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EDITORIAL

# COVID-19-associated vasculitis and vasculopathy

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**Abstract**
The COVID-19 pandemic now totaling 13,000,000 cases and over 571,000 deaths has continued to teach the medical, scientific and lay communities about viral infectious disease in the modern era. Among the many lessons learned for the medical community is the potential for transmissibility and host infectivity of the SARS–CoV-2 virus. Moreover, it has become clear that the virus can affect any organ including the circulatory system, directly via either tissue tropism or indirectly stemming from inflammatory responses in the form of innate immunity, leukocyte debris such as cell-free DNA and histones and RNA viral particles. The following review considers COVID-19-associated vasculitis and vasculopathy as a defining feature of a virus-induced systemic disease with acute, subacute and potential chronic health implications.

**Keywords** COVID-19 · Vasculitis · Vasculopathy

## Establishing a foundation for COVID-19 and vascular pathology

### The vascular system

The vascular system also referred to as the circulatory system or vascular tree carries blood, oxygen and essential elements to all metabolically active tissues and organs of the body and carries waste materials and by-products away. There are five distinct components of the circulatory system: arteries and arterioles (arterial system), veins and venules (venous system) and capillaries (microvascular system) that link arterioles and venules. The dimensions of blood vessels vary by an order of several thousand-fold with capillaries as small as 10 μm to the aorta of 25 mm (Fig. 1).

Endothelial cells respond to injury in several stages (reviewed in Abraham). While there may be injurious agent-specific responses, in a majority of cases the initial event is triggered by infection (viral, bacterial), oxidative stress, hypoxia, turbulent blood flow and shear stress, environmental toxins and circulating elements that follow tissue injury with the release of cell-free nucleic acids, histones, chemokines, cytokines and damage-associated proteins.

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The two-level response to endothelial cell injury includes an initial rapid response and a slower phenotypic response (reviewed in Abraham) [1]. Briefly, the initial response causes sudden changes in endothelial cell protective or integrity proteins, including nitric oxide, prostaglandins, endothelins, von Willebrand factor (VWF) and tissue plasminogen activator. The slower phenotype response reflects structural changes of endothelial cell topography, cell orientation, basement membranes and surrounding smooth muscle cells. In addition to the extent of initial injury, phenotypic changes follow a response to injury with release of endocrine and paracrine factors, primarily growth factors that provoke the deposition of extracellular matrix and the activation and proliferation of smooth muscle cells, pericytes and mesenchymal cells within the vessel wall. Vessel remodeling can occur with changes in cellular architecture and function [2, 3] (Fig. 2).

## The vascular endothelium: structure and function

### Vascular endothelial cells

The complex structure–function relationship of vascular endothelial cells has fascinated pathologists, physiologists, protein chemists and scientists for centuries. The structural aspects of endothelial cells are themselves deceivingly

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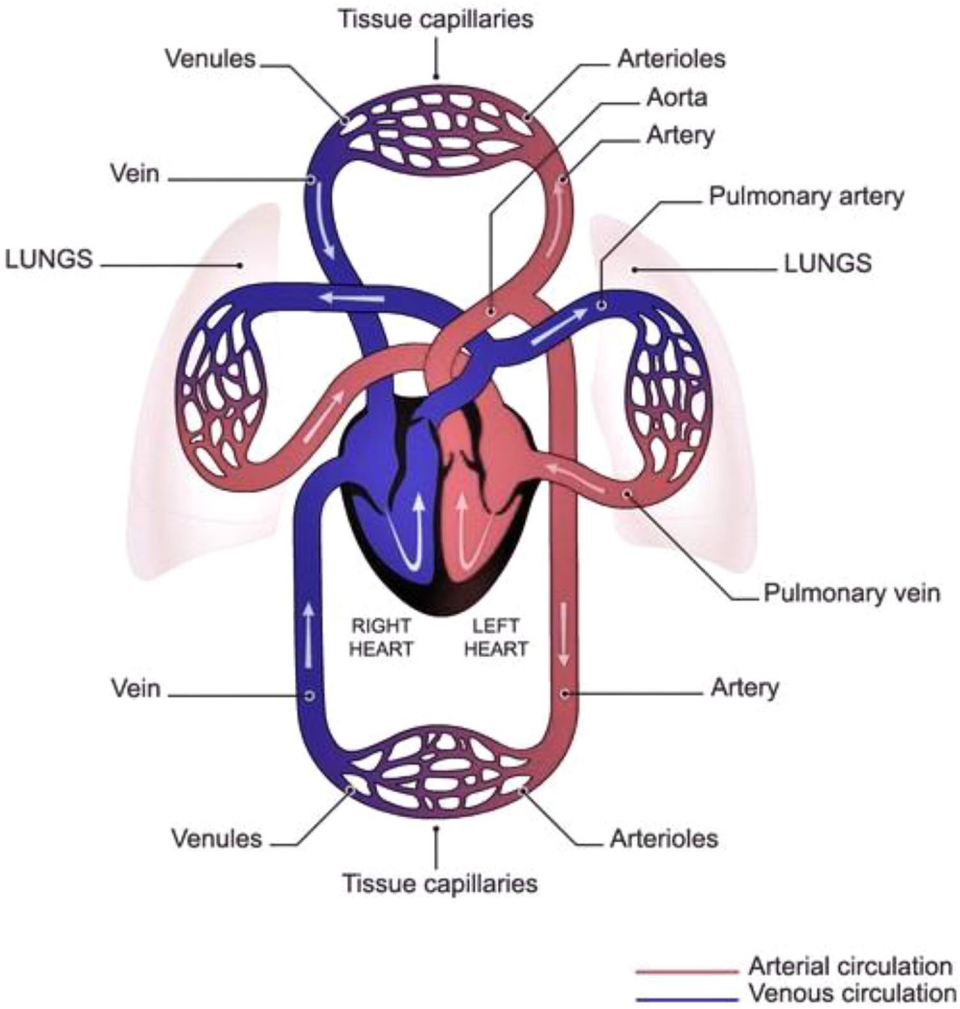


**Fig. 1** The circulatory system consists of the heart and large, medium and small arteries (arterioles), capillaries, small veins (venules, sinusoids) and large veins. Normal function depends on the flow of blood (and nutrients) to and from vital organs; however, the microvessels (arterioles, capillaries and venules) are responsible for vascular tone, homeostasis and tissue perfusion. From

simple and divided into three distinct surfaces: the *luminal surface* (non-thrombogenic), the *cohesive junctional surface* and an *adhesive abluminal surface* (reviewed in Tucker) [4]. The functional roles and broad-reaching intricacies of each surface are highly complex and, in many ways, distinguish normal physiology from pathological conditions [5].

The vascular endothelium's functional role is separated into distinct parts: (1) *barrier function*—highly selective and regulates inflammatory and immune responses, (2) *transport function*—responsible for cell–cell signaling and pinocytosis (i.e. particles in extracellular fluid enter the cell through invaginations or clefts in the cell membrane), (3) v*ascular repair function*-restores structural and functional normalcy, (4) *angiogenesis function*-reparative and adaptive to injurious conditions, (5) *thromboregulation function*- supports physiological blood flow and prevents unwanted (or needed) blood clotting, (6) *vasoregulation function*—responds to local conditions and signals vasodilation or vasoconstriction, (7) *metabolic function*—responsible for a highly regulated synthesis of growth factors, adhesion molecules and receptors; and (8) *immune function*-responds to a variety of immune cells, expresses histocompatibility antigens and regulates antigen presenting cells [6] (Fig. 3).

The vascular endothelium constitutes an inner lining of arteries, veins and capillaries. Accordingly, it is in direct communication with circulating blood components and tissues (reviewed in Krüger-Genge) [7]. In addition to its fundamental substrate delivery capabilities, the vascular endothelium is an active endocrine and paracrine organ. Moreover, it is tissue-specific, carrying out specialized functions as needed under highly dynamic conditions.

Even a brief summary of vascular endothelium structure and function underscores its critical role in human health and disease, and the potential consequences of injury and resulting dysfunction. These include, but are not limited to, vascular integrity, permeability, cellular/tissue cross talk, and the regulation of vasomotor activity, coagulation and inflammation [7, 8].

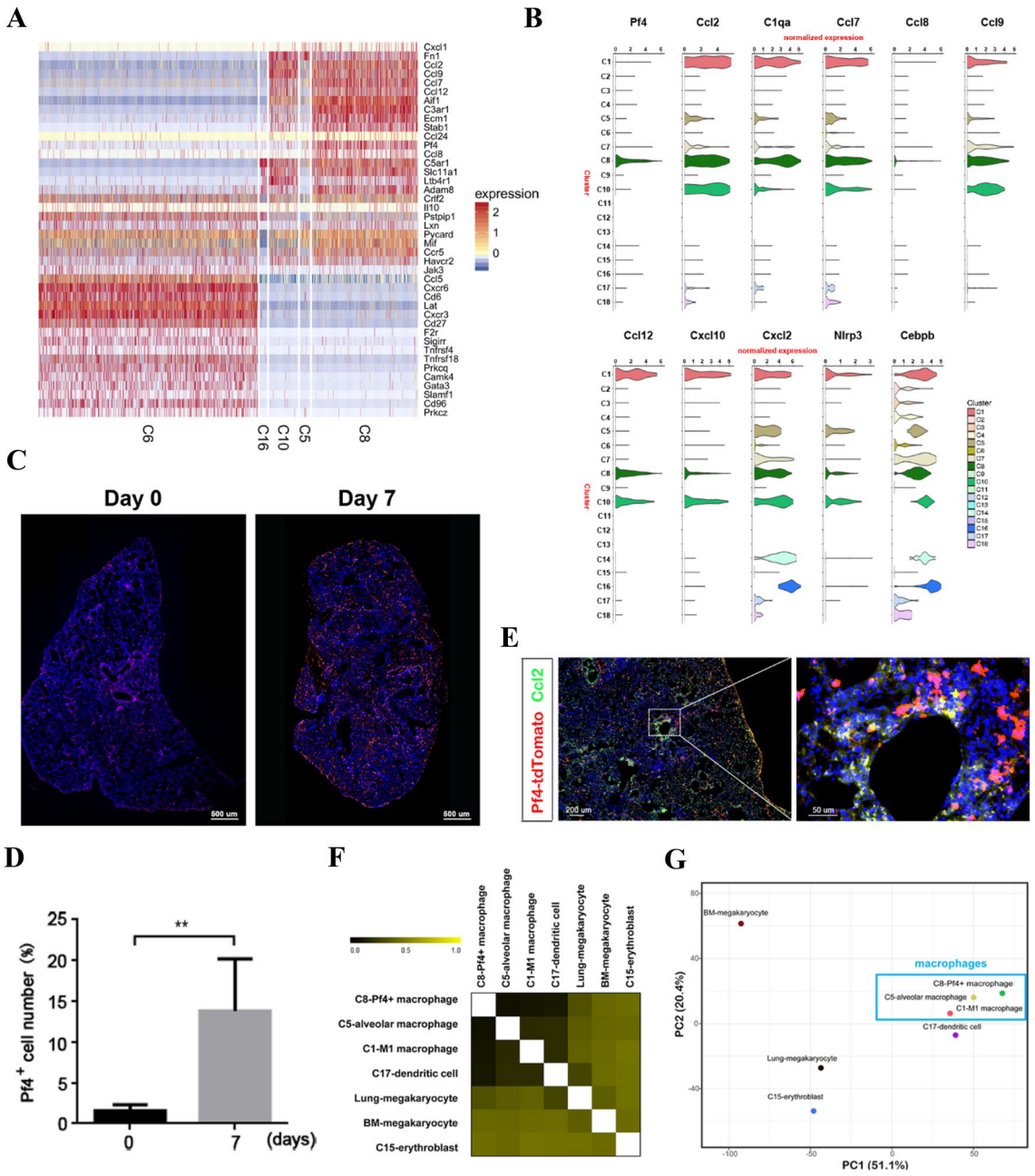


**Fig. 2** Pf4$^+$-macrophages are the major resource to generate second wave of pro-inflammatory factors at late stage of IAV-driven pneumonia. **a** Heat-maps showing the normalized expression (Z-score) of the pro-inflammatory genes in the various cells of clusters with high ratios at day 7 p.i.. **b** The normalized expression (UMI counts) of some significant genes with high expression in different clusters at day 7 p.i.. **c** Pf4$^+$ cells in the lung after IAV infection. The tdtomato-Pf4 mice were uninfected or infected with 0.5 $LD_{50}$ of influenza A/PR/8/34 (H1N1) viruses. At day 7 p.i, the tdtomato-Pf4$^+$ cells in the lung were scanned. The nucleus was stained with DAPI (blue) and tomato-Pf4 (red) was shown in red. Scale bars, 500 μm. **d** At day 0 and day 7 p.i., the tdtomato-Pf4$^+$ cells in the lung were calculated. At least 300 cells in each group from three independent assays were scored. Data are shown as the mean ± SD. **, $P < 0.01$ (Student $t$ test, $n = 3$). **e** The expression of Ccl2 in Pf4$^+$ cells. The tdTomato-Pf4 mice were infected with 0.5 $LD_{50}$ of influenza A/PR/8/34 (H1N1) viruses. At day 7 p.i, the tdTomato-Pf4$^+$ cells in the lung were stained with anti-Ccl2 antibodies (green). The nucleus was stained with DAPI (blue) and Pf4-tdTomato (red) was shown in red. Scale bars, left, 200 μm; right, 50 μm. **f** Heatmap showing the scaled distances calculated based on Pearson correlations for relationships between the z-score normalized mean expression profiles in all the indicated cells. **g** PCA plot showing the relationships among the indicated cell clusters and the megakarycytes from lung and bone mellow described by others (SRP097794, NCBI) (From Zhang J. PLoS Pathol 2020;16: e1008334. With permission)

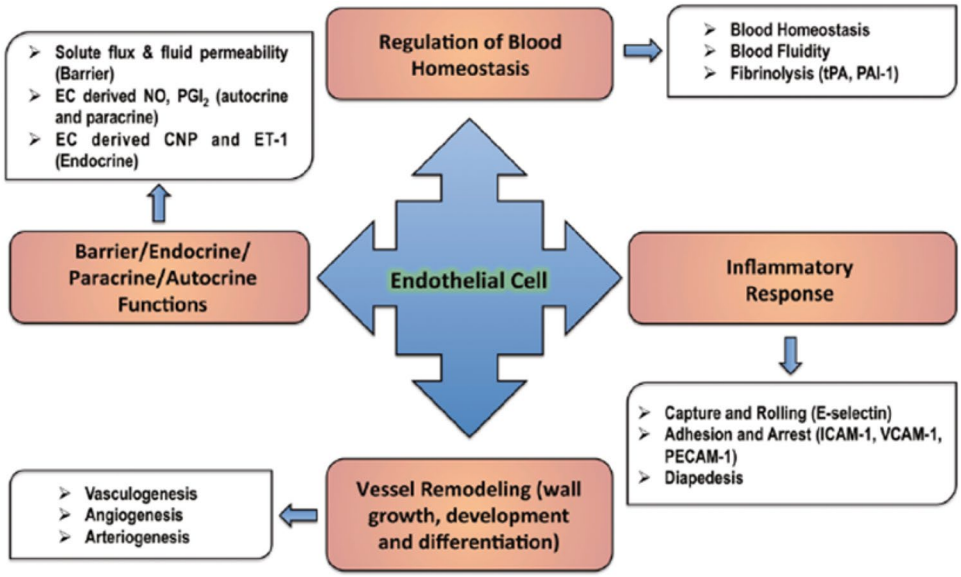


**Fig. 3** Endothelial cells exhibit a broad range of functions that include physical barrier, endocrine, paracrine and autocrine, vascular remodeling and repair, regulation of thrombosis, regulation of inflammation, cell migration and cellular signaling. Endothelial cell (EC), nitric oxide (NO), prostacyclin ($PGI_2$), endothelin (ET), tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI)-1, inter-cellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, platelet/endothelial cell adhesion molecule (PECAM)-1

## Microvascular endothelial cells

The microcirculation is represented by blood vessels of the smallest diameter (terminal arterioles, capillaries, and venules), but overall greatest surface area. In addition, the microcirculation plays a critical role in tissue perfusion and exchange of vital substrates. While smooth muscle cells are present within the walls of microvessels, specialized cells known as pericytes embedded in the basement membrane also play an important role in regulating tone, maintaining vascular integrity and phagocytosing cellular debris [9] (reviewed in Lee L.)

## Vascular endothelial glycocalyx

The luminal surface of endothelial cells within arteries, veins and microvessels is coated with a thin (~500 nm) glycocalyx layer of plasma proteins, sulfated proteoglycans, glycoproteins and hyaluronan (reviewed in Weinbaum) [10]. Endothelial cell glycocalyx has several recognized functions, including maintaining vascular integrity, permeability, shear stress, mechanosensing and inflammatory responses. Leukocytes traversing a small-caliber capillary actually crush the glycocalyx. The transient deformation quickly corrects due to the elasticity of core proteins that behave like elastic fibers [11].

The properties of vascular endothelial glycocalyx layer change under inflammatory conditions. Cytokine-mediated activation of proteases partially degrade the layer permitting leukocyte rolling, tethering and recruitment [12]. An intact glycocalyx can regulate the degree of leukocyte capture, recruitment and extravasation.

Endothelial glycocalyx degradation occurs in chronic disease states like diabetes mellitus [13], significantly impacting responses to acute infectious and metabolic conditions [14, 15] (Fig. 4).

## Baroreceptors

The arterial baroreceptor system is intimately involved with maintaining vascular tone and blood pressure homeostasis [16]. Arterial baroreceptors (stretch receptors located in the carotid sinuses and aortic arch) provide continuous feedback on blood pressure to the central nervous system, which responds with physiological efferent autonomic activity. Activation of arterial baroreceptors in response to increased blood pressure causes activation of vagal cardio-inhibitory neurons and a decrease of sympathetic neuron discharges to the heart and peripheral resistance bed [17]. The end-result is a decrease in heart rate, cardiac contractility, peripheral vascular resistance and venous return. By contrast, a decrease in sympathetic activity and vagal inhibition, leads to tachycardia and heightened cardiac contractility, vascular resistance and venous return.

Baroreflex activity responds to the influence of many factors, including respiratory, behavioral and environmental factors. Common cardiovascular diseases, ranging from coronary artery disease, myocardial infarction, essential hypertension and heart failure are associated with baroreceptor reflex abnormalities, primarily chronic adrenergic activation [18].

Whether or not COVID-19 associated vascular injury causes baroreceptor reflex abnormalities is a question under investigation in our laboratory.

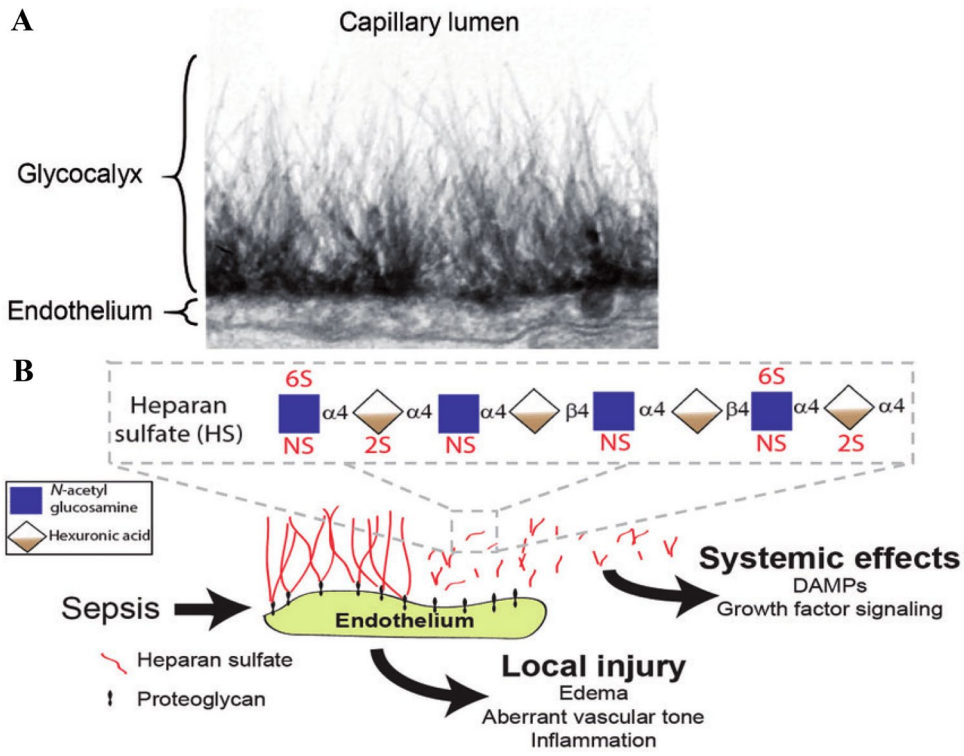


**Fig. 4** Structure of the endothelial glycocalyx/endothelial surface layer. **a** Endothelial glycocalyx thickness is larger than the endothelial cell itself, as demonstrated by electron microscopy of ruthenium-red labeled rat myocardial capillaries. In vivo, the glycocalyx forms an even more substantial ESL, with thickness > 1 µm. **b** Pathological degradation of the glycocalyx/ESL during critical illnesses (such as sepsis) causes not only local endothelial injury, but also releases biologically active heparan sulfate fragments into the circulation that may influence signaling processes in an endocrine fashion. For simplicity, chondroitin sulfate and hyaluronic acid are not shown. α4 and β4 refer to glycosidic bonds connecting constituent saccharides. Inset: structure of a heparan sulfate octasaccharide fragment, demonstrating potential sites of sulfation within constituent disaccharide units (From Oshima K. Pulmonary Circulation 2017; 8: 1–10. With permission)

## How do endothelial cells regulate inflammation?

The anti-inflammatory properties that characterize normal vascular endothelium are governed by a variety of external signals and intracellular mediators. The operative external signals include anti-inflammatory cytokines, transforming growth factor β, interleukin (IL)-10, IL-1 receptor agonist, and high-density lipoprotein cholesterol. Laminar shear stress, through the generation of nitric oxide, is of particular importance in maintaining inflammoresistance [19, 20].

## How do endothelial cells regulate thrombosis?

The normal vascular endothelium contains natural anticoagulants, platelet inhibitors, and fibrinolytic proteins that function in an integrated fashion to maintain vital organ perfusion. Because tissue factor, expressed locally at sites of vessel wall injury and from circulating monocytes [21] plays a pivotal role in the thrombotic phenotype of coronary atherosclerosis, an important surface protein antagonist, tissue factor pathway inhibitor (TFPI), has gained considerable attention. A variety of other surface proteins, including protein C, protein S, protein Z, nitric oxide, glycosaminoglycans, β2-glycoprotein 1, tissue plasminogen activator, urokinase-like plasminogen activator and thrombomodulin among others play critical roles [22–24].

## How do endothelial cells facilitate repair?

Angiopoietin-1 tyrosine protein kinase receptor related Tie-2 signaling in endothelial cells plays a pivotal role in wound healing, vascular integrity and angiogenesis [25]. Individually, angiopoietin (ANG)-1 is essential for blood vessel growth and maturation, and ANG-2 acts in combination with vascular endothelial cell growth factor (VEGF) to initiate angiogenesis. In conditions like cancer, there is an upregulation and over-expression of ANG-2 [25].

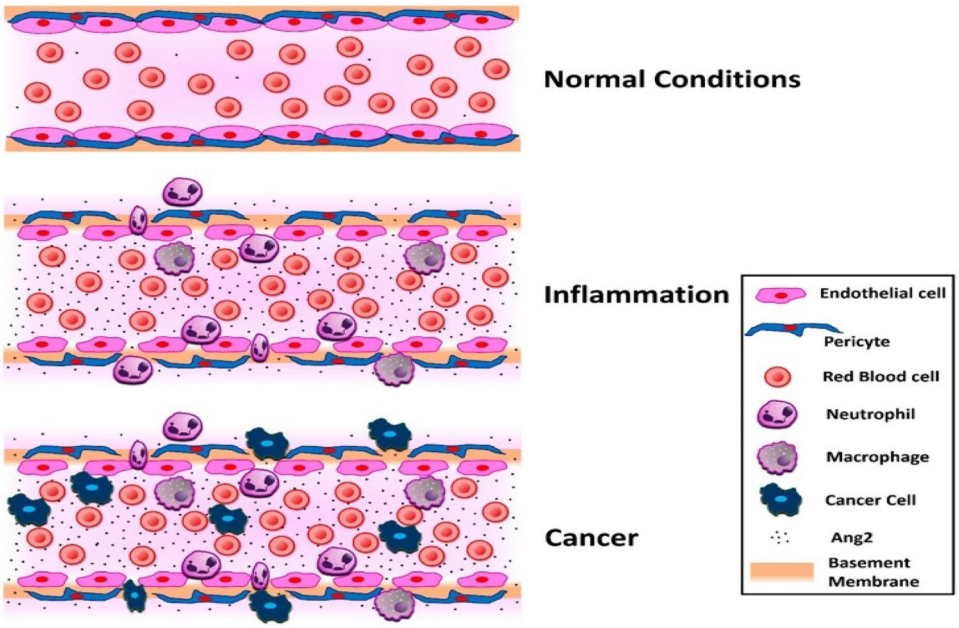


**Fig. 5** Schematic representation of the Ang2 effect on the vascular bed in *normal* conditions, inflammation, and cancer. Under normal physiological conditions, Ang2 levels are low, but are upregulated during inflammation or cancer. Ang2 acts on endothelial cells, increasing endothelial permeability and also on the pericytes, causing pericyte detachment from the basement membrane, further inducing vascular leakiness, immune or/and cancer cell trans-endothelial migration, and deterioration of the condition. Ang2 has been proposed as a marker for inflammatory conditions (From Akwii RG. Cells 2019; 8:471. With permission)

ANG-1 is chemotactic for endothelial cells, but neither ANG-1 nor ANG-2 exert proliferative effects [26]. ANG-2 is a natural inhibitor of ANG-1. Endothelial cells express ANG-2 mRNA and protein, supporting the potential for autocrine activation of angiopoietin/Tie2. ANG-1 and Tie-2 are highly expressed in both arteries and veins [27] (Fig. 5).

The tyrosine kinase family of cell surface proteins plays an important role in vascular biology. In response to a variety of conditions/environment-specific signals, tyrosine kinases engage in proliferation, migration, differentiation and morphologic organization that aligns with surroundings tissues [28]. Tyrosine kinases are commonly distinguished from one-another according to structural and sequence characteristics e.g. vascular endothelial growth factors (VEGF-$R_1$, VEGF-$R_2$ and VEGF-$R_3$). Each plays an essential role in maintaining vascular integrity [29].

The Tie [tyrosine kinase with immunoglobulin and epidermal growth factor (EGF) homology domains] receptor family represent a second sub-family of endothelial cell receptor tyrosine kinases identified as Tie-1 and Tie-2 [30]. Tie-1 and Tie-2 are vital to maintain growth and integrity of the vasculature, including endothelial cell-smooth muscle cell communication in vascular morphogenesis (see discussion above).

Infectious diseases affecting the lungs cause varying degrees of inflammation. Dysregulated inflammation is particularly deleterious and often associated with endothelial cell dysfunction. Trent et al. [31] reported dysregulated pulmonary inflammation and Tie-2-related endothelial dysfunction contributing to lung damage and mortality in a murine model of Orienta Tsutsugamushi infection. Tissue findings included a high level of Ang-2 proteins in pulmonary endothelial cells, a progressive loss of endothelial cell quiescent and junction proteins, and a substantial decrease in Tie-2 receptor at the transcriptional and functional levels. In-vitro infection of primary human endothelial cells demonstrated similar findings.

Tie-1 is upregulated by oscillating shear stress and differentially expressed in a dynamic pattern with disturbed flow [32]. Tie-1 deletion in mice causes abnormal extracellular matrix deposition and remodeling characterized by increased glycosaminoglycan and decreased collagen content. The findings suggest that abnormal blood flow is a stimulus for endothelial cell Tie1-mediated paracrine signaling.

## The contribution of platelets to vascular integrity, growth and repair

The interactions between platelets and the vascular endothelium are a tightly orchestrated. In response to inflammatory stimuli, P-selectin rapidly translocates from membranes of storage granules (Weibel-Palade bodies) to the plasma membrane. GPIbα present on platelets recognizes and binds to endothelial cell P-selectin. Firm adhesion of platelets to intact endothelial cells depends on platelet integrin αIIbβ3 bridging to endothelial receptors such as αVβ3 and intercellular adhesion molecule-1. Ligands for bridging include fibrinogen, fibronectin, and von Willebrand factor (VWF) [33]. Inflammatory cytokines augment platelet adhesion.

Platelets are essential for maintaining vascular integrity [34] and endothelial barrier function, particularly in the setting of inflammation [35]. In addition to physical

interactions, platelets promote vascular integrity through synthesis and release of bioactive mediators [36].

## Vascular endothelial cell pathology in COVID-19

The vascular pathology of COVID-19 is a topic of great interest [37]. Briefly, necropsy and post-mortem biopsies of decedents with COVID-19 reveal macro and microvascular thrombosis involving arteries, veins, arterioles, capillaries and venules in all major organs. Varga and colleagues describe endothelial cell involvement and endotheliitis across vascular beds [38]. Accumulation of inflammatory cells and viral inclusions by histology and electron microscopy, respectively, occurred within the vascular endothelium of the heart, small bowel, kidneys, and lungs. In autopsy and surgical tissues, there was diffuse lymphocytic endotheliitis and apoptotic bodies. It is important to consider that apoptosis may *not* require host cell viral entry, but rather binding to the cell surface and subsequent proinflammatory and apoptotic pathway signaling [39].

## Endothelial cells are a target for inflammatory mediators

Metabolic abnormalities, oxidative stress, chemokines, cytokines and by products of DAMPs cause endothelial cell injury [40]. While the toxic effect(s) can be direct, impaired epi-genetic regulation and activation of resident neutrophils and macrophages also contribute. Products of vascular injury recruit neutrophils through several signaling pathways, including PI3K/AKt/eNOS/NF-K$^{\beta}$ and ERK1/2/P38 MAPK-activated protein kinases. Recruited neutrophils subsets promote inflammation and further injury by releasing TNF-α, IL-1 and IL-8, and forming NETs [41, 42]. Endothelial cells produce macrovesicles in response to inflammatory conditions and inflammatory mediators, including cytokines, thrombin and complement 5a [43]. In turn, the endothelial cell macrovesicles impair adherans junctions, promote neutrophil binding and release NETs.

Released during periods of cell death and immune activation, histone, nucleosomes and NETs induce cytotoxicity by altering cell membrane permeability to calcium ions, activating TLRs on innate immune cells, stimulating NLRP3 inflammasome and complement systems, resulting in a sterile pro-inflammatory environment [44].

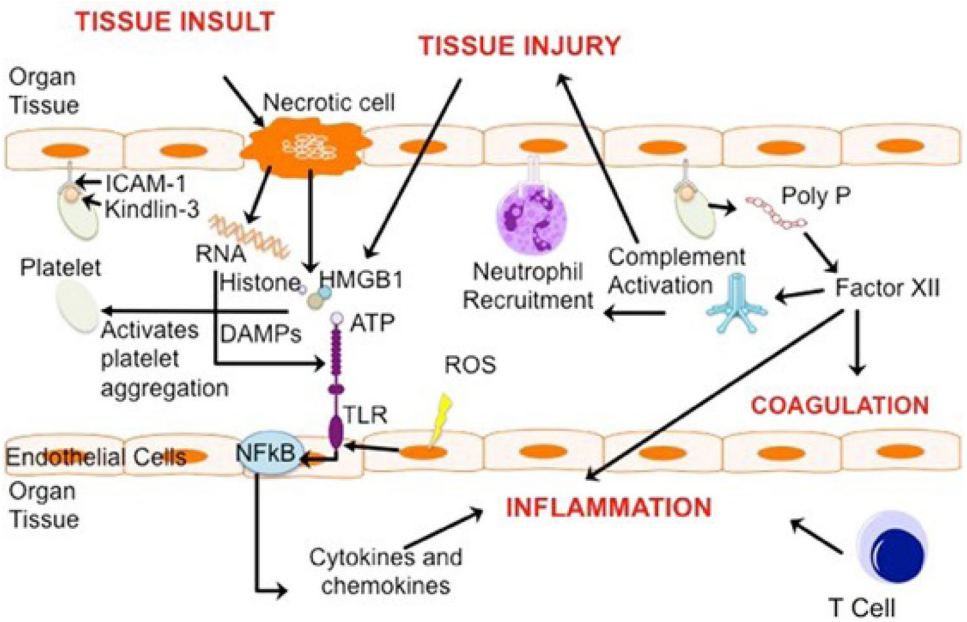


**Fig. 6** Mechanisms of Sterile Organ Injury. Toxic insults initiate both controlled and uncontrolled cell death in endothelial cells leading to apoptotic/necrotic tissue and release of intracellular cell components into the extracellular space. These include immunogenic compounds such as RNA and DAMPs (HMGB1, ATP and Histone) which bind to and activate specific TLRs, driving the NFkB-mediated transcription of pro-inflammatory cytokines. Platelets adhere to the endothelium via ICAM-1 and Kindlin-3. Activated platelets release Poly P, which activates Factor XII, and subsequently, complement. This results in activation of the coagulation pathways and further tissue injury, edema and inflammation. Activated T cells release pro-inflammatory mediators and can cause direct cytotoxicity. High mobility group box (HMGB)-1, damage associated molecular patterns (DAMPS), toll-like receptors (TLR), reactive oxygen species (ROS), polyphosphates (Poly-P), adenosine triphosphate (ATP) (From Silk E et al. Cell Death Disease 2017; 8: e2812. With permission)

### Histones cause endothelial cell injury

Five major families of histones exist: H1/H5, H2A, H2B, H3 and H4. Histones H2A, H2B, H3 and H4 are known as the core histones, while histones H1 and H5 are known as the linker histones. The core histones are dimers and all possess the histone fold domain (reviewed in Simpson) [45].

Extracellular histones are cytoxic and cause endothelial cell injury and dysfunction [46]. The cytotoxicity primarily occurs within the microcirculatory system, and causes ultrastructural changes and dysfunction. Altered flow dynamics cause further endothelial cell damage and glycocalyx shedding [47] Inflammatory conditions with high concentrations of extracellular histones and cytokines damage the endothelial glycocalyx accompanied by its degradation shedding of syndecan-1, heparan sulfate, and hyaluronan [47].

Cytokine-induced endothelial cell injury occurs in a variety of conditions including acute infection. Tumor necrosis factor (TNF)-α is particularly cytotoxic [48]. The mechanism(s) for injury include recruitment and binding of monocytes, up-regulation of caspase-1, IL-1β and expression of pyroptosis-related factors (Fig. 6).

### Neutrophil activation causes endothelial cell injury

Neutrophil activation and neutrophil extracellular traps (NETs) cause endothelial cell glycocalyx injury [49]. The concentration of circulating histones is directly proportional to the degree of inflammation and end organ dysfunction in trauma or sepsis-like conditions. Exposure of endothelial cells to histones causes decreased vasodilation and cell death in 25% of cells [50]. Citrullinated histones 3 (H3CiT) can directly contribute to NET-associated inflammatory responses and opens cell–cell adherans junctions impairing vascular integrity [51]. The bioactive proteins released from NETs that cause tissue injury include myeloperoxidase (MPO), neutrophil elastase (NE), matrix metalloproteinase (MMP)-9, high-mobility group box (HMGB)-1, proteinase (PTN)-3 and properdin [52].

## Vasculitis in COVID-19

Endothelial cell inflammation, apoptosis and dysfunction occur in patients with COVID-19 [37]. The interface of endothelial cells and viruses is of longstanding interest. For example, a major viral attachment and entry site for viruses is heparan sulfate. This is found on the endothelial surface and consists of repeating disaccharide unites of glucosamine and uronic acid with interspaced sulfate group attachments (reviewed in Agelidis) [53]. The highly sulfated state results in a negative density and binding capacity for a variety of positively charged ligands. A partial but representative summary of individual sites of vasculitis is provided (Table 1) [54–69].

Urticarial vasculitis occurred in two patients with COVID-19 [70]. While several skin manifestations of COVID-19 occur, including varicella-like exanthemas, dengue-like petechial rashes and urticaria, urticarial vasculitis is a form of leukocytoclastic vasculitis with deposition of immunocomplexes.

Pinot et al. [71] reported a case of central nervous system vasculopathy with antimyelin oligodendrocyte glycoprotein antibodies in a patient with COVID-19. There was rapid clinical improvement following immunomodulating treatment. Autoimmune disorders, such as Giullain–Barre' syndrome have been reported [72].

A lymphocytic vasculitis presenting with skin lesions on the toes, feet, heals and hands occurs in COVID-19. Most cases have been in children and adolescents, but not solely [56, 73]. Histopathology of biopsy-derived material show dermatitis and vascular degeneration of the basal epidermal layer. Endotheliitis within lymphocytic infiltration of the dermal vesicles and arterioles, and microthrombosis of papillary dermal capillaries are common findings. Immunohistochemistry reveals an inflammatory infiltrate predominately comprised of mature T cells with a predominance of helper t lymphocytes. Cytoplasmic granular positivity for SARS–CoV-2 spike protein is present in endothelial cells of the capillary and post-capillary vesicles and in epithelial cells of eccrine units. Coronavirus-like particles are detectable on electron microscopy.

Digital video capillaroscopy of patients with dermal lesions, including erythema nodosum shows pericapillary edema, dilated and abnormal appearing capillaries and microhemorrhages. In children with chilblain lesions, IgA antibodies to SARS–CoV-2 spike protein S1 domain are observed, suggesting that their immune response represents mucosal protection that lessens the likelihood of triggering an IgG response. Acro-ischemia with accompanying skin lesions (bulla, cyanosis) and dry gangrene is likely a combination of arterial vasculitis and coagulopathy compromising perfusion to the fingers, toes and legs. While thrombosis commonly accompanies vasculitis, obliterating arteriolitis can also be a cause for tissue injury [62].

### Kawasaki Disease

Kawasaki Disease is a systemic vasculitis that predominantly affects small and medium-sized arteries. It si associated with the development of coronary artery aneurysms in up to one-third of untreated patients, and both systemic and cerebral artery aneurysms in 1–2% of patients [74]. The cause of

**Table 1** COVID-19 vasculitis

| Patient (n) | Age (Y) | Sex | Country | Organ system | Signs and symptoms | Diagnostic test | Treatment | Outcomes | References |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 69 | M | Brazil | CNS (VBS) | Trochlea Nerve palsy | MRI MR | IV Methyl-prednisone | Resolved | De Oliveira |
| 1 | NR | NR | NR | CNS | Corpus Callosum infarct | MRI | NR | NR | Varatharaj |
| 7 | 11–17 | 4M 3F | Spanish | Skin | Chilblains "COVID-Toes" | Biopsy | Observation | Resolved 8 weeks | Colmenero |
| 17 | 15–63 | 11M 6F | France | Skin | Chilblains Toes, heels, fingers | Biopsy | N | NR | Kanitakis |
| 19 | 11–17 | 14M 5F | Italy | Skin | Chilblains Toes, heels, soles | Biopsy | NR | Resolution ≥30days | El-Hachem |
| 1 | 65 | M | France | CNS | Altered mental status | MRA MRI | Supportive | NR | Hanafi |
| 1 | 50 | M | Asia | Kidney Liver Lung | Sepsis Hypoxia | Necropsy Biopsy | Supportive | Deceased | Xu |
| 1 | NR | NR | NR | GI Tract | Diarrhea | Biopsy | Supportive | Recovered | Carnevale |
| 10 | 5–16 | 7M 3F | Italy | Coronary Arteries | Fever Skin rash Diarrhea Hypotension | Clinical Echocardiography | IVIG Aspirin | Recovered | Verdoni |
| 1 | ≥53 | NR | Switzerland | Lung | Dyspnea Fever | Necropsy | NR | Deceased | Menter |
| 4 | 50–76 | 3M 1F | Spain | Aorta | Acute Limb Ischemia Stroke | CTA | Thrombectomy Anticoagulation | 3 discharged 1 deceased | Gomez Arbelaez - |
| 1 | 67 | M | Italy | Aortic Prosthetic graft | Respiratory failure | Arterial Duplex | Supportive | Deceased | Giacomelli |
| 2 | 60, 75 | M | UK | Mesentery Aorta | Acute Limb ischemia Abdominal pain | CTA CTA | Thrombectomy Bowel Resection | Discharged | Villliany |
| 5 | 57–71 | 3M 2F | France | Aorta | Acute limb ischemia | CTA Arterial Duplex | Surgery Anticoagulation | Amputation | Kashi |
| 1 | NR | NR | Spain | Retinal Artery | No symptoms | Fundoscopy | Observation | No symptoms | Quintana-Castanedo |

*VBS* vertebrobasilar system, *NR* not reported, *IVIG* intravenous immunoglobulin, *CTA* Computed Tomography Angiography, *UK* United Kingdom

KD has not been determined, but a framework for making the diagnosis is as follows [75]: a genetic predisposition to KD, immunomodulation related to habitual exposures and environmental factors and contact with disease triggers.

## Kawasaki-like disease

Kawasaki Disease (KD) follows an excess innate immune response to viral pathogens. Several investigators have proposed involvement of the stimulator of interferon genes (STING) pathway inhibited upstream by aspirin and intravenous immunoglobulins [76]. The same mechanism may operate in COVID-19 where SARS–COV-2 binding to ACE2 increases STING pathway activation. In most instances, activation occurs during the second phase of illness with immune hyper-responses, decreased lymphocyte counts, increased monocyte populations that secrete cytotoxic cytokines and heightened B and T cell responses as well [77].

Kawasaki-like disease with accompanying toxic shock syndrome or multi-systemic inflammatory disease has been reported in children with COVID-19 [78, 79]-moderate coronary dilations were present in 25% of patients (age range 3–17 years). Myocarditis is also seen [80]. Cardiac MRI showed diffuse myocardial edema on T2-STIR sequences and Native-T1 mapping, with no evidence of late gadolinium enhancement [81].

The pediatric inflammatory multisystem syndrome (PIMS) and KD-like disease described in COVID-19 shares similarities with traditional KD, but there are several differences. PIMS occurs in older children (age 9 years or greater), children of African American, Caribbean, European and Hispanic ancestry rather than Asian ancestry. Gastrointestinal symptoms and a lack of mucocutaneous and lymphatic signs are also differentiating factors. Myocarditis is a distinguishing feature of PIMS as well at times requiring mechanical circulatory support [82].

Adult-onset Kawasaki Disease Shock Syndrome complicated by coronary aneurysms occurred in a 20-year-old man of East Asian ancestry [83]. He received corticosteroids and intravenous immunoglobulin. Securing a diagnosis is critical as early treatment ($\leq$4 days) reduces the development of coronary arterial aneurysms and with shock syndrome improves left ventricular performance.

## COVID-19 and vascular dysfunction

There is a proclivity for SARS–CoV-2 binding to endothelial cells with resulting inflammation (reviewed in Becker) [37]. Moreover, many of the predisposing comorbid conditions for COVID-19, including advanced age, diabetes mellitus, hypertension and obesity are associated with vascular dysfunction and altered endothelial cell metabolism [84].

## Distinguishing vascular inflammation and dysfunction in COVID-19

Vascular disease has many distinct phenotypes and associated functional abnormalities. While systemic conditions, ranging from metabolic to inflammatory and degenerative diseases often determine the location and make-up of accompanying vascular abnormalities, some conditions display a predominant vascular phenotype.

A discussion of vascular disease should distinguish causal, pathological, structural and functional elements. The term "vasculopathy" represents any abnormality within a blood vessel- small, medium and large caliber, veins or arteries (reviewed in Seshan) [85]. Degenerative, metabolic and inflammatory conditions, embolic diseases and coagulation disorders are responsible for acute, subacute or chronic endothelial cell injury. In many cases, non-inflammatory (necrotizing) vascular injury causes accumulation of immune complexes within the vessel's wall. A thickened intima with immunoglobulin and complement deposition, without inflammatory lymphocyte infiltration or atherosclerotic change are typical features of an autoimmune vasculopathy [86].

The pathological features are distinct and include endothelial cell swelling, vessel wall fragmentation, vessel wall fragmentation, endothelial cell pyknosis and karyorrhexis. Pyknosis is the irreversible condensation of chromatin in the nucleus of a cell undergoing necrosis or apoptosis. Karyorrhexis, or fragmentation of the nucleus can follow if injury is severe or sustained.

Vasculitis displays classic histological findings of predominantly neutrophilic infiltrates affecting small and medium-sized blood vessels. Large vessel vasculitis occurs in some cases. Fibrinoid deposits, endothelial edema, and extravasation of red blood cells are common. A mixed inflammatory infiltrate occurs, particularly in subacute stages older lesions. The functional and phenotypic heterogeneity of the vascular endothelial lining, which is the primary target of injury, dictates different types of vascular lesions in the various organs, variability in clinical presentation, prognosis and therapy [85].

## Clinical trials targeting vascular pathology in COVID-19

The ubiquitous involvement of EC in the phenotypic expression and natural history of COVID-19 establishes a firm basis for targeted therapies. Ongoing studies target one or more vascular-specific proteins and signaling pathways, including angiopoietin-2 (NCT04342897), VEGF (NCT 04344782, NCT04275414, and NCT04305106) [87]. Endothelial cell markers of injury and function are included in several of the trials as surrogate or exploratory outcomes. The biomarkers include vascular endothelial growth factor A, vascular endothelial growth factor receptor type 1, Syndecan-1 (marker of glycocalyx degradation), and VWF.

## Conclusions and future directions

COVID-19 is a SARS–CoV-2 syndrome that can involve all organs, including the circulatory system. Endothelial cell inflammation occurs within arteries, arterioles, capillaries, venules and veins and contributes to pathological

events; including tissue hypoperfusion, injury, thrombosis and vascular dysfunction in the acute, subacute and possibly chronic stages of disease. Beyond re-writing the textbooks that hence will include SARS–CoV-2 as a causal pathogen for multi-bed vasculitis, the data will show that it is a new category of systemic vasculitis forever captured in the annals of medicine. As clinicians and scientists, we have but to understand, prevent, treat, document and inform at every step along the way.

*"Yes we can, we must"*
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