## Early View

Editorial

# Inflammation and Intussusceptive Angiogenesis in COVID-19: everything in and out of Flow

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**Editorial**

The human body contains 60,000 miles of blood vessels, including at least 19 billion capillaries, so that under physiological conditions cells are located no further than 100-200µm from the nearest capillary. In those, endothelial cells and pericytes seem to play a pivotal role in COVID-19 by binding SARS-CoV-2 to the angiotensin-converting-enzyme 2 (ACE-2) (1,2). In the lung, the transmembrane ACE-2 receptor is predominantly expressed in endothelial cells, perivascular pericytes, and type 2 cells (2,3).

We recently showed that SARS-CoV-2-infection leads to angiocentric inflammation in COVID-19-induced respiratory failure with a greater number of ACE2-positive endothelial cells compared to uninfected controls or to post mortem lung tissue from patients succumbed to influenza A related ARDS (1). Although the SARS-CoV-2 detection of SARS-CoV-2 in post mortem tissue by transmission electron microscopy is a challenging task (4), replicated virus-like particles were observed enveloped in endothelial cells (1,5), lymphatic cells (6) , but also in type 2 and 1 pneumocytes (6,7). Increasing clinical evidence shows that endothelial dysfunction is a common denominator after  SARS-COV-2 infection in the multi-organ complexity and severity of COVID-19 (3). COVID-19 related endothelial dysfunction is characterized by acute vascular inflammation and perivascular T-cell recruitment leading to disruption of alveolar-capillary barrier and increased permeability (1-3). The endothelial cells surrounded by T-lymphocytes show features of strong activation referred to as "endothelialitis", a process typically seen during rejection of solid organ transplants. The infection of endothelial cells by SARS-CoV-2 results in swelling and disruption of the endothelial cell barriers, an anomalous microvascular architecture, and an endothelial dysfunction (1,3). These vascular injuries  are accompanied by thrombosis, vasoconstriction and distinct intussusceptive angiogenesis, a unique rapid process of blood vessel neoformation by splitting a vessel in two lumens by an incorporation of circulating angiogenic cells (1,3). (Fig. 1A).  In the pulmonary circulation of COVID-19 autopsies, we observed a distinct occurrence of intussusceptive angiogenesis not only in early SARS-CoV-2 infected lungs, but also in lung tissue with an infection lasting

more than 20 days. Beyond these findings in COVID-19 post mortem lung tissue, we revealed distinctive features of compensatory angiogenesis by intussusception in many other organs as heart, liver, kidney, brain and lymphoreticular organs in patients succumbed to COVID-19. The chaotic vessel regulation of focally vasoconstricted and progressively dilated vessel segments results in severe disturbances of physiological laminar flow. Two major forms of thrombi have been reported so far in COVID-19 patients (8).  Pulmonary embolism in larger pulmonary vessels probably based on DVT were seen in a minority of COVID-19 patients whereas the vast majority demonstrated platelet aggregates obstructing the microvasculature and the peripheral vascularity by fibrin strands, activated platelets, deformed neutrophils, and neutrophil extracellular traps (8, 9). Viral-associated thrombotic microangiopathies have been described in numerous inflammatory cardiorespiratory diseases (e.g. influenza (10) or myocarditis (11)). We compared post-mortem lung tissues from patients who died from COVID-19 with severe ARDS and diffuse alveolar damage due to influenza A (H1N1) infection. Thereby, we realized nine times more microthrombi in COVID19-lungs compared to influenza A (H1N1)-lungs (1). The microangiopathy observed in COVID-19 patients—specifically, the vasoconstriction and clotting in smaller blood vessels- results in hypoxia, shunting and an increase of pulmonary vascular resistance (8). Interestingly, COVID-19 does not show characteristics of a "typical" ARDS (12). The discrecancy between a general well-preserved lung mechanics and the severity of hypoxemia could be explained by a decreased capacity of vascular tone in venules and the capillary plexus.  Our molecular data on COVID-19 lung tissue gave evidence of a significant upregulation of vasoconstrictive mediators such as prostaglandins (phospholipase A, leukotrienes) (1) and as well as an increase of nitric oxide synthase (NOS). Nitric oxide (NO) is produced in endothelial cells by the enzyme endothelial nitric oxide synthase (eNOS) or in monocytes and macrophages by the inducible nitric oxide synthase (iNOS). The rheologic properties of blood flow (laminar vs. turbulent) and vessel morphology determine the shear stress on the vascular wall (13). In general, high shear stress, as observed in physiological laminar flow, is considered, angioprotective promoting endothelial cell survival, vasodilation, and anticoagulation (14,15). Low shear stress, on the other hand, results in the secretion of

vasoconstrictors, platelet aggregation, coagulation, and pathological reshaping of microvascular architecture (15-17). The pathologic consequences of these blood flow dynamics have been described in many diseases such as atherosclerosis (18), inflammatory diseases (15,17), and malignancies (16). Our own hemodynamic studies on inflammatory-related changes of the blood flow (13,14,17) revealed heterogeneity in flow patterns with dispersed flow velocities, occluded vessel segments and platelet aggregates associated with upregulation of thrombotic agonists.

The structural adaption of the microvascular architecture, the transmigration of lymphocytes and the "cytokine storm" observed in COVID-19 patients is a response to SARS-CoV-2-induced cellular damage. Many cytokines appear to be involved in enhancing lymphocyte recruitment. TNFα is known to increase the adhesion of lymphocytes by activating the SDF-1/CXCR4 pathways. The T-lymphocyte/ endothelial interaction likely contributes to the prolonged interstitial inflammation in COVID-19. Activated T-cells attracted by chemotactic chemokines (e.g. CCL17, CCL8, or CCR1) (1) preferentially adhere to activated endothelial cells (19,20). Despite an increase in inflammatory blood flow and increased wall shear stress, transendothelial lymphocyte recruitment can occur in selected capillary beds (liver and lung), post-capillary venules (most parenchymal organs), and even specialized vascular segments that acquire structural modifications that reduce flow velocity and wall shear stress (21). Therefore, the structure of the microcirculation is continuously adapting to metabolic demands and immunosurveillance. The close association of inflammation and angiogenesis represents a pivotal pillar in perpetuating inflammatory processes during wound healing and infections such as COVID-19. Inflamed human endothelial cells and pericytes express high levels of toll-like receptors (TLRs) which are recognized together with their intracellular adaptor protein MyD88 as sentinels of the innate immune system (22). SARS-Co-V and other coronaviruses may be recognized by TLRs and MyD88 (23, 24). Stimulation of endothelial TLRs and MyD88 results in a release of cytokines (e.g. IFNγ, TNFα, Il1α, G-CSF), chemokines, leucocyte adhesion molecules (e.g. E-selectin, ICAM1, VCAM1), procoagulation mediators (e.g. fibrin, PAI, vWF), and proangiogenic factors (e.g. VEGF, NOS, or CD14 monocytes) (25).

"Intussusceptive" (non-sprouting) angiogenesis is a well-characterized morphogenetic process in cancer (26), inflammatory diseases and tissue regeneration (27). Distinct from intussusceptive angiogenesis, sprouting angiogenesis is characterized by sprouts composed of endothelial cells. The endothelial sprouts typically grow toward an angiogenic stimulus (such as VEGF-A) and add vessels to tissues devoid of blood vessels. Intussusceptive angiogenesis is a rapid process of intravascular septation that produces two lumens from a single vessel within minutes.  The process appears to recruit bone-marrow derived mononuclear cells—expanding and adapting capillary plexuses without requiring active proliferation of endothelial cells (Figure 1B) (28). The newly formed "intussusceptive pillars" (Fig. 1C) are then permeated by pericytes and myofibroblasts providing mechanical stabilization of the transcapillary pillar core. We previously showed that this formation of intussusceptive pillars is primarily located in dilated vascular segments with low blood flow velocity and reduced wall shear stress (12,13). Recently, CXCL12/CXCR4 signaling has been identified as an important molecular regulator of intussusceptive angiogenesis and hypoxia (29):  the positive feedback loop between vascular shear stress, CXCL12 (SDF1)-expression, hypoxia and the release of eNOS has been identified as an adaptation of the vascular system to maintain blood flow responsive to the demands of prolonged inflammation.  Therefore, the pronounced release of eNOS cascade is a pivotal physiological process to maintain blood flow into tissues with occluded vessels and to initiate tissue repair by expanding the vascular architecture by intussusceptive angiogenesis. In our own studies, we observed abundant intussusceptive angiogenesis in the disrupted pulmonary vascular architecture of patients who died of COVID-19 (Fig. 1C, D), stated in numbers nearly three times higher than in influenza A (H1N1)-lungs. Furthermore, the expression of CXCL12 and CXCR4 was highly upregulated in these COVID-19 lungs and was associated with dense T-cell infiltration.   These findings are consistent with inflammation-induced angiogenesis observed in other conditions such as colitis (30,31) and malignant tumors (26).

In a recent morphomolecular study published in the *European Respiratory Journal* (32), we demonstrated the presence and impact of microvascular alterations in fibrotic interstitial lung diseases. We observed a higher frequency of intussusceptive features in

the injury patterns of NSIP and AFE fibrotic lungs whereas UIP lungs revealed compensatory angiogenesis predominantly by sprout formation (32, 33). In addition, intussusceptive angiogenesis was observed in chronic pulmonary vascular diseases with variable degree of thrombosis, such as CTEPH (34), pulmonary capillary hemangiomatosis (35,36), and pulmonary veno-occlusive disease (PVOD) (35) (Table 1). Although the pathologic mechanisms underlying fibrotic remodeling in pulmonary thromboembolic occlusions are poorly understood, thrombofibrosis and endothelial-mesenchymal transition seem to be promoted by hypoxia-induced activation of endothelial cells, intussusceptive angiogenesis, activation of mesenchymal cells and immune cells (31-34). There is a compelling evidence that at least the progress and severity of progressive interstitial lung disease may be influenced by coagulation and fibrinolytic capacities and vascular permeability (38,39), although the therapeutic use of orally-administered anticoagulants has been critically evaluated in IPF patients (40). Especially in the light of inestimable long-term complications in COVID-19, further experimental and observational studies should investigate the contribution and the interplay between the overwhelming angiocentric T-cell inflammation, thrombotic microangiopathy and the compensatory flow-regulated intussusceptive angiogenesis in the increased morbidity and mortality COVID-19.

## References

1. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 May 21. doi: 10.1056/NEJMoa2015432. Epub ahead of print

2. Cardot-Leccia N, Hubiche T, Dellamonica J, Burel-Vandenbos F, Passeron T. Pericyte alteration sheds light on micro-vasculopathy in COVID-19 infection. Intensive Care Med. 2020 Jun 12:1–2. doi: 10.1007/s00134-020-06147-7.

3. Huertas A, Montani D, Savale L, Pichon J, Tu L, Parent F, Guignabert C, Humbert M. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? Eur Respir J. 2020 Jul 30;56(1):2001634. doi: 10.1183/13993003.01634-2020.

4. Goldsmith CS, Miller SE, Martines RB, Bullock HA, Zaki SR. Electron microscopy of SARS-CoV-2: a challenging task. Lancet. 2020 May 30;395(10238):e99. doi: 10.1016/S0140-6736(20)31188-0. Epub 2020 May 19.

5. Ackermann M, Mentzer SJ, Jonigk D. Pulmonary Vascular Pathology in Covid-19. Reply. N Engl J Med. 2020 Aug 27;383(9):888-889. doi: 10.1056/NEJMc2022068. Epub 2020 Jul 17.

6. Martines RB, Ritter JM, Matkovic E, Gary J, Bollweg BC, Bullock H, et al. Pathology and Pathogenesis of SARS-CoV-2 Associated with Fatal Coronavirus Disease, United States. Emerg Infect Dis. 2020;26(9):2005-2015

7. Bradley BT, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T, Yarid N, Marshall DA. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. Lancet. 2020 Aug 1;396(10247):320-332. doi: 10.1016/S0140-6736(20)31305-2. Epub 2020 Jul 16

8. Price LC, McCabe C, Garfield B, Wort SJ. Thrombosis and COVID-19 pneumonia: the clot thickens! Eur Respir J. 2020 Jul 30;56(1):2001608. doi: 10.1183/13993003.01608-2020.

9. Leppkes M, Knopf J, Naschberger E, Lindemann A, Singh J, Herrmann I, Stürzl M, Staats L, Mahajan A, Schauer C, Kremer AN, Völkl S, Amann K, Evert K, Falkeis C, Wehrfritz A, Rieker RJ, Hartmann A, Kremer AE, Neurath MF, Muñoz LE, Schett G, Herrmann M. Vascular occlusion by neutrophil extracellular traps in COVID-19. EBioMedicine. 2020 Aug;58:102925. doi: 10.1016/j.ebiom.2020.102925. Epub 2020 Jul 31.

10. Sugiyama MG, Gamage A, Zyla R, Armstrong SM, Advani S, Advani A, Wang C, Lee WL. Influenza Virus Infection Induces Platelet-Endothelial Adhesion Which Contributes to Lung Injury. J Virol. 2015 Dec 4;90(4):1812-23. doi: 10.1128/JVI.02599-15.

11. Ackermann M, Wagner WL, Rellecke P, Akhyari P, Boeken U, Reinecke P. Parvovirus B19-induced angiogenesis in fulminant myocarditis. Eur Heart J. 2020 Mar 21;41(12):1309. doi: 10.1093/eurheartj/ehaa092.

12. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020 May 15;201(10):1299-1300. doi: 10.1164/rccm.202003-0817LE.

13. Lee GS, Filipovic N, Miele LF, Lin M, Simpson DC, Giney B, Konerding MA, Tsuda A, Mentzer SJ. Blood flow shapes intravascular pillar geometry in the chick chorioallantoic membrane. J Angiogenes Res. 2010 Jul 7;2:11. doi: 10.1186/2040-2384-2-11.

14. Filipovic N, Tsuda A, Lee GS, et al. Computational flow dynamics in a geometric model of intussusceptive angiogenesis. Microvascular Research. 2009 Dec;78(3):286-293. DOI: 10.1016/j.mvr.2009.08.004.

15. Ravnic DJ, Konerding MA, Tsuda A, et al. Structural adaptations in the murine colon microcirculation associated with hapten-induced inflammation. Gut. 2007 Apr;56(4):518-523.

16. Jain RK, Tong RT, Munn LL. Effect of vascular normalization by antiangiogenic therapy on interstitial hypertension, peritumor edema, and lymphatic metastasis: insights from a mathematical model. Cancer Research. 2007 Mar;67(6):2729-2735.

17. Miele LF, Turhan A, Lee GS, et al. Blood flow patterns spatially associated with platelet aggregates in murine colitis. Anat Rec (Hoboken). 2009;292(8):1143‑1153.

18. Napoli C, Ignarro LJ. Nitric oxide and pathogenic mechanisms involved in the development of vascular diseases. Arch Pharm Res. 2009 Aug;32(8):1103-8. doi: 10.1007/s12272-009-1801-1. Epub 2009 Aug 29.

19. von Andrian UH, Mackay CR. T-cell function and migration. Two sides of the same coin. N Engl J Med. 2000;343(14):1020-1034. doi:10.1056/NEJM200010053431407

20. Li X, Abdi K, Rawn J, Mackay CR, Mentzer SJ. LFA-1 and L-selectin regulation of recirculating lymphocyte tethering and rolling on lung microvascular endothelium. Am J Respir Cell Mol Biol. 1996 Apr;14(4):398-406. doi: 10.1165/ajrcmb.14.4.8600945

21. Secomb TW, Konerding MA, West CA, Su M, Young AJ, Mentzer SJ. Microangiectasias: structural regulators of lymphocyte transmigration. Proc Natl Acad Sci U S A. 2003 Jun 10;100(12):7231-4. doi: 10.1073/pnas.1232173100. Epub 2003 Jun 2.

22. Ranchoux B, Antigny F, Rucker-Martin C, Hautefort A, Péchoux C, Bogaard HJ, Dorfmüller P, Remy S, Lecerf F, Planté S, Chat S, Fadel E, Houssaini A, Anegon I, Adnot S, Simonneau G, Humbert M, Cohen-Kaminsky S, Perros F. Endothelial-to-mesenchymal transition in pulmonary hypertension. Circulation. 2015 Mar 17;131(11):1006-18.

23. Andonegui G, Bonder CS, Green F, et al. Endothelium-derived Toll-like receptor-4 is the key molecule in LPS-induced neutrophil sequestration into lungs [published correction appears in J Clin Invest. 2003 Oct;112(8):1264]. J Clin Invest. 2003;111(7):1011-1020.

24. Butchi N, Kapil P, Puntambekar S, et al. Myd88 Initiates Early Innate Immune Responses and Promotes CD4 T Cells during Coronavirus Encephalomyelitis. Journal of Virology. 2015 Sep;89(18):9299-9312. DOI: 10.1128/jvi.01199-15.

25. Khakpour S, Wilhelmsen K, Hellman J. Vascular endothelial cell Toll-like receptor pathways in sepsis. Innate Immun. 2015;21(8):827-846. doi:10.1177/1753425915606525

26. Ackermann M, Morse BA, Delventhal V, Carvajal IM, Konerding MA. Anti-VEGFR2 and anti-IGF-1R-Adnectins inhibit Ewing's sarcoma A673-xenograft growth and normalize tumor vascular architecture. Angiogenesis. 2012 Dec;15(4):685-95. doi: 10.1007/s10456-012-9294-9

27. Ackermann M, Houdek JP, Gibney BC, Ysasi A, Wagner W, Belle J, Schittny JC, Enzmann F, Tsuda A, Mentzer SJ, Konerding MA. Sprouting and intussusceptive angiogenesis in postpneumonectomy lung growth: mechanisms of alveolar neovascularization. Angiogenesis. 2014 Jul;17(3):541-51. doi: 10.1007/s10456-013-9399-9. Epub 2013 Oct 23.

28. Mentzer SJ, Konerding MA. Intussusceptive angiogenesis: expansion and remodeling of microvascular networks. Angiogenesis. 2014 Jul;17(3):499-509. doi: 10.1007/s10456-014-9428-3. Epub 2014 Mar 26

29. Dimova I, Karthik S, Makanya A, et al. SDF-1/CXCR4 signalling is involved in blood vessel growth and remodelling by intussusception. J Cell Mol Med. 2019;23(6):3916-3926.

30. Konerding MA, Turhan A, Ravnic DJ, et al. Inflammation-induced intussusceptive angiogenesis in murine colitis. Anatomical Record (Hoboken, N.J. : 2007). 2010 May;293(5):849-857.

31. Ackermann M, Tsuda A, Secomb TW, Mentzer SJ, Konerding MA. Intussusceptive remodeling of vascular branch angles in chemically-induced murine colitis. Microvasc Res. 2013 May;87:75-82. doi: 10.1016/j.mvr.2013.02.002. Epub 2013 Feb 26.

32. Ackermann M, Stark H, Neubert L, Schubert S, Borchert P, Linz F, Wagner WL, Stiller W, Wielpütz M, Hoefer A, Haverich A, Mentzer SJ, Shah HR, Welte T, Kuehnel M, Jonigk D. Morphomolecular motifs of pulmonary neoangiogenesis in interstitial lung diseases. Eur Respir J. 2020 Mar 12;55(3):1900933. doi: 10.1183/13993003.00933-2019.

33. Yanagihara T, Jones KD. Demystifying morphomolecular alterations of vasculature in interstitial lung diseases. Eur Respir J. 2020;55(3):1902446. Published 2020 Mar 12. doi:10.1183/13993003.02446-2019

34. Ackermann M, Gaumann A, Mentzer SJ, Hinrichs JB, Warnecke G, Hoeper MM, Braubach P, Kuehnel M, Maegel L, Jonigk D. Plexiform Vasculopathy in Chronic Thromboembolic Pulmonary Hypertension. Am J Respir Crit Care Med. 2017 Oct 15;196(8):e48-e51. doi: 10.1164/rccm.201703-0591IM.

35. Neubert L, Borchert P, Shin HO, Linz F, Wagner WL, Warnecke G, Laenger F, Haverich A, Stark H, Hoeper MM, Kuehnel M, Ackermann M, Jonigk D. Comprehensive three-dimensional morphology of neoangiogenesis in pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. J Pathol Clin Res. 2019 Apr;5(2):108-114. doi: 10.1002/cjp2.125. Epub 2019 Feb 27.

36. Weatherald J, Dorfmüller P, Perros F, Ghigna MR, Girerd B, Humbert M, Montani D. Pulmonary capillary haemangiomatosis: a distinct entity? Eur Respir Rev. 2020 May 27;29(156):190168. doi: 10.1183/16000617.0168-2019.

37. Bochenek ML, Rosinus NS, Lankeit M, Hobohm L, Bremmer F, Schütz E, Klok FA, Horke S, Wiedenroth CB, Münzel T, Lang IM, Mayer E, Konstantinides S, Schäfer K. From thrombosis to fibrosis in chronic thromboembolic pulmonary hypertension. Thromb Haemost. 2017 Apr 3;117(4):769-783

38. Wuyts WA, Agostini C, Antoniou KM, Bouros D, Chambers RC, Cottin V, Egan JJ, Lambrecht BN, Lories R, Parfrey H, Prasse A, Robalo-Cordeiro C, Verbeken E, Verschakelen JA, Wells AU, Verleden GM. The pathogenesis of pulmonary fibrosis: a moving target. Eur Respir J. 2013 May;41(5):1207-18. doi: 10.1183/09031936.00073012. Epub 2012 Oct 25.

39. Probst CK, Montesi SB, Medoff BD, Shea BS, Knipe RS. Vascular permeability in the fibrotic lung. Eur Respir J. 2020 Jul 16;56(1):1900100. doi: 10.1183/13993003.00100-2019.

40. Kreuter M, Wijsenbeek MS, Vasakova M, Spagnolo P, Kolb M, Costabel U, Weycker D, Kirchgaessler KU, Maher TM. Unfavourable effects of medically indicated oral anticoagulants on

survival in idiopathic pulmonary fibrosis. Eur Respir J. 2016 Jun;47(6):1776-84. doi: 10.1183/13993003.02087-2015. Epub 2016 Apr 21

**Figure**
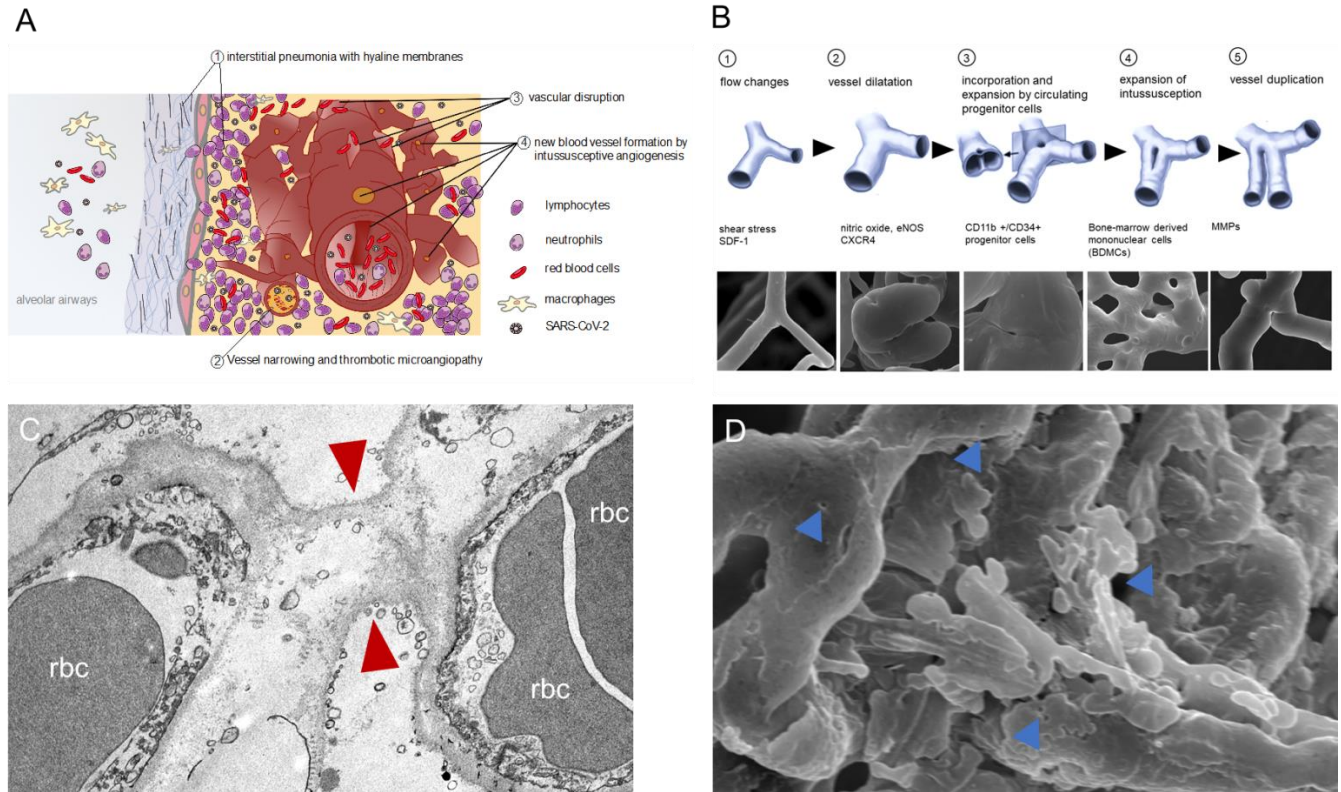


(A) Schematic of pulmonary endothelialitis, thrombosis, and intussusceptive angiogenesis in COVID-19. (B) Intussusceptive angiogenesis is a morphogenetic process which rapidly expands the vascular plexus. (C) Transmission electron micrograph of lung tissue of a deceased COVID-19 patient highlights the formation of an intussusceptive pillar (red arrowheads) which spans the lumen of the vascular walls. (D) A disrupted vascularity with distorted vessels and intussusceptive pillars (blue arrowheads) is observed in COVID-19 lungs, as depicted as scanning electron micrograph of microvascular corrosion casts of COVID19 autopsies.