diffusion and lethality of the virus were significantly lower.\textsuperscript{71} Fattorini and Regoli\textsuperscript{72} analysed the data on air pollution distribution and days exceeding regulatory limits during the last 4 years (2016–19), and years of the last decade (2010–19) in which pollution limits have been exceeded for at least 35 days. The authors highlighted that long-term air quality data were significantly correlated with cases of COVID-19 in up to 71 Italian provinces, providing further evidence that chronic exposure to atmospheric contamination may represent a favourable context for the spread of the virus. Similarly, Conticini et al.\textsuperscript{73} showed that the high levels of atmospheric pollution (PM\textsubscript{10} and PM\textsubscript{2.5}) in Northern Italy can be considered as an additional cofactor of the high level of lethality recorded in that area. These observations corroborated the findings from China, which showed that meteorological factors, such as humidity and temperature along with air pollution, can influence COVID-19 outcomes. The authors have concluded that PM\textsubscript{2.5} and humidity are associated with increased risk, and PM\textsubscript{10} and temperature could substantially decrease the risk of COVID-19 incidence.\textsuperscript{73} Further, Zhu et al. demonstrated that a 10 μg/m\textsuperscript{3} increase (lag0–14: cumulative lag effect of different air pollutants from day 0 to day 14) in PM\textsubscript{10}, PM\textsubscript{2.5}, NO\textsubscript{2}, and O\textsubscript{3} was associated with a 2.24% [95% confidence interval (CI) 1.02–3.46], 1.76% (95% CI 0.89–2.63), 6.94% (95% CI 2.38–11.51), and 4.76% (95% CI 1.99–7.52) increase in the daily counts of COVID-19 confirmed cases, respectively.\textsuperscript{74} Similarly, a survey carried out by the Harvard School of Public Health in the USA found that an increase of 1 μg/m\textsuperscript{3} in long-term PM\textsubscript{2.5} exposure is associated with an 8% increase in COVID-19 mortality rate.\textsuperscript{23} Yao et al.\textsuperscript{75} further found in 49 Chinese cities that COVID-19 mortality is higher where PM\textsubscript{2.5} and PM\textsubscript{10} concentrations were greater. In another study, Fronza et al.\textsuperscript{76} analysed PM levels in relation to COVID-19 cases from four European countries (Italy, France, Germany, and Spain) and found
positive correlations between PM$_{2.5}$ and infection frequency. A similar potential correlation between air pollution and COVID-19 mortality has also been described in several other studies.\textsuperscript{77,78} These initial data clearly indicated that PM not only favours the virus pathogenicity but also increased the effectiveness of virus spread (by creating a suitable microenvironment for its persistence) and mortality rates due to COVID-19. These observations also corroborate previous studies demonstrating that PM may act as a ‘carrier’ for the viral droplet nuclei, eventually leading to the spreading of viral infections.\textsuperscript{21,60}

### 3.3 Cardiovascular effects of PM exposure

The majority of reports have focused on the pulmonary effects of PM compared with cardiovascular effects, leading to some doubt about the causal association between pollution and cardiovascular mortality. There is now convincing evidence from animal as well as human studies that PM has direct interactions at sites remote from the lungs. A study conducted in hamsters demonstrated that a substantial fraction of intratracheally instilled ultrafine particles (radiolabelled denatured albumin with diameter <100 nm) diffuses from the lungs into the systemic circulation.\textsuperscript{79} Another study in rats showed that ultrafine silver particles entered the systemic pathways after inhalation.\textsuperscript{80} Similarly, PM was shown to pass directly into the circulation in human studies.\textsuperscript{81} In contrast, a study conducted by Mills et al.\textsuperscript{82} in humans showed that inhaled carbon nanoparticles do not pass directly from the lungs into the systemic circulation. These contradictory results, therefore, show the need for more confirmatory studies. Based on the studies so far, it can be said that upon inhalation, PM particles (aerodynamic diameter 2.5–0.1 µm) travel deep into the lungs and presumably translocate into the blood stream to reach the heart. PM exposure is able to elicit indirect lung-mediated (pulmonary inflammation resulting in systemic inflammation) as well as direct cardiovascular effects (vascular dysfunction, oxidative stress, and dysregulation of calcium channels/levels) (reviewed in Tanwar et al.\textsuperscript{83}). There are several experimental and epidemiological studies which have documented the deleterious direct and indirect PM-induced cardiovascular effects.\textsuperscript{84,85} In addition, positive associations between short-term air pollution and viral infections have also been reported.\textsuperscript{86} The severity of viral infections is influenced by the number of extra-pulmonary manifestations, including cardiovascular complications,\textsuperscript{87} such as myocarditis, ischaemic heart disease, and idiopathic diabetic cardiomyopathy (IDCM).\textsuperscript{87} Furthermore, due to an imbalance between increased metabolic demand and reduced cardiac reserve in the wake of viral infection, chronic CVD may become unstable.

### 3.4 Cardiovascular complications of COVID-19

The combined impact of (i) the PM–SARS-CoV-2 interaction, (ii) pre-existing heart conditions, and (iii) the lone effects of PM on an individual’s cardiovascular system is not yet fully elucidated. Thus, the question remains as to how PM-aided SARS-CoV-2 entry into the heart affects cardiovascular outcomes in COVID-19 patients (with or without pre-existing conditions).

Evidence from previous viral disease outbreaks, such as SARS and MERS, indicate that coronaviruses affect the cardiovascular system.\textsuperscript{88,89} Despite COVID-19’s initial categorization as a respiratory-dominant illness, many patients present with cardiovascular symptoms, such as heart palpitations and chest tightness, according to the National Health Commission of China (NHC). The NHC further stated that 11.8% of deceased COVID-19 patients without underlying CVD had evidence of substantial heart damage,\textsuperscript{9} which suggests that SARS-CoV-2 can inflict cardiac damage without any pre-existing conditions. One of the more profound effects of SARS-CoV-2 is the myocardial injury observed in some severely ill patients. One study revealed that 5 out of 41 patients with COVID-19 in Wuhan, China experienced myocardial injury, which was identified by increased levels of cardiac TnI.\textsuperscript{7} There have been more reports of acute cardiac injury evidenced by electrocardiogram and echocardiogram changes, in addition to elevated troponins.\textsuperscript{10–12}90 Additionally, there have been reports of new-onset arrhythmias particularly due to electrolyte imbalances,\textsuperscript{10,91} as well as cases of venous thrombo-embolism\textsuperscript{18,19} and cardiomyopathy.\textsuperscript{16,17} Furthermore, similar to what was seen with MERS, instances of fulminant myocarditis have also been reported in COVID-19 patients,\textsuperscript{13–15} in addition to heart failure complications.\textsuperscript{12,92}

It remains unclear whether pre-existing cardiovascular conditions, such as hypertension and CVD, increase susceptibility to infection. However, there has been increasing evidence showing that severely ill COVID-19 patients have one or more pre-existing cardiovascular conditions which might have contributed to their increased susceptibility, poor prognosis, and higher mortality rates.\textsuperscript{7,93} Based on early-stage analyses of the COVID-19 outbreak in China, the Centers for Disease Control and Prevention found that the case fatality rate (CFR) for those with underlying CVD is 10.5%, the highest among all other comorbid conditions (Figure 2).\textsuperscript{94} According to the NHC, data on COVID-19 mortality cases revealed 35% of patients with a history of hypertension and 17% with underlying coronary heart disease.\textsuperscript{2} Furthermore, the systemic inflammatory response elicited by the infection, along with increased shear stress from increased coronary blood flow, can cause plaque rupture and subsequent MI in patients with underlying CAD.\textsuperscript{95} SARS-CoV-2 causes microvascular dysfunction, notably pericyte injury particularly in patients with heart failure.\textsuperscript{96} Additionally, COVID-19 infection can cause decompensation of underlying heart failure, increasing the risk for mixed shock (septic and cardiogenic).\textsuperscript{77} Further, special consideration has been suggested for those with inherited arrhythmia syndromes due to the arrhythmogenic potential of COVID-19.\textsuperscript{91} It is becoming more apparent that SARS-CoV-2 can lead to both novel cardiovascular effects and exacerbation of existing cardiovascular comorbidities, resulting in a higher rate of mortality.
3.5 Indirect (lung-mediated) cardiovascular effects of SARS-CoV-2

On both a physiological and pathological basis, a strong heart–lung connection exists. In the setting of severe pulmonary infections, the exaggerated inflammatory response induced by cytokines is thought to affect other organs, such as the heart, by ‘spilling over’ into the systemic circulation.98 This ‘spill over’ has been proposed as an indirect mechanism for myocardial injury.99 Moreover, it has also been suggested that the potential for myocardial damage seen in infected patients can be indirect due to reduced oxygen supply, severe lung failure, and/or the previously discussed cytokine storm.100 The severe hypoxia and ARDS that accompany severe respiratory infections, such as COVID-19 has been suggested as a key contributor to development of this myocardial injury,90 mainly due to oxidative stress and increased cardiometabolic demand.95 Conversely, it is proposed that the myocardial damage may be directly due to ACE2 down-regulation in the cardiac tissue,100 as discussed previously. The presence of this vigorous inflammatory response in the myocardium can also lead to myocarditis, heart failure, cardiac arrhythmias, and even sudden cardiac death.10

Despite the majority of available clinical analyses being preliminary with small sample sizes, great consideration and further investigation is warranted regarding the potential for cardiovascular complications, both direct and indirect, in COVID-19 patients.

4. Plausible mechanisms for exacerbated myocardial injury in COVID-19: role of PM exposure

First, SARS-CoV-2 infects cardiac tissue using ACE2 as ‘entry gates’ present on cardiomyocytes, pericytes, and endothelial cells96 and causes direct damage to the myocardium. It has been shown previously that chronic exposure to PM2.5 increases both pulmonary101 and circulatory ACE2 expression.102 The massive viral binding to ACE2 reduces its availability, resulting in decreased production of angiotensin 1–7 (vasodilator) and an excess of angiotensin II (vasoconstrictor). Virus-mediated depletion of ACE2 appears to be crucial in mediating cardiac injury.29,100 In an attempt to investigate how PM2.5 up-regulates ACE2 expression, Borro et al.103 recently performed a bioinformatics analysis of the ACE2 gene promoter region. The authors reported the presence of consensus sequences for the transcription factor aryl hydrocarbon receptor (AhR) in the promoter region of the ACE2 gene. AhRs primarily mediate a protective adaptive response by inducing detoxifying xenobiotic enzymes,104 microbial defence, immunity, and inflammation.105 Polycyclic aromatic hydrocarbons (PAHs) present in PM2.5 particles106 stimulate AhRs, which in turn activate the expression of target genes by binding to a DNA consensus sequence, canonical and non-canonical xenobiotic responsive elements (XRE and NC-XRE).107–109

The authors identified nine such consensus sequences in the promoter region of the ACE2 gene. Although these results provide the first evidence of pollution-induced overexpression of ACE2, the authors indicated the need for future studies to validate that AhR may control the level of ACE2 at the translational level.

We speculate that patients who were exposed to high levels of PM2.5 overexpress ACE2, which in turn facilitates more viral binding and consequent ACE2 depletion, leading to exaggerated disease response. Thus, it can be hypothesized that in areas where PM levels are high, such as Northern Italy, COVID-19 patients present with exaggerated cardiac complications.

Secondly, smaller PM particles (particles with an aerodynamic diameter <2.5 μm) are known to enter the heart directly via translocating into the blood stream, resulting in inflammation.83 Recent reports indicated that SARS-CoV-2 absorbs and can remain viable on the surface of PM (PM–SARS-CoV-2 interaction). The PM–SARS-CoV-2 interaction might be responsible for giving additional access to the virus in reaching distal airway/alveoli and travelling indirectly to the heart. Where exposure to PM is associated with cytokine/chemokine production and inflammation,110 SARS-CoV-2 also elicits an exaggerated host immune response.111 It is thus conceivable that both PM and SARS-CoV-2 together elicit a high grade systemic inflammatory state (‘cytokine storm’) characteristic of COVID-19.90 In this regard, the presence of myocardial inflammation and viral particles has been reported recently in the endomyocardial biopsy of a COVID-19 patient.112 Other reports in COVID-19 patients have found high viral load-induced fulminant myocarditis with inflammatory cell infiltration.41,113

Interestingly, studies have shown that inflammatory signals are capable of increasing the expression of ACE2 in the respiratory epithelium114,115 and that increased ACE2 exerts anti-inflammatory action.116–118 The crucial role of ACE2 in defending lung epithelial cells from the inflammatory action of PM2.5 has also been shown previously by Lin et al. However, in the current context, we speculate that the up-regulation of anti-inflammatory ACE2 (in response to pro-inflammatory stimuli) is unable to counteract augmented inflammation because the virus, by binding to ACE2, blocks its activity and probably contributes to severe SARS-CoV-2 infection.

Thirdly, the role of exosomes appears to be crucial in mediating COVID-19 cardiovascular pathology. Exosomes are extracellular membrane vesicles released by different cells that are capable of transferring cellular information to recipient cells. Recently, Kwon et al.119 demonstrated that secreted exosome-containing SARS-CoV-2 RNA from A549 lung epithelial cells can be taken up by human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), suggesting indirect routes of viral entry into cardiomyocytes. The authors further demonstrated induction of proinflammatory genes in hiPSC-CMs, which may potentially lead to cardiac dysfunction. Supporting this observation, a recent study by Wichmann et al.18 detected SARS-CoV-2 RNA in the hearts of COVID-19 patients, which may indicate the potential involvement of exosomes in mediating viral entry into the myocardium. Interestingly, short- and long-term exposures to PM have been shown to be associated with exosome release in the lung epithelial cells120,121 and blood.122,123 Circulating exosomes are implicated in sepsis-mediated heart failure,124 whereas pulmonary exosomes mediate local and systemic inflammation.125 It is thus reasonable to propose that exosomes, released in response to PM exposure, might be serving as viral vectors carrying SARS-CoV-2 RNA to the myocardium and thus exacerbating myocardial inflammation by its own as well as virus-mediated mechanisms.

Based on the above speculations, it could be proposed that PM exposure influences the adverse cardiovascular outcomes of COVID-19 by exerting its own deleterious effects and serving as a carrier for SARS-CoV-2. Together, PM and SARS-CoV-2 exert ‘double trouble’ to the heart by altering ACE2 function and influencing the inflammatory response, thus increasing the baseline risk of complications that are known to increase the severity of viral infections (Figure 3). In a recent study, Frontera et al.126 highlighted an association between low levels of atmospheric pollution and COVID-19 presentation. The authors found that...
in the Italian municipality of Vo` near Padua where atmospheric pollution levels remain relatively low (annual PM$_{2.5}$ and NO$_2$ of 19 and 14 µg/m$^3$, respectively), an exceptionally high number of COVID-19-positive cases were present and 50–75% of the positive cases were asymptomatic. It has also been demonstrated that patients with serious COVID-19 have 60 times higher viral loads compared with mild cases, suggesting that higher viral loads might be associated with more severe clinical outcomes.\(^{129}\) Thus, it can be postulated that less exposure to PM$_{2.5}$ could lead to lower expression of ACE2 and subsequently less viral load and mild symptoms.\(^{126}\)

### 5. Therapeutic concern of RAS inhibitors in COVID-19

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are RAS-inhibiting agents that are considered as important first-line drugs to treat hypertension, hypertrophic cardiomyopathy, and heart failure.\(^{128-130}\) Because of structural dissimilarity to ACE,\(^{131}\) RAS inhibitors do not bind and inhibit the active site of ACE2 and hence it is not their direct target. However, several clinical\(^{132-137}\) and laboratory studies have demonstrated increased expression of ACE2 with the use of ACEIs and ARBs.\(^{138-140}\) and hence they could potentially affect COVID-19 virulence in the ongoing pandemic. As uncertainty around possible associations of these drugs with COVID-19 has caused widespread debate, regulatory bodies do not support discontinuation of these medications\(^{141}\) and have called for outcome studies.

A retrospective study from Wuhan, China included 126 COVID-19 patients with pre-existing hypertension (43 out of 126 were on either an ACEI or an ARB) and 125 age- and sex-matched COVID-19 patients without hypertension. The clinical outcomes indicated that the use of ACEIs/ARBs is not associated with increased risk of morbidity or mortality in COVID-19 patients. Another study from China\(^{142}\) enrolled 1178 COVID-19 patients (362 with hypertension out of which 115 were on ACEI/ARB therapy). The results demonstrated that the percentage of patients with hypertension taking ACEIs/ARBs did not differ between those with severe and non-severe infections (32.9% vs. 30.7%; \(P = 0.65\)) nor did it differ between non-survivors and survivors (27.3% vs. 33.0%; \(P = 0.34\)). A case–control study from Lombardy, Italy, which included 6272 patients with COVID-19 and 30 759 controls showed no evidence that ACEIs or ARBs affected the risk of COVID-19.\(^{143}\) However, due to a higher prevalence of CVD, the use of ACEIs and ARBs was more frequent among patients with COVID-19 than among controls. A study from Spain (1139 cases and 11 390 population controls) demonstrated that RAS inhibitors do not increase the risk of COVID-19 requiring admission to hospital, including fatal cases.\(^{144}\) Another study using data from Danish national administrative registries concluded that prior use of ACEIs/ARBs was not significantly associated with COVID-19 diagnosis in patients with hypertension or with severe disease.\(^{145}\) In addition, ACEIs/ARBs were not found to be associated with COVID-19 severity in a study conducted in the USA.\(^{146}\) Furthermore, a few observational studies also found that ACEI/ARB use was not associated with increased severity of COVID-19 illness.\(^{142,147-154}\)

The results from these retrospective and observational studies suggest that treatment with ACEIs or ARBs is not associated with worse outcomes in infected patients.

### 6. Limitations of current evidence on PM and COVID-19 association

All of the studies systemically reviewed and included in this manuscript indicate that both long- and short-term exposures to high levels of pollutants are positively correlated with increased COVID-19 contagion worldwide. However, several other critical factors responsible for the high contagiousness and fatality of COVID-19 are not considered, which could potentially have affected the end results. Hence, the analysis presented in this article may also be subject to limitations. First, in ecological\(^{75}\) and/or cross-sectional studies, (i) measures of exposure are only a proxy based in the population and, therefore, caution is required while applying grouped results to the individual level; (ii) there are potential systemic differences between areas in the measurement of exposures and recording disease frequency; (iii) there is an inability to control confounding; and (iv) there is a lack of evidence of a temporal relationship between exposure and outcomes as both are simultaneously assessed. Secondly, the presence of confounding factors may mask an actual association between the exposure and outcome. Some studies did not include variables, such as age, gender, lifestyle factors (e.g. diet or smoking habits), socio-economic status, prevalence of pre-existing conditions, such as CVD, respiratory disease, and diabetes, emotional stress, physical activity, genetic predisposition, effect of other co-pollutants and all meteorological variables, the capacity of the healthcare system, or the case identification practices (e.g. the percentage of the population that were tested and the percentage of positive tests relative to the total number of tests), which might have confounded the findings.\(^{22,72-74,102}\)
7. Conclusion and future directions

Tak en a compelling association between PM and SARS-CoV-2 appears to exist, and this association facilitates the longevity of virus particles in the atmosphere, increases transmission and pathogenicity, and influences the incidence and severity of COVID-19 cardiovascular outcomes. In such a context, it would be valuable to carry out additional experimental studies to (i) screen PM for virus contamination; (ii) determine the particle size to which the virus binds; (iii) confirm the presence of the SARS-CoV-2 RNA on PM; and (iv) investigate the duration for which the virus remains active and infectious in association with PM. Further investigations to study the effect of the virus within the myocardium will probably facilitate future diagnostic and therapeutic modalities that may improve treatment and management of this novel disease.

COVID-19 exerts severe pathophysiological impacts on the cardiovascular system; under this scenario, discontinuing RAS inhibitors in COVID-19 patients is unwarranted. In fact, serious complications due to discontinuation of these drugs have far more adverse consequences than the surmised adverse effects. It is likely that due to pneumonia, COVID-19 patients will experience adverse CVD outcomes in the future. Thus, follow-up studies are essential amongst survivors. Future studies also warrant detailed randomized controlled epidemiological studies in multiple geographic regions affected by COVID-19.

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