

Endothelial Dysfunction and Microcirculatory Impairment as a Unifying Pathway of Post-COVID-19 Organ Injury: From Vascular Inflammation to Hypoxic Tissue Remodeling

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially regarded as a pathogen of the respiratory epithelium, yet clinical, histopathological and functional observations have shown that the vascular endothelium is one of the most consistently affected tissues during and after COVID-19. Background. Post-COVID-19 condition is characterised by fatigue, dyspnoea, exercise intolerance, cognitive complaints and multisystem symptoms that often cannot be explained by a single organ lesion. Materials and Methods. A structured narrative review of peer-reviewed publications and documents of international health organisations was performed, focusing on endothelial activation, coagulation abnormalities, capillary perfusion, tissue hypoxia and their downstream structural consequences in the lungs, heart, kidneys, skeletal muscle and nervous system. Results. The analysed evidence indicates that endothelial injury links several otherwise separate processes: increased vascular permeability, leukocyte adhesion, platelet activation, procoagulant activity, reduced nitric oxide-dependent vasodilation and impaired capillary oxygen delivery. Chronic microvascular hypoperfusion may sustain oxidative stress, mitochondrial dysfunction and profibrotic signalling, thereby converting a transient inflammatory injury into persistent tissue remodeling. The vascular contribution is best documented in the lungs after severe disease, but plausible microcirculatory correlates have also been described in myocardium, kidneys, skeletal muscle and the neurovascular unit. The strength of evidence differs between organs, and concepts such as persistent “microclots” still require validation. Conclusion. Endothelial dysfunction can be considered a cross-organ pathogenetic axis of post-COVID-19 condition rather than a local vascular complication. Assessment of vascular function, coagulation status and tissue perfusion may help to stratify patients and to design targeted rehabilitation and follow-up strategies.

Keywords: SARS-CoV-2, post-COVID-19 condition, long COVID, endothelial dysfunction, microcirculation, coagulation, tissue hypoxia, oxidative stress, mitochondrial dysfunction, fibrosis, skeletal muscle, multiorgan injury.

Introduction.

Since the beginning of the COVID-19 pandemic, the understanding of SARS-CoV-2 infection has shifted from that of a primarily pulmonary disease to that of a systemic disorder in which the vascular bed plays a decisive role. The clinical picture of severe COVID-19 — hypoxaemia disproportionate to radiological findings, thrombotic events, multiorgan dysfunction and marked elevation of coagulation markers — pointed early to the involvement of blood vessels and, in particular, of the endothelium.[1][2]

The endothelium is a metabolically active organ that regulates vascular tone, permeability, coagulation, fibrinolysis, leukocyte trafficking and the delivery of oxygen and nutrients to every tissue. Because all organs depend on an intact capillary network, a disturbance of endothelial function is capable of producing simultaneous changes in organs that have no direct anatomical connection with each other.[3]

Most patients recover from acute COVID-19 without lasting structural consequences. However,

according to the World Health Organization, a clinically relevant proportion of people develop post-COVID-19 condition, which includes fatigue, shortness of breath, cognitive dysfunction, muscle and joint pain, sleep disturbances and other symptoms that limit daily activity. Current WHO estimates of its frequency are lower than those reported early in the pandemic, but the burden remains substantial.[4]

Contemporary hypotheses of long COVID include persistence of viral antigens or reservoirs, immune dysregulation, autoimmunity, reactivation of latent viruses, abnormal coagulation, autonomic dysfunction and residual organ injury. Notably, endothelial dysfunction and microvascular impairment intersect with almost every one of these mechanisms, which makes the vascular bed a logical candidate for a unifying pathophysiological framework.[5]

Previous reviews have predominantly described post-COVID-19 changes organ by organ. Far less attention has been given to the question of how a shared vascular disturbance may translate into organ-specific structural remodeling. Addressing this question is important for explaining why patients with only minimal residual radiological abnormalities may still experience disabling multisystem symptoms.

Aim of the study

The aim of this study was to analyse the role of endothelial dysfunction and microcirculatory impairment as a common pathway of post-COVID-19 tissue injury, to characterise the sequence of events leading from vascular inflammation to hypoxic and fibrotic remodeling, and to summarise the organ-specific consequences of this process.

Materials and Methods

The study was designed as a structured narrative review and organised according to the IMRD (Introduction, Methods, Results, Discussion) format. Scientific publications describing vascular, coagulation and tissue changes after acute SARS-CoV-2 infection were analysed.[6]

Sources included peer-reviewed original studies, systematic reviews and narrative reviews indexed in international databases, as well as official documents of the World Health Organization defining post-COVID-19 condition. Publications describing histological, molecular, radiological, biochemical and functional findings were prioritised.[7]

The analysis was organised around three questions: (1) which mechanisms damage the endothelium during and after COVID-19; (2) how endothelial and microcirculatory abnormalities lead to tissue hypoxia, metabolic stress and fibrosis; and (3) which organ systems show structural or functional signs consistent with this vascular pathway.[8]

Each body of evidence was additionally appraised for the type of population studied (hospitalised, critically ill or non-hospitalised patients), the presence of control groups and the possibility of confounding by critical illness, mechanical ventilation, immobilisation or pre-existing disease. Where findings were derived mainly from autopsy or severe-disease cohorts, this was explicitly considered when interpreting their relevance to the broader post-COVID population.

Since the study did not involve recruitment of patients or experimental interventions, no original clinical dataset was generated and ethical approval was not required. The results represent a structured synthesis of published evidence.[9]

Results

1. Mechanisms of endothelial injury in SARS-CoV-2 infection

Endothelial injury in COVID-19 appears to arise from both direct and indirect influences. Histopathological studies of severe cases have described endothelial cell damage, perivascular inflammation (“endotheliitis”) and microthrombi in pulmonary and extrapulmonary vessels. Indirect mechanisms include exposure of endothelial cells to high concentrations of cytokines, activated complement components, neutrophil extracellular traps and hypoxaemia.[10]

Activated endothelium loses its physiological anticoagulant and anti-inflammatory phenotype. It expresses adhesion molecules, recruits leukocytes and platelets, increases vascular permeability and shifts the haemostatic balance towards thrombosis. At the same time, reduced bioavailability of nitric oxide impairs vasodilation and the ability of the microcirculation to match blood flow to tissue metabolic demand.[11]

After clearance of the virus from the respiratory tract, this process does not necessarily resolve completely. Several studies have reported persistent markers of endothelial activation, altered coagulation and platelet hyperreactivity months after infection, particularly in patients with ongoing symptoms.

Table 1. Endothelial and microcirculatory mechanisms and their consequences in post-COVID-19 tissue injury

Vascular mechanism	Effect on tissue	Possible clinical manifestation
Endothelial activation	Increased permeability, leukocyte adhesion	Interstitial oedema, organ dysfunction
Reduced nitric oxide bioavailability	Impaired vasodilation and flow regulation	Exercise intolerance, dyspnoea
Procoagulant shift and platelet activation	Microthrombosis, capillary obstruction	Hypoxia-related symptoms
Capillary rarefaction and hypoperfusion	Reduced oxygen and substrate delivery	Fatigue, muscle weakness
Oxidative stress	Membrane and mitochondrial damage	Reduced cellular energy production
Profibrotic signalling from injured vessels	Fibroblast activation, matrix deposition	Tissue stiffness, reduced organ reserve
Blood–brain barrier dysfunction	Neuroinflammation, glial activation	Cognitive impairment, headache

2. From microvascular dysfunction to tissue hypoxia and metabolic stress

The functional unit linking vascular injury to tissue damage is the capillary network. When capillary perfusion becomes heterogeneous or reduced, oxygen extraction by the surrounding cells is limited even if arterial oxygen saturation is normal. This mechanism may explain why some patients experience dyspnoea and early fatigue in the absence of significant changes on lung imaging.

Prolonged relative hypoxia favours the formation of reactive oxygen species, damages cellular membranes and impairs mitochondrial oxidative phosphorylation. Reduced ATP generation, in turn, limits the capacity of cells to repair themselves and to sustain physical work, creating a self-perpetuating cycle of vascular dysfunction, metabolic insufficiency and inflammation.

Evidence regarding persistent fibrin-amyloid “microclots” in the circulation of patients with long COVID is still evolving. Their diagnostic value and causal role have not been established, and standardised methods of detection are lacking. Nevertheless, abnormal coagulation and platelet activation remain biologically consistent with the microcirculatory hypothesis and are active areas of investigation.[12]

3. Pulmonary vascular and parenchymal remodeling

In the lungs, the alveolar–capillary barrier represents the closest anatomical interface between epithelium and endothelium. Severe COVID-19 causes diffuse alveolar damage, endothelial injury, microthrombosis and disruption of this barrier, and in some cases is accompanied by abnormal angiogenesis.

During convalescence, incomplete restoration of the capillary bed may coexist with dysregulated epithelial repair. Follow-up imaging of previously hospitalised patients has revealed residual ground-glass opacities, reticulation, parenchymal bands and fibrotic-like changes. Persistent interstitial abnormalities have been reported in up to approximately 30% of such patients, although many of them improve over time and irreversible fibrosis appears to develop only in a smaller subset.

Reduced capillary surface area and fibrotic thickening of the interstitium both decrease diffusing capacity, which is consistent with persistent exertional dyspnoea and reduced exercise tolerance in these patients.[13]

4. Myocardial microcirculation and cardiovascular consequences

Myocardial involvement after COVID-19 may reflect inflammatory injury, ischaemia caused by microvascular dysfunction, thromboembolic events or stress-related damage. Coronary microvascular dysfunction can limit myocardial perfusion reserve without obstruction of the major epicardial arteries.

In the post-acute period, palpitations, chest discomfort, reduced exercise capacity and autonomic symptoms are common complaints. However, structural cardiac damage is not found in all symptomatic individuals, and these symptoms therefore require careful differential diagnosis. When significant myocardial injury has occurred, fibrotic remodeling may alter ventricular relaxation, conduction and contractile reserve.[14]

5. Renal microvascular and tubular injury

The kidneys are particularly sensitive to disturbances of perfusion because of their high metabolic activity and complex microvascular architecture. During severe COVID-19, renal injury results from haemodynamic instability, endothelial damage, microthrombosis, systemic hypoxia, inflammation and nephrotoxic exposures. Acute tubular injury is the most frequently described histological finding.

Incomplete recovery from acute kidney injury may contribute to the development or progression of chronic kidney disease. Patients with severe acute kidney injury, diabetes, hypertension, pre-existing renal disease or advanced age therefore warrant monitoring of serum creatinine, estimated glomerular filtration rate and urinary protein excretion.

6. Skeletal muscle perfusion and bioenergetics

Skeletal muscle is a tissue in which the consequences of impaired oxygen delivery become clinically evident during exertion. Muscle weakness, myalgia, exercise intolerance and post-exertional symptom exacerbation are among the most disabling manifestations of long COVID.

A 2024 muscle-biopsy study in patients with long COVID and post-exertional malaise demonstrated structural abnormalities, reduced mitochondrial function and further deterioration of muscle tissue after exercise. These data indicate that, at least in some patients, post-exertional symptoms have measurable biological correlates and cannot be explained by deconditioning alone. Impaired capillary function and altered substrate utilisation may act together with mitochondrial dysfunction to produce early fatigue.

Table 2. Organ-specific vascular manifestations of post-COVID-19 condition and suggested methods of assessment

Organ / tissue	Vascular and structural alterations	Suggested assessment
Lungs	Capillary injury, microthrombi, interstitial and fibrotic-like changes	CT, spirometry, DLCO
Heart	Coronary microvascular dysfunction, inflammation, focal fibrosis	ECG, echocardiography, cardiac MRI
Kidneys	Tubular injury, impaired renal perfusion	Creatinine, eGFR, urinary protein
Skeletal muscle	Reduced capillary oxygen delivery, mitochondrial impairment	Exercise testing, functional scales
Nervous system	Blood–brain barrier dysfunction, neuroinflammation	Cognitive testing, neuroimaging
Systemic vasculature	Endothelial activation, procoagulant state	D-dimer, endothelial function tests

7. Neurovascular unit and central nervous system

Neurological manifestations of post-COVID-19 condition include impaired concentration and memory, headache, sleep disturbances, sensory symptoms, dysautonomia and fatigue. The neurovascular unit — endothelium, pericytes, astrocytes and neurons — provides a structural basis for linking vascular dysfunction with these symptoms.

Disruption of the blood–brain barrier, microvascular abnormalities and persistent activation of microglia and astrocytes are among the mechanisms under investigation. Autopsy studies have detected SARS-CoV-2 material in many tissues, including the brain, mainly in severe fatal cases; however, these findings do not prove that ongoing viral replication in the nervous system underlies neurological symptoms in all patients.

8. Fibrosis as the end stage of vascular-driven tissue remodeling

Fibrosis develops when normal reparative processes become excessive or fail to terminate. Injured endothelial cells and infiltrating immune cells release cytokines and growth factors, including transforming growth factor-beta, which activate fibroblasts and promote their differentiation into myofibroblasts. These cells deposit collagen, fibronectin and other matrix proteins.

Chronic hypoxia further supports this process, since hypoxic signalling enhances profibrotic gene expression. The lung provides the clearest clinical example of post-COVID fibrosis. The benefit of routine antifibrotic therapy in this setting remains uncertain, and systematic reviews have concluded that current evidence is insufficient to support its indiscriminate use.[15]

Discussion

The analysed literature supports the view that the vascular endothelium is a central, cross-organ target of SARS-CoV-2-related injury. Whereas classical descriptions of post-COVID-19 complications list organ lesions separately, the vascular approach explains why diverse organs may be affected simultaneously and why symptom severity does not always correlate with visible structural damage.

The proposed sequence of events can be summarised as follows: acute endothelial injury and inflammation lead to a procoagulant and vasoconstrictive state; impaired capillary perfusion causes tissue hypoxia; hypoxia and inflammation promote oxidative stress and mitochondrial dysfunction; and persistent cellular injury activates profibrotic pathways that, in susceptible tissues, result in structural remodeling.

This framework is compatible with other leading hypotheses of long COVID. Immune dysregulation — including changes in T-cell and B-cell populations, interferon signalling and monocyte phenotypes — maintains endothelial activation. Persistent viral components in selected tissues may act as a continuous antigenic stimulus for both immune cells and endothelium. Autonomic dysfunction may further disturb the regulation of vascular tone and regional blood flow.

From a clinical perspective, the vascular model has practical implications. It suggests that functional assessment of perfusion, exercise capacity and coagulation may be informative even when conventional imaging is unremarkable. It also supports individually dosed rehabilitation, because exercise that exceeds the capacity of an impaired microcirculation may worsen symptoms, as demonstrated in patients with post-exertional malaise.

Several limitations must be acknowledged. A considerable proportion of the histological evidence originates from autopsy series of patients who died with severe disease and cannot be directly extrapolated to non-hospitalised individuals with long COVID. Post-COVID cohorts differ in age, vaccination status, viral variant, comorbidities, treatment and time since infection.

It is also difficult to separate vascular damage caused by SARS-CoV-2 itself from damage attributable to critical illness, mechanical ventilation, prolonged immobilisation, secondary infections or pre-existing cardiovascular and metabolic disease. Validated biomarkers of endothelial dysfunction suitable for routine practice are still lacking. Prospective studies with matched control groups and repeated measurements of vascular function are needed to confirm causality.

Conclusion

Endothelial dysfunction and microcirculatory impairment represent a plausible unifying pathway that connects the pulmonary, cardiac, renal, muscular and neurological manifestations of post-COVID-19 condition.

The main links of this pathway include endothelial activation, a procoagulant shift, reduced vasodilatory capacity, capillary hypoperfusion, tissue hypoxia, oxidative stress, mitochondrial dysfunction and profibrotic signalling, which in some patients culminate in persistent structural remodeling.

The vascular perspective helps to explain multisystem symptoms in patients without major residual imaging abnormalities and supports a personalised approach that combines assessment of organ structure with evaluation of vascular and metabolic function.

Further prospective clinical, histological, molecular and imaging studies are required to identify reliable markers of endothelial injury, to distinguish reversible from irreversible changes and to determine which patients may benefit from targeted vascular, anti-inflammatory, metabolic, rehabilitative or antifibrotic interventions.

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