


# Vascular Dysfunction and Its Cardiovascular Consequences During and After COVID-19 Infection: A Narrative Review

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**Abstract:** The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory coronavirus 2 (SARS-CoV2) has brought out changes in our daily life and has caused severe morbidity and mortality across the globe. Especially, post covid complications may remain a threat to the patient's life. It may also increase the burden on existing health infrastructure and the country's economy. This disease affects the respiratory system and other organ systems of the body, such as the cardiovascular system. The aim of the present narrative review is to understand how COVID-19 infection deranges vascular homeostasis, leading to endothelial dysfunction and arterial stiffness in the acute phase and following infection. To this effect, definite keywords were employed to obtain relevant information using PubMed database and Google Scholar search engines. It was documented that preexisting cardiovascular disease enhances morbidity in COVID-19 patients. Moreover, an elevated risk of development of new onset cardiovascular events has also been reported. Even a small amount of myocardial injury was significantly associated with death. The presence of virus in myocardial cells has also been documented. Furthermore, endothelial dysfunction and arterial stiffness were documented in the acute phase and 3–4 weeks to 4 months after COVID infection. The virus enters endothelial cells by binding with ACE2 “receptor” on its surface and deranges cellular machinery. It results in reduced conversion of Ang II to Ang (1–7). Accumulated Ang II then activates PI3K-Akt signaling pathway and regulates endothelial activation and production of IL-6 and reactive oxygen species (ROS). An imbalance between renin angiotensin aldosterone system (RAAS) and kallikrein kinin system (KKS) also occurs, which may cause endothelial dysfunction. It is understandable that the underlying pathophysiology of this altered arterial stiffness is multifactorial, involving various cellular and immunological biomolecules.

**Keywords:** arterial stiffness, endothelial dysfunction, COVID-19

## Introduction

The emergence of the Corona virus disease 2019 (COVID-19) pandemic caused by severe acute respiratory corona virus 2 (SARS-CoV2) has changed the way the whole world used to live and carry out daily activities. It not only affects respiratory system, but also inflicts other organ systems of the body including cardiovascular system. It causes cardiovascular complications like heart failure, venous thromboembolism, cerebrovascular events.<sup>1</sup> The endothelium is an integral part of the vascular conduit, essential for vascular homeostasis. Therefore, any perturbation of the vascular endothelial layer causes cardiovascular derangement. However, the data regarding vascular reactivity and arterial stiffness in COVID-19 infection is sparse. Most of the studies aimed to evaluate the arterial stiffness and endothelial function in the COVID patients during acute phase and following the infection. Furthermore, the investigators of few studies intended to understand the mechanism of vascular dysfunction in COVID-19 infection, which leads to cardiovascular complications. To this end, the present narrative review aims to understand how COVID-19 infection deranges vascular homeostasis, which eventually is reflected as endothelial dysfunction and arterial stiffness in acute phase and following infection.

## Method

The definite keywords used as search strategies to obtain relevant information were arterial stiffness, endothelial dysfunction, and COVID-19. The search engines used were PubMed database and Google Scholar. Total 27 articles have been found, inclusive of case report and reviews. Out of them, 15 articles have been discussed in the present narrative review. The overview of the research articles has been discussed in [Table 1](#).

## Endothelial Dysfunction, Arterial Stiffness, and Health Outcome

Before understanding how COVID-19 infection disrupts vascular homeostasis, it is worth understanding the cardiovascular health outcome because of endothelial dysfunction and arterial stiffness. Conventionally the physiological indices for assessing vascular functions include assessment of arterial stiffness, pulse wave reflection, and endothelial function.<sup>2</sup> Understandably, vascular conduit structural changes are more gradual than functional derangement. Therefore, functional assessment of vasculature is more sensitive than structural/morphological assessment during acute exposure of the disease process or risk factors affecting the vascular conduits.<sup>3</sup> Clinical studies have revealed that there is an association between brachial-ankle pulse wave velocity (a marker of arterial stiffness) with the markers of inflammation, oxidative stress, and high sympathetic tone.<sup>4,5</sup> An increase in arterial pulse wave velocity reflects an increase in arterial stiffness, culminating in an increase in summated forward and reflected pulse wave. The reflected pulse wave during the cardiac cycle increases afterload to the heart, thereby reducing the heart's stroke volume. It results in impairment of coronary arterial flow that eventually leads to ischemia of the heart generating arrhythmia and heart failure.<sup>6,7</sup> Attenuating the cushioning effect of elastic arteries enhances the transmission of pulsatile energy to peripheral microcirculation, causing its damage. Therefore, the end organs with high blood flow such as brain and kidney may suffer from deterioration in its microcirculation.<sup>3</sup> Ratchford et al (2021) reported that endothelial dysfunction and arterial stiffness can occur in young adults with COVID-19.<sup>8</sup>

## Role of Viral Infection in Endothelial Dysfunction and Arterial Stiffness

In general, the viral infection may affect endothelium by various mechanisms and may lead to endothelial dysfunction. Several mechanisms are involved in this process, such as (1) viral infection leading to the inflammation may derange the function of renin-angiotensin system and enhances the production of reactive oxygen species, (2) viral infection directly increase the production of reactive oxygen species also, (3) it increases the synthesis of pro-inflammatory cytokines ie, interleukin-6, which may cause derangement of vascular tone, thereby may enhance functional arterial stiffness. Besides it, (4) activation of neutrophils leads to the release of various vasoactive substances such as prostanoids, lysosomal enzymes, and reactive oxygen species. Myeloperoxidases released from azurophil granules of neutrophils may attenuate NO bioavailability. Overall, these abnormalities may enhance endothelial dysfunction, thereby increasing functional arterial stiffness.<sup>3</sup>

## COVID-19 and Cardiovascular Dysfunction

It has been previously mentioned that SARS-Cov2 also affects cardiovascular system besides its infliction on the respiratory system. Various clinical studies though few in number, reported it. It has been observed that the cardiovascular morbidity is more in those COVID patients who have a history of preexisting cardiovascular disease.<sup>9</sup> Interestingly, an elevated risk of development of a new cardiovascular event has also been reported in COVID patients. Right and left diastolic dysfunction was reported in 39% and 16% patients with COVID-19.<sup>10</sup> This indicates the involvement of small vessels and capillaries. Interestingly, an increased level of troponin-I has been documented in a significant number of patients, associated with a worse prognosis.<sup>11</sup> It was reported that even small amounts of myocardial injury (troponin I level >0.03–0.09 ng/mL) were significantly associated with death.<sup>12</sup> Then the question arises what could be the reason behind this elevated serum level of troponin I. The reports indicate that it may be due to non-ischaemic myocarditis. Furthermore, observed diastolic dysfunction may also be attributed to non-ischemic myocarditis.<sup>13</sup> In consecutive autopsies from COVID-19 patients, viral presence within the myocardium was documented.<sup>14</sup> Moreover, the infected myocardium was infiltrated with a higher number of leukocytes. In the same study, higher expression of mRNA

**Table 1** Overview of the Studies Determining Endothelial Dysfunction and Arterial Stiffness in COVID Patients During Acute Phase and Following Infection

First Author (Reference No.)	Mean Age	Number of Cases and Controls	Design	Methods for Assessment of Vascular Health	Outcomes Reported
Nakano et al., 2021 <sup>3</sup>				Narrative review	ACE-2 receptor activity is inhibited in COVID-19, thereby it affects vascular function. The study suggested that pulse wave velocity (PWV) can be employed to assess functional arterial stiffness during acute phase of COVID-19
Ratchford et al., 2020 <sup>8</sup>	Case - 20.2 ± 1.1 years Control - 23.0 ± 1.3 years	Case – 11 Control - 20	Cross-sectional case control	FMD in the arm and sPLM in the leg, cfPWV	FMD was lower in SARS-CoV-2 group. sPLM was lower in the SARS-CoV-2 group compared with the control. cf PWV was higher in SARS-CoV-2 group than control group.
Lala et al., 2020 <sup>12</sup>	Median age –66.4 years	Case-2736, Non-survivor- 506	Cross-sectional, observational study	Demographics, medical histories, admission laboratory results	Small amounts of myocardial injury (troponin I >0.03–0.09 ng/mL) were significantly associated with death, while greater amounts of troponin I >0.09 ng/dl were significantly associated with higher risk.
Lindner et al., 2020 <sup>14</sup>	78–89 years	Consecutive autopsy cases-39	Cross-sectional, observational study	Incidence of SARS-CoV-2 positivity in cardiac tissue and CD3+, CD45+, and CD68+ cells in myocardium and gene expression of tumor necrosis growth factor $\alpha$ , interferon $\gamma$ , chemokine ligand 5, as well as interleukin-6, –8, and –18	Viral presence within the myocardium was documented. A response to this infection was reported in cases with higher virus load.
Judd et al., 2021 <sup>15</sup>	Case – 24 years	1 COVID-19 patient during acute phase, but asymptomatic	Case report	FMD, NMD, aortic PWV, Alx and cIMT	Decreased FMD and NMD in comparison to reference values No remarkable change in PWV (5.9 m/s), Alx (27%) and cIMT Decreased FMD 6 weeks after Covid-19 infection
Nandadeva et al., 2021 <sup>16</sup>	23 ± 3 years	Case- 16, 4wk past COVID-19 diagnosis [8 – asymptomatic (ASYMP), 8- symptomatic (SYMP)] Control- 12	Case control	FMD and reactive hyperemia, CVMR and cfPWV	FMD was lower in SYM than ASYM and control CVMR and arterial stiffness were not different between any groups

(Continued)

Table 1 (Continued).

First Author (Reference No.)	Mean Age	Number of Cases and Controls	Design	Methods for Assessment of Vascular Health	Outcomes Reported
Schnaubelt et al., 2021 <sup>17</sup>	67–84 years	Case- 77 Control- 22	Case control	baPWV and cfPWV	baPWV and cfPWV were higher in COVID-19 patients than in controls. In multiple regression analysis, COVID-19 was independently associated with higher cfPWV and baPWV
Szeghy et al., 2021 <sup>18</sup>	20 ± 1 years	Case – 15 Control- 15	Cross-sectional case control	Carotid stiffness, cIMT, aortic Alx and PWA measurement	Higher carotid artery stiffness, Young's modulus and aortic stiffness ie, aortic Alx than control
Rodilla et al., 2021 <sup>19</sup>	67.5 years	12,170 patients admitted to 150 Spanish Centres included in the SEMI-COVID-19 Network. (2606 non-survivors, 9564 survivors)	Observational, retrospective, multi-center cohort study	Admission pulse pressure ≥60 mm Hg	Increased AS and systolic BP <120 mm Hg significantly and independently predicted all-cause in-hospital mortality (odds ratio: 1.27, P = 0.0001)
Kumar et al., 2021 <sup>20</sup>	-	23 Mild, 21 Moderate and 20 Severe COVID-19 patients	Prospective non-randomized observational study	cfPWV, ANI_cfPWV	cfPWV was significantly lower in mild patients than both moderate and severe patients. ANI_cfPWV in moderate and severe patients was significantly higher than mild patients.
Lambadiari et al., 2021 <sup>21</sup>	>18 years	Cases-70 four months after COVID-19 infection, positive control-70 untreated hypertensive patients, Healthy control-70	Case-control prospective study	PBR of the sublingual arterial microvessels, FMD, CFR, PWV, global LV and RV GLS, serum MDA, thrombomodulin and vWF levels	COVID-19 patients had similar CFR and FMD with hypertensives but lower values than controls. Compared to controls, both COVID-19 and hypertensives had greater PBR, higher PWV and impaired LV and RV GLS. MDA and thrombomodulin were higher in COVID-19 patients than both hypertensives and controls.
Stamatelopoulos et al., 2021 <sup>22</sup>	55–87 years	Case- 1671 Control- 934	Retrospective, longitudinal cohort study	ePWV was calculated using age and MBP (derived from cfPWV data)	Calculation of ePWV, a readily applicable estimation of arterial stiffness and it may serve as an additional clinical tool to refine risk stratification beyond established risk scores
Aydin et al., 2021 <sup>23</sup>	65.7 ± 10.7 years	Case- 65 Control-50	Prospective case control study	Systolic and diastolic blood pressure, urea, creatinine, eGFR at admission, serum lipid profile, BMI, CAVI, and ABPI	Right and left cardio-ankle vascular index values were increased in COVID-19 patients which was thought to be prognostically significant

Judd P et al., 2021 <sup>24</sup>	>18 years	Case – 14 Healthy control- 14 ASCVD control cohort - 14	Cross-sectional, observational study	FMD, NMD, PWV, Aix, IMT, compounds of arginine and kynurenine metabolism, homocysteine, vWF, EMP, antiendothelial cell antibodies, inflammatory, and immunological parameters, as well as nailfold capillary morphology	FMD and NMD (parameters of endothelial dysfunction) and inflammation were altered in post-COVID-19 patients
Bruno et al, 2021 [Covid-19 effects on ARTERial Stiffness and vascular AgeiNg (CARTESIAN) study] <sup>25</sup>	Not mentioned	Group 1–3 Patients tested for SARS-CoV-2 requiring 1.hospitalization in intensive care unit 2.hospitalization in medical ward 3.no hospitalization Group 4 Patients tested negative and presenting at Emergency department	Case control, longitudinal, multicentric study	Mandatory - cf PWV, brachial blood pressure, central blood pressure, carotid ultrasound, brachial FMD, Recommended - cardiac ultrasound, 24 h blood pressure, thoracic aortic calcification	“At the time of writing (10 November 2020), 43 centres from 21 countries had expressed interest in participating with a total expected number of >2500 included patients.”

**Abbreviations:** FMD, flow-mediated dilation; NMD, nitroglycerin-mediated dilation; PWV, aortic pulse wave velocity; Aix, augmentation index; cIMT, carotid intima-media-thickness; CVMR, cerebral vasomotor reactivity to hypercapnia; cfPWV, carotid-femoral pulse wave velocity; baPWV, brachial ankle pulse wave; PWA, pulse wave analysis; sPLM, single passive limb movement; AS, arterial stiffness; ANI\_cfPWV, age-normalized increase in cfPWV; CFR, coronary flow reserve; PBR, perfused boundary region; GLS, global left (LV) and right (RV) ventricular longitudinal strain; MDA, malondialdehyde; vWF, von Willebrand factor; ePWV, estimated pulse wave velocity; CAVI, cardio-ankle vascular index; ABPI, ankle-brachial pressure index; vWF, von Willebrand factor; EMP, endothelial microparticles.

transcripts of pro-inflammatory genes was also reported in infected myocardium.<sup>14</sup> It was observed that the stoppage of ACE2 inhibitor in COVID-positive patients caused an increase in cardiac afterload because of increased blood pressure and /or arterial stiffness. Enhanced cardiac afterload then leads to impaired myocardial circulation.<sup>3</sup> Overall, these pathophysiological mechanisms along with myocardial injury due to hypoxaemia and severe respiratory failure may lead to increased mortality in patients with COVID-19.<sup>3</sup>

It was reported that in a young, COVID-19 patient without any associated cardiovascular morbidity, FMD and NMD were decreased in comparison to reference values. This decreased FMD value persisted even after 6 weeks of infection.<sup>15</sup> In another case-control study, significant decrease of FMD value was demonstrated in symptomatic, young adults even after acute phase of disease (more than 4 weeks from diagnosis). However, there was no significant difference of cerebro vasomotor reactivity to hypercapnia (CVMR) and arterial stiffness observed between groups.<sup>16</sup> This is suggestive of the persistent effect of COVID-19 infection on vascular function even after acute phase of COVID-19. Interestingly, in a case-control study, brachial-ankle pulse wave velocity (baPWV) and carotid-femoral pulse wave velocity (cfPWV) were significantly higher in COVID-19 patients than in control. Furthermore, multiple regression analysis revealed COVID-19 was independently associated with baPWV and cfPWV.<sup>17</sup> Moreover, carotid artery stiffness and aortic augmentation index were found to be higher in young adults 3–4 weeks after being COVID positive than control.<sup>18</sup> In another case-control study, FMD and single passive leg movement (sPLM) –related blood flow was lower in the COVID patients 3–4 weeks after testing positive than control, but cfPWV was higher in the study group.<sup>8</sup> Rodilla et al (2021) reported that increased arterial stiffness and systolic BP <120 mm Hg significantly and independently can predict all-cause in-hospital mortality.<sup>19</sup> It was documented that cfPWV was significantly lower in mild COVID patients than both moderate and severe patients. Age-Normalized increase in cfPWV (ANI\_cfPWV) in moderate and severe patients was significantly higher than mild patients.<sup>20</sup> Lambadiari et al (2021) reported that 4 months after COVID-19 infection, COVID-19 patients had similar coronary flow reserve (CFR) and FMD with hypertensives but lower values than controls. Moreover, both COVID patients and hypertensives had higher PWV. Serum markers of oxidative stress i.e; malondialdehyde and endothelial function (thrombomodulin), were higher in COVID patients.<sup>21</sup> In a retrospective longitudinal cohort study, estimated pulse wave velocity (ePWV) has been calculated using age and mean blood pressure (MBP) [derived from cfPWV data] and the study has concluded that calculation of ePWV, may serve as an additional clinical tool to refine risk stratification of hospitalized patients with COVID-19 besides already established risk factors and scores.<sup>22</sup> A prospective, case-control study reported that right and left cardio-ankle vascular index values (one of the non-invasive surrogate markers of the arterial stiffness) were more in COVID-19 patients and have a prognostically significance.<sup>23</sup> Another cross-sectional, observational study reiterated the previous findings i.e; most of the parameters of endothelial dysfunction (FMD, NMD) and inflammatory vasculopathy were altered in COVID patients.<sup>24</sup> A multicentric, case-control, longitudinal study entitled “Covid-19 effects on ARTERial Stiffness and vascular AgeiNg (CARTESIAN) study” has been designed, which is being conducted in 43 centres from 21 countries involving >2500 COVID patients. The broader objective of this study is to evaluate the presence of Early Vascular Ageing (EVA) 6 and 12 months after COVID-19 infection. Estimation of cfPWV, brachial blood pressure, central blood pressure, carotid ultrasound, brachial FMD are employed mandatorily and cardiac ultrasound, 24 h blood pressure, thoracic aortic calcification are being recommended.<sup>25</sup>

## The Pathophysiological Mechanism of Endothelial Dysfunction and Arterial Stiffness in COVID-19

The clinical studies suggested various pathophysiological mechanisms underlying increased arterial stiffness in COVID-positive patients. One such mechanism is indirect endothelial damage because of acute inflammatory response and release of a plethora of cytokines in response to SARS COVID-19 infection. Expression of ACE2 has been particularly detected on arterial smooth muscle cells and both arterial and venous endothelial cells.<sup>18</sup> The spike-glycoproteins of SARS CoV-2 virus binds with ACE2, thereby using it as its portal to enter the cell and replicates within the cell. It results in down-regulated expression of ACE2 and the cell surface trans-membrane protease serine 2 (TMPRSS2).<sup>26</sup> Consequently, the conversion of Ang II to Ang (1–7) is reduced and Ang II accumulates within the cell. Ang II is a

known potent vasoconstrictor. However, excessive accumulation of it activates PI3K-Akt signaling pathway through AT1 receptor and thereby regulate endothelial activation and production of IL-6 and ROS.<sup>27</sup> Loss of ACE2 leads to imbalance of renin–angiotensin–aldosterone system (RAAS) and the kallikrein–kinin system (KKS). Activated KKS then may cause endothelial dysfunction, which may promote enhanced leukocyte adhesion, complement activation.<sup>27</sup> The resulting endothelial dysfunction may affect vascular tone and its permeability also. Vascular endothelial damage may lead to platelet aggregation and blood coagulation. It also enhances the synthesis and secretion of pro-inflammatory cytokines (cytokine storm) such as IL-2, IL-7, IL-10, MCP-1, TNF $\alpha$  from adjoining tissues and blood mononuclear cells.<sup>28</sup> This infection may cause decrease in CD4<sup>+</sup> and CD8<sup>+</sup> T cell count as well as IFN- $\gamma$  induced CD4<sup>+</sup> T cell production, which might be correlated with disease severity.<sup>28</sup> The pro-coagulant and pro-inflammatory nature of blood may increase the risk of plaque rupture and thromboembolism, which eventually leads to myocardial infarction. It provides an additional evidence for detrimental effects of SARS-CoV-2 on young, adult vasculature.<sup>17</sup> Besides it, damaged endothelial cells promote hypercoagulable state, which also dysregulates normal vascular tone.<sup>18</sup> The endothelium is not just a mere barrier. It is comprehensible that endothelial cells have location specific functional specializations and activation status. Accumulating pieces of evidence point towards the role of endothelial cells in maintenance of immunological homeostasis.<sup>29</sup> It also acts as a sensor to immunological threat which may be of viral origin. It was also demonstrated that serum level of E-selectin and angiopoietin-2, considered to be as circulating biomarker of perturbation of endothelial function, were also highly increased in a cohort of COVID positive patients and it was associated with the degree of severity of the disease process.<sup>29</sup> Understandably, the endothelial cells get activated from bio-signals emanated from the infected tissue or from the virus. It induces a pro-adhesive and chemokine-secreting phenotype of endothelial cells, which in turn helps in the recruitment of circulating blood cell and becomes instrumental in producing “cytokine storm”.<sup>30</sup> This “cytokine storm” further perturbs endothelial functionality and enhances arterial stiffness. Therefore, it may be concluded that the role of vascular endothelial cells is pivotal in maintaining vascular homeostasis. Severe systemic inflammation also brings about changes in hormonal balance, maintaining vascular tone. It also causes vascular adrenoceptor hyporeactivity, decreased level of endogenous vasopressin, and corticosteroid insufficiency. Altogether these may reduce vascular tone and may affect arterial stiffness.<sup>31</sup>

## Conclusion

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory coronavirus 2 (SARS-CoV2) has caused severe morbidity and mortality across the globe. Especially, post-covid complications may remain a threat to the patient’s life. Though the symptoms reported are mainly respiratory in origin, other organ systems are also affected by this virus, such as the cardiovascular system. The preexisting cardiovascular disease enhances the morbidity due to COVID-19. However, newly onset cardiovascular event has also been reported in COVID-positive patients. The endothelium is an integral part of vascular conduit and is essential for vascular homeostasis. Any perturbation of the vascular endothelium may cause cardiovascular derangement, which has been reported in COVID-positive patients as assessed by the altered parameters of arterial stiffness such as pulse wave velocity, aortic augmentation index, and flow-mediated vasodilatation. The underlying pathophysiology of this altered arterial stiffness is multifactorial involving various cellular and immunological biomolecules.

## Disclosure

The author reports no conflicts of interest in this work.

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