

Assessing and Treating the Emergence of Micro-Clotting

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CEO of MedHelp Clinics



S1 Spike Protein Alone Can Catalyze Fibrin(ogen) Formation

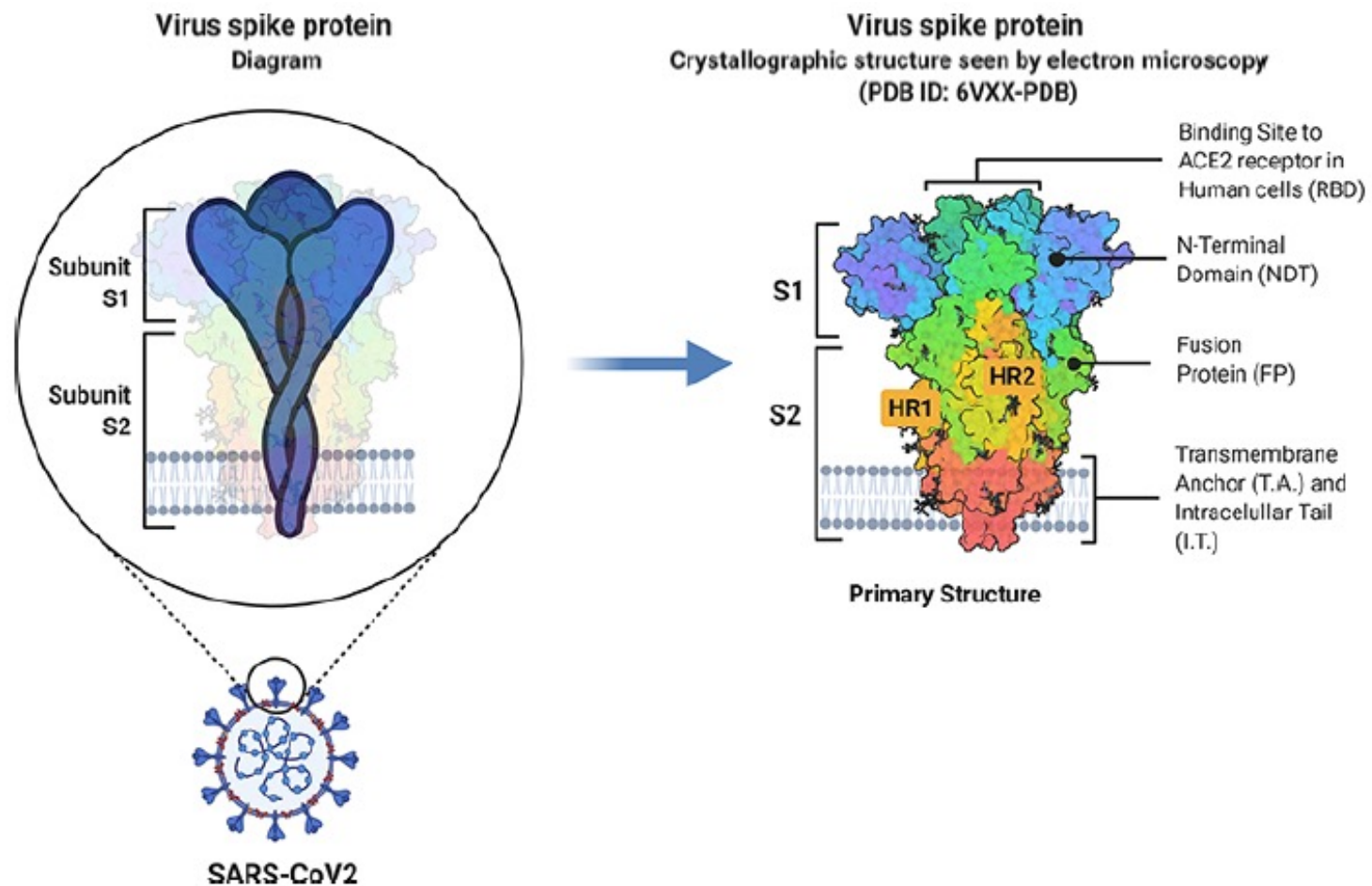
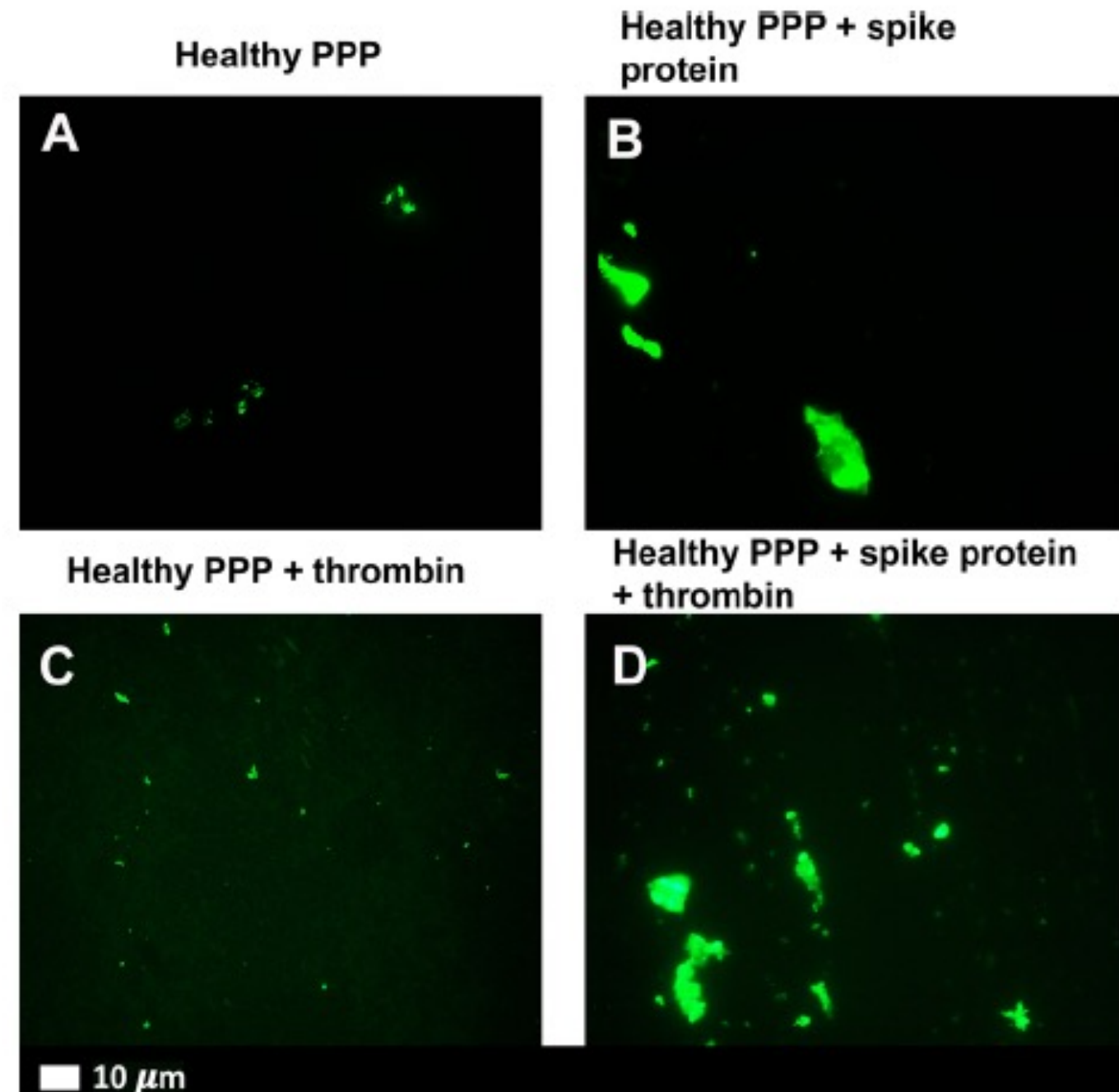
Bioscience Reports (2021) 41 BSR20210611
<https://doi.org/10.1042/BSR20210611>



Research Article

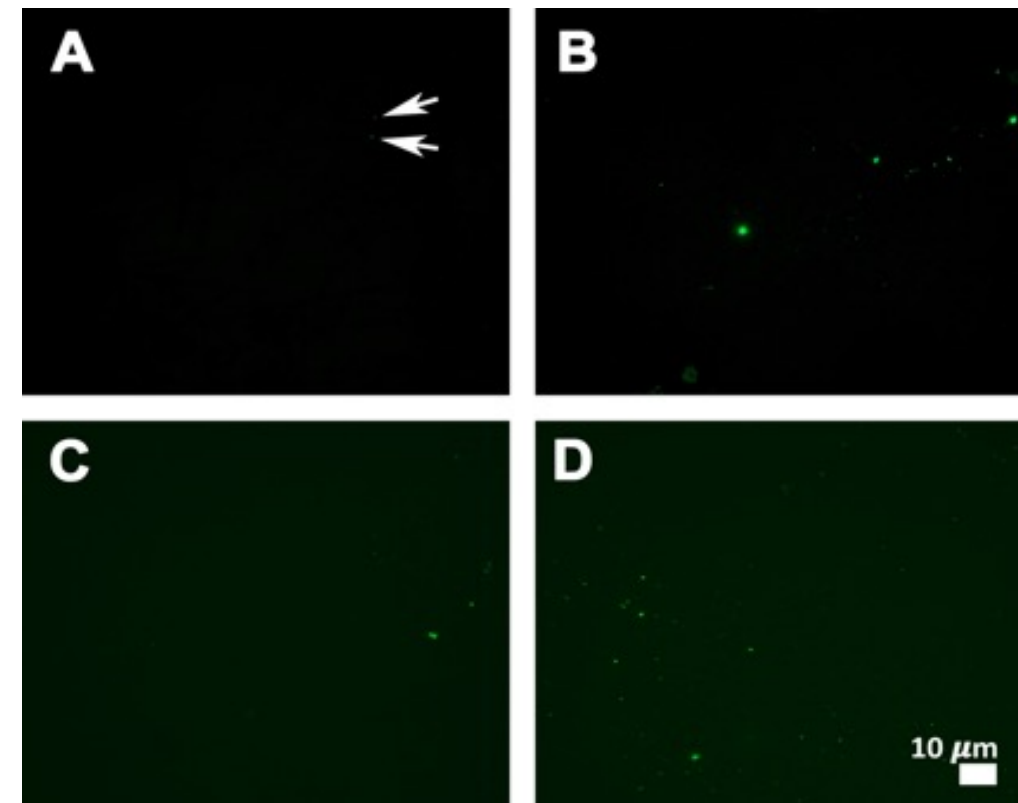
SARS-CoV-2 spike protein S1 induces fibrin(ogen) resistant to fibrinolysis: implications for microclot formation in COVID-19

Lize M. Grobbelaar¹, Chantelle Venter¹, Mare Vlok², Malebogo Ngoepe^{3,4}, Gert Jacobus Laubscher⁵, Petrus Johannes Lourens⁵, Janami Steenkamp^{1,6}, Douglas B. Kell^{1,7,8} and Ethersia Pretorius¹

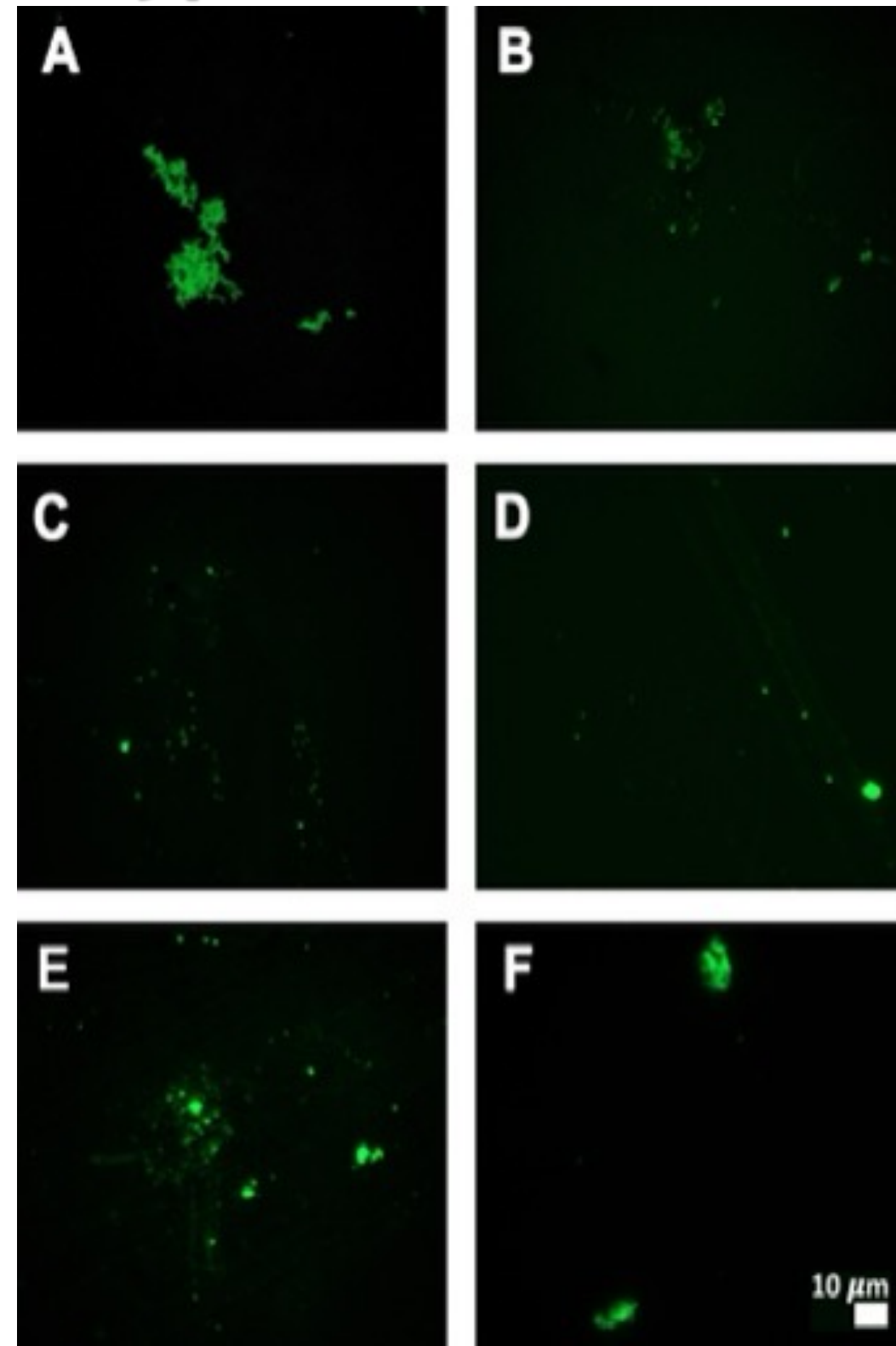


Structural Changes in Fibrin(ogen) in Disease

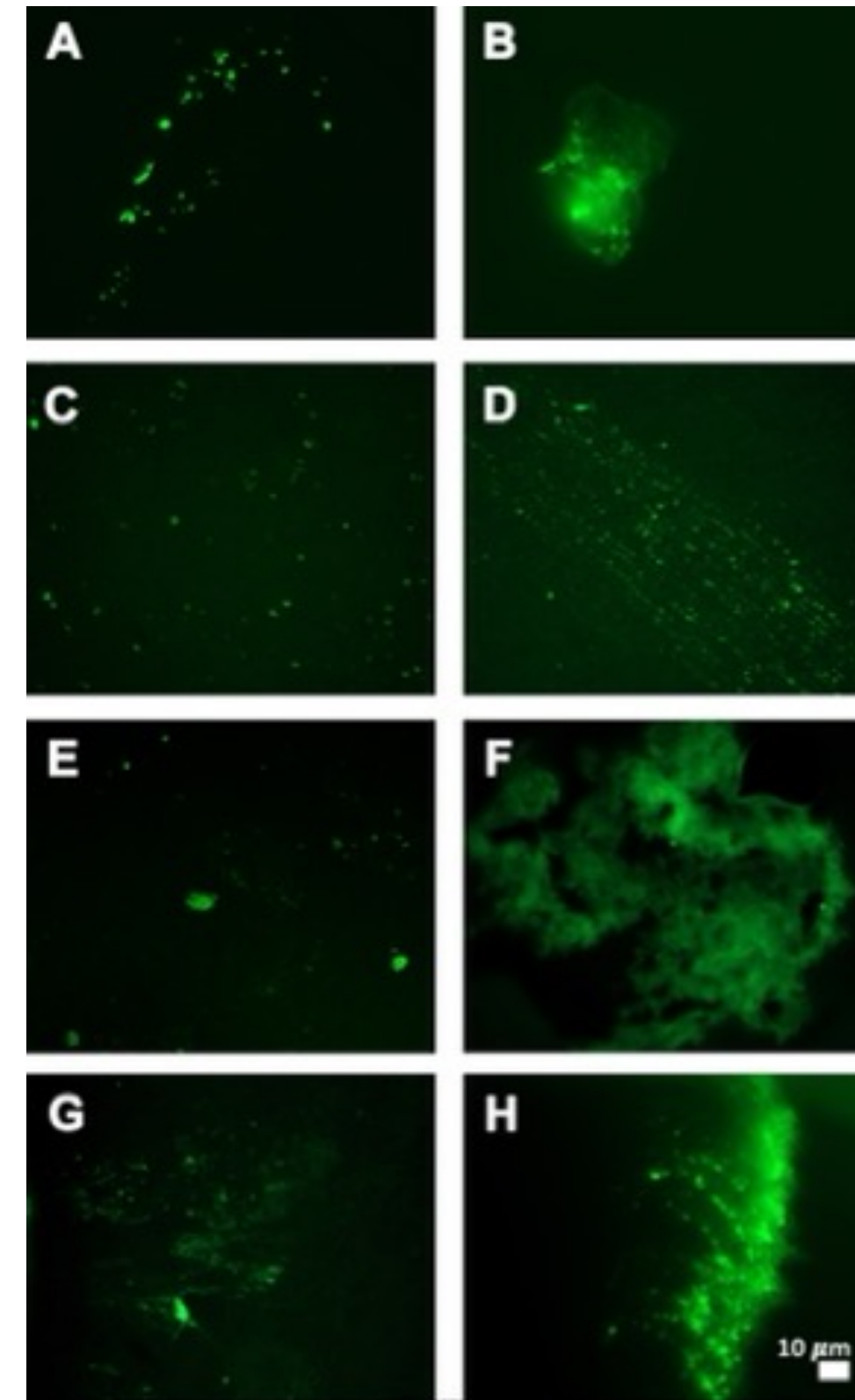
Healthy Plasma



Type 2 DM Plasma

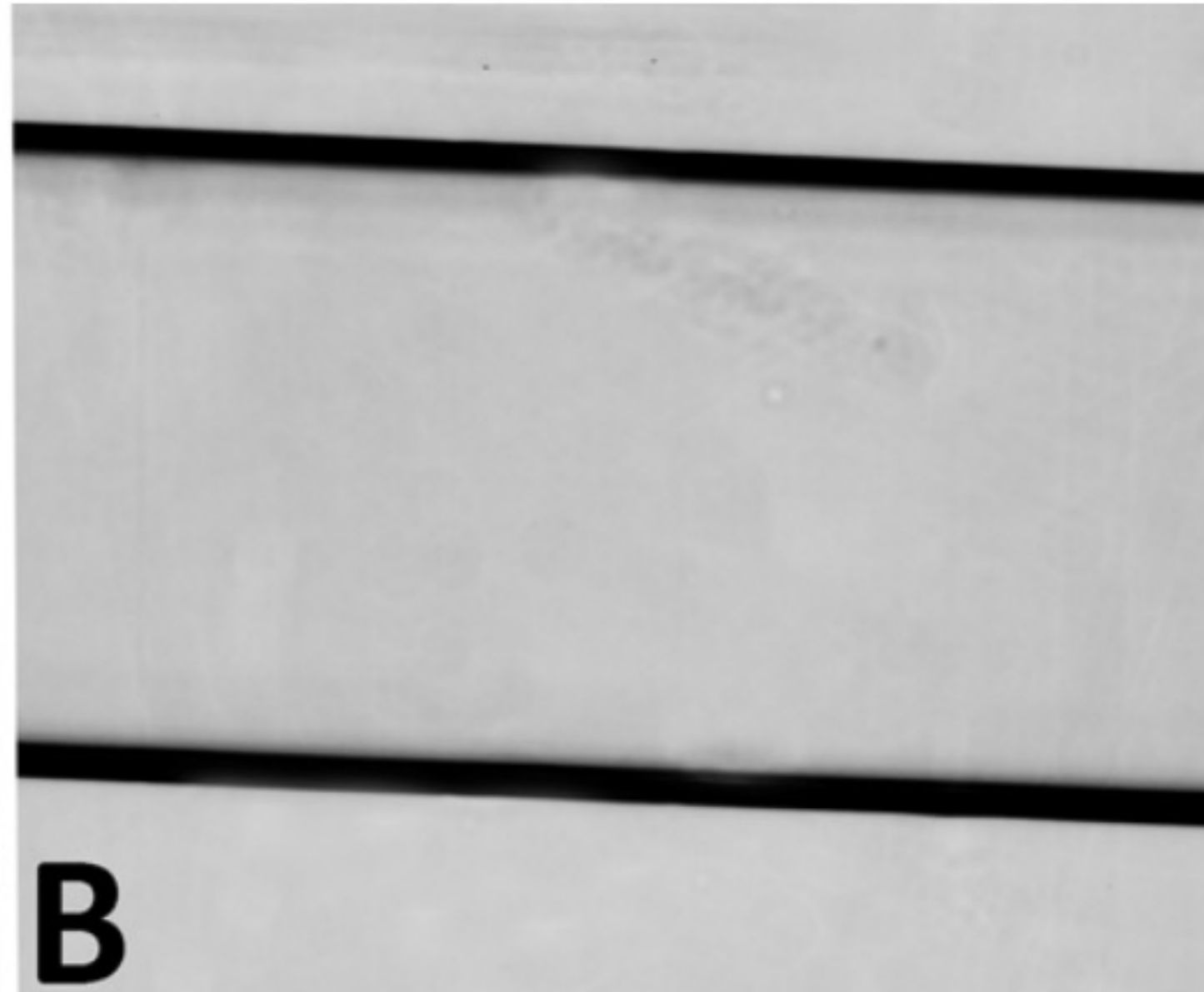
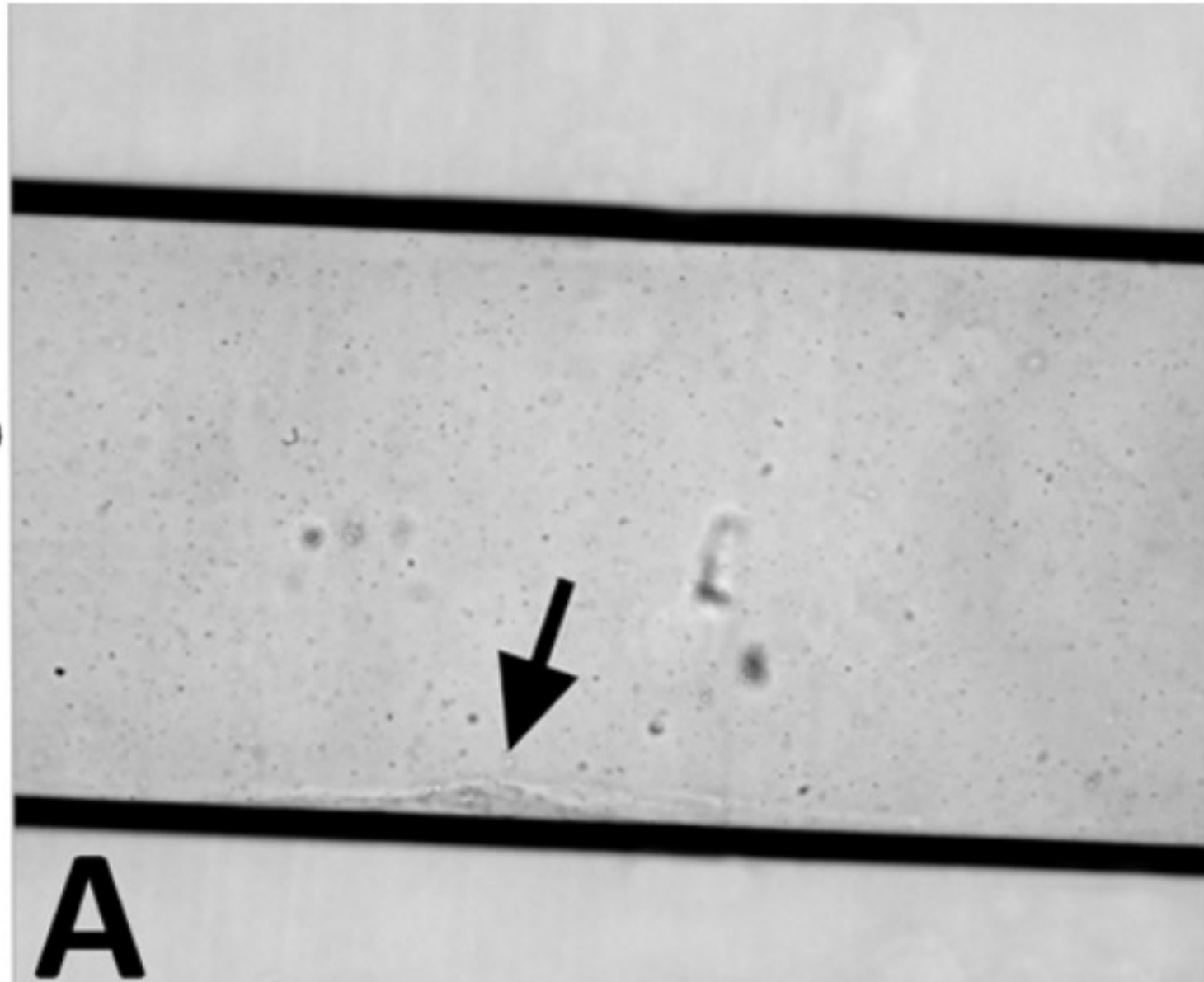


COVID-19 Plasma



Microfluidic Channel and PPP

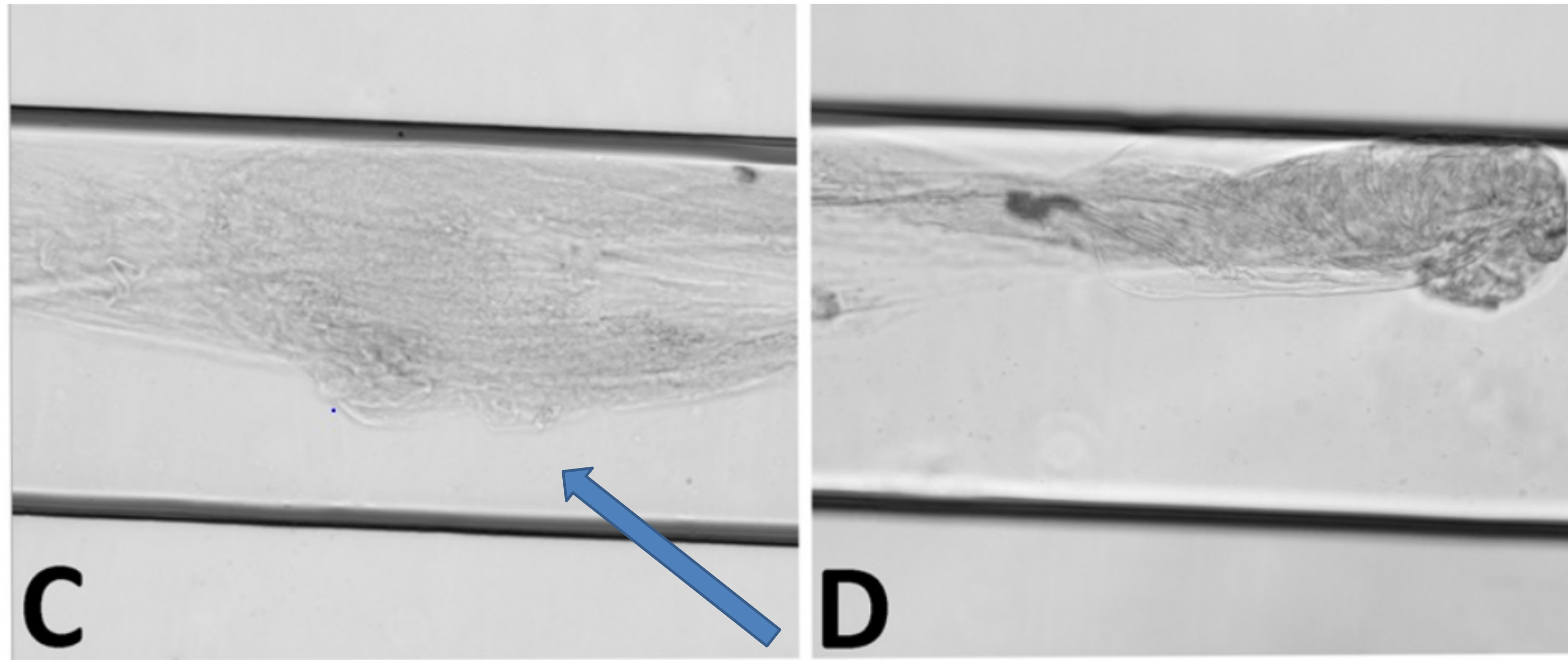
Healthy PPP



Bioscience Reports (2021) 41 BSR20210611 <https://doi.org/10.1042/BSR20210611>

Microfluidic Channel and PPP

COVID-19



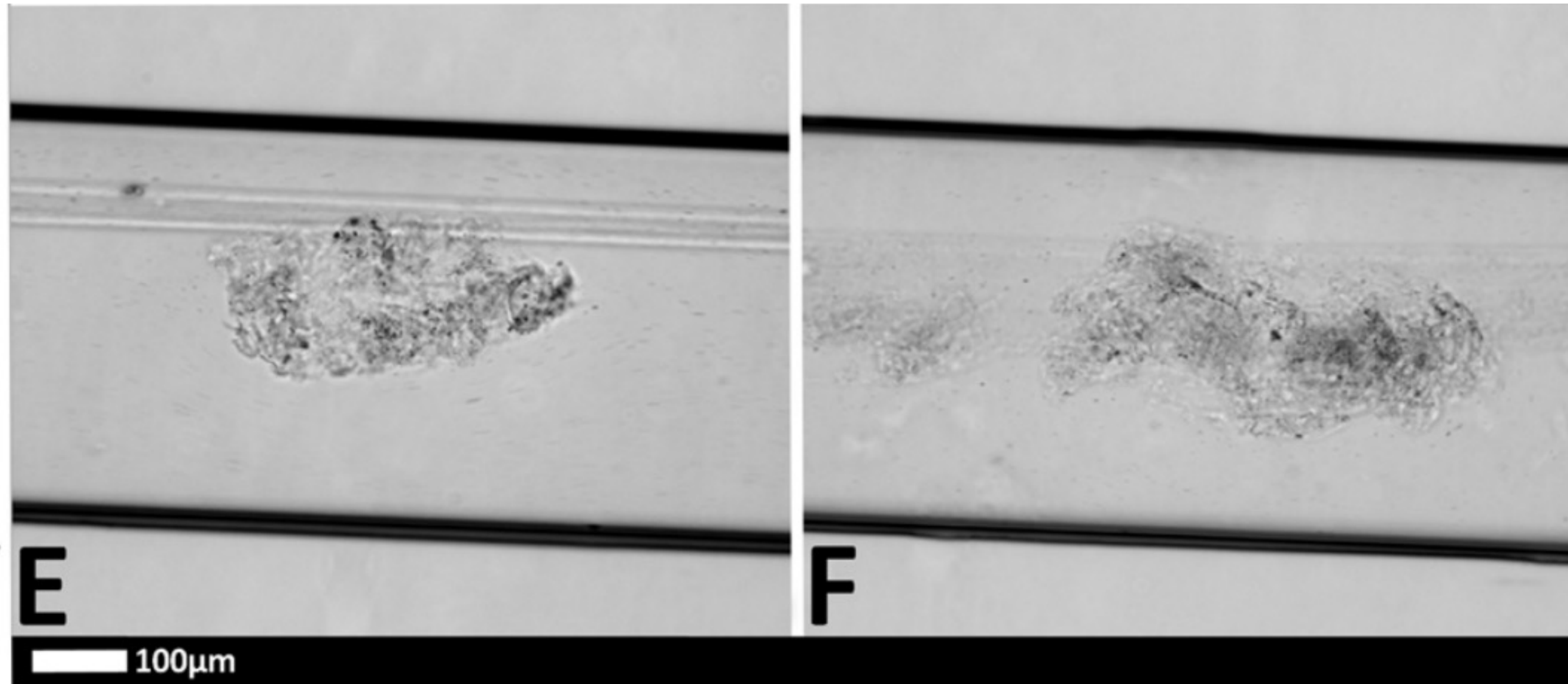
Not Totally Occluded

Bioscience Reports (2021) 41 BSR20210611 <https://doi.org/10.1042/BSR20210611>



Microfluidic Channel and PPP

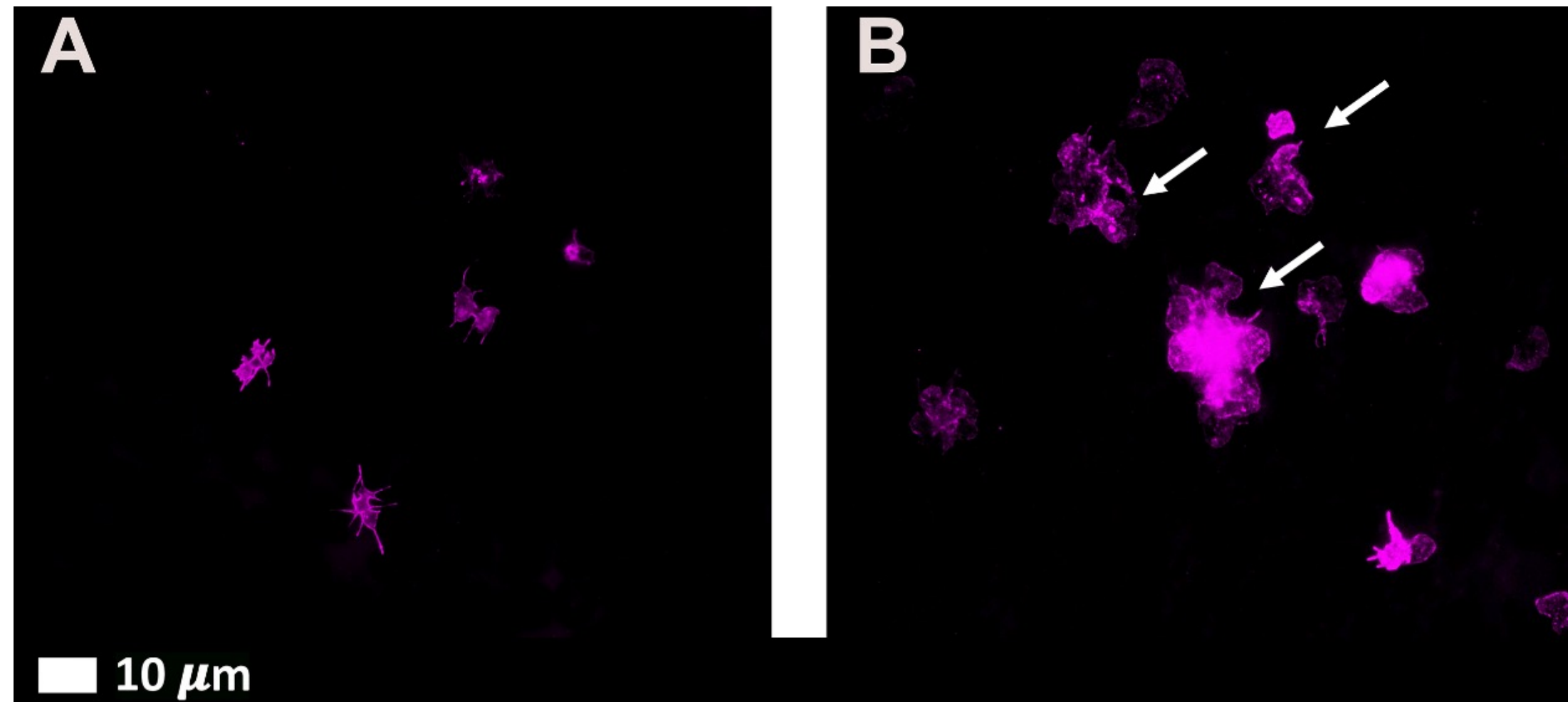
Spike Protein



Bioscience Reports (2021) 41 BSR20210611 <https://doi.org/10.1042/BSR20210611>

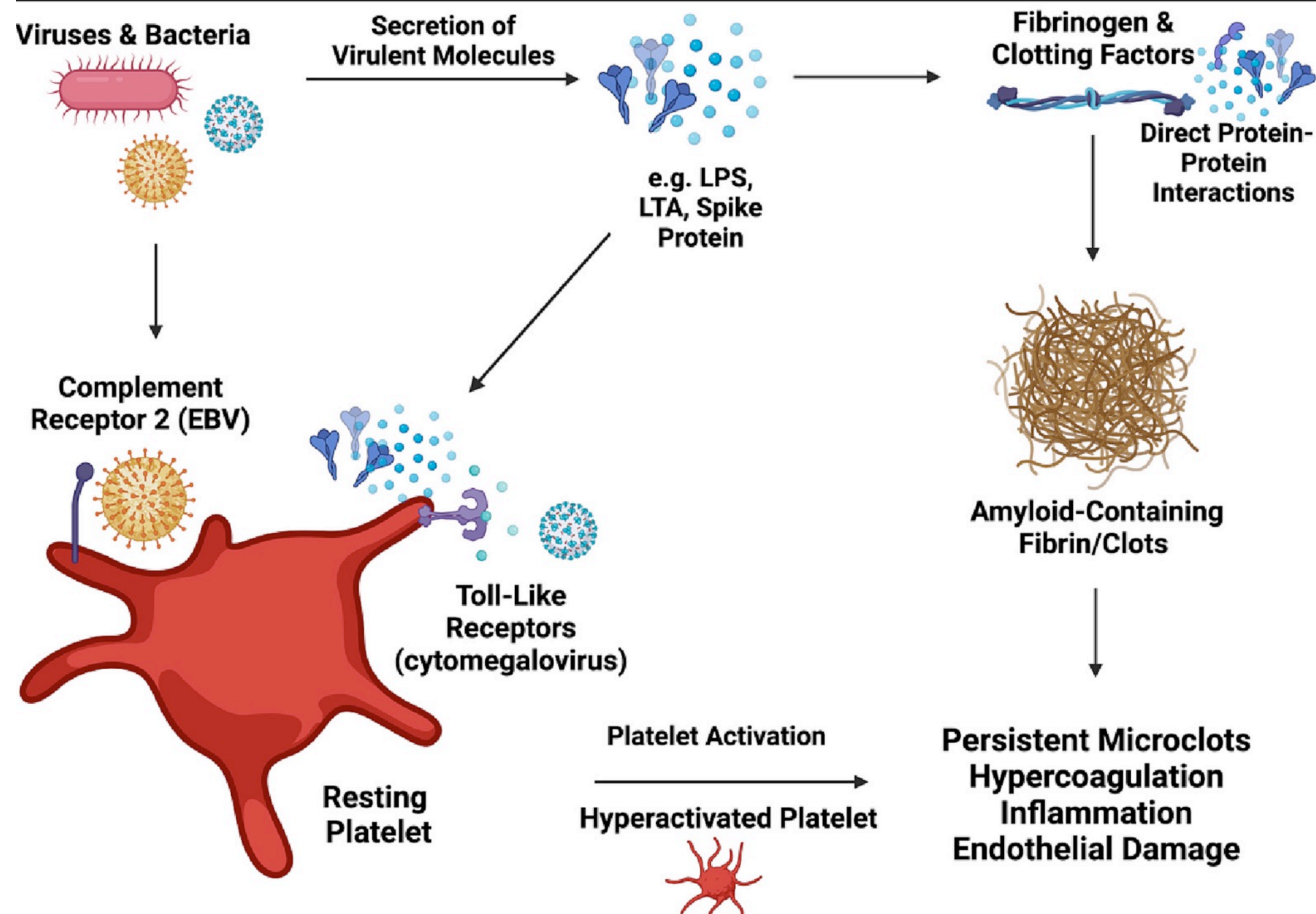


Platelets Before and After Exposure to Spike Protein



Fluorescence microscopy micrographs of platelets, before and after exposure to spike protein (A) Representative platelets from hematocrit incubated with fluorescent marker, CD62P-PE. (B) Representative micrographs showing activated platelets after exposure to spike protein. The white arrows point to hyperactivated activated platelets. White arrows show hyperactivated platelets clumping together.

A Nasty Sludge of a Mess



Nunes JM, Kell DB, Pretorius E. Cardiovascular and haematological pathology in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A role for viruses. Blood Rev. 2023 Mar 20:101075. doi:10.1016/j.blre.2023.101075. Epub ahead of print. PMID: 36963989; PMCID: PMC10027292.



Micro-Clots and Symptoms of Long COVID

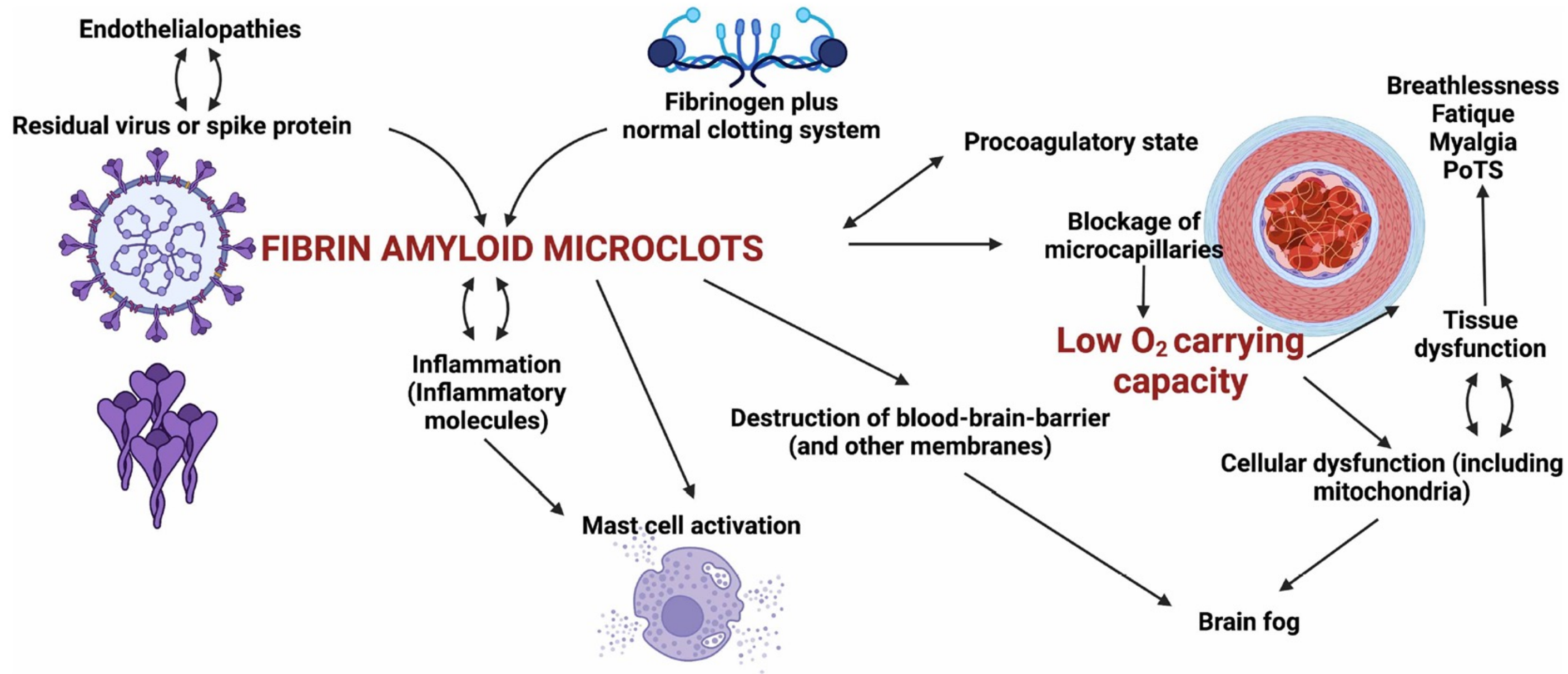


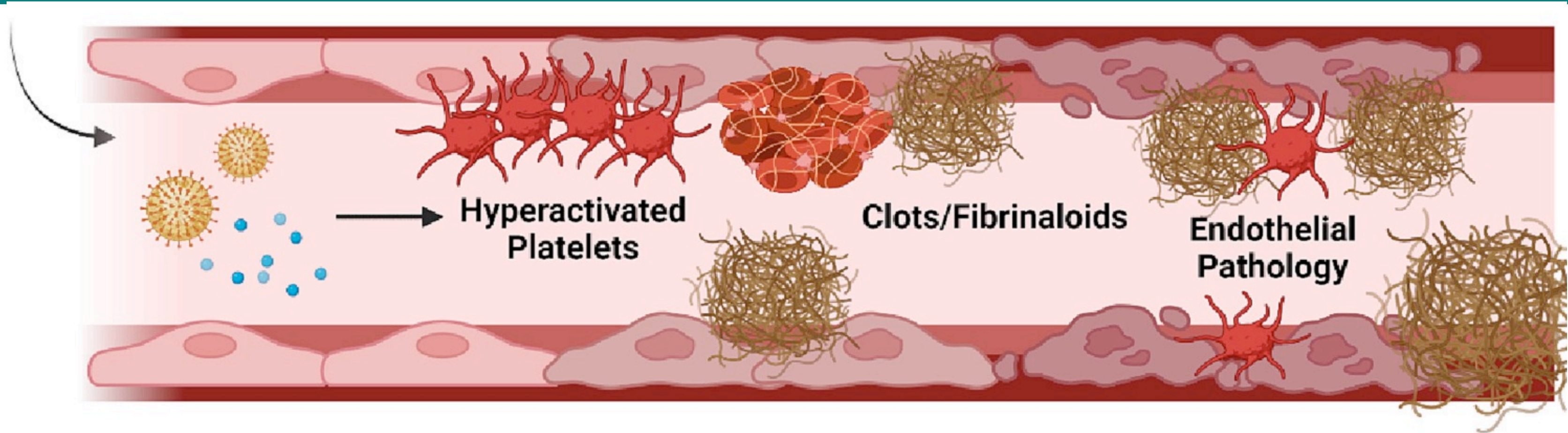
Figure 10. Some of the sequelae of fibrinaloid microclot formation in the symptomology of Long COVID.

Many others, such as a role for auto-antibodies, are not shown.

Douglas B. Kell, Etheresia Pretorius; The potential role of ischaemia–reperfusion injury in chronic, relapsing diseases such as rheumatoid arthritis, Long COVID, and ME/CFS: evidence, mechanisms, and therapeutic implications. *Biochem J* 31 August 2022; 479 (16): 1653–1708. doi: <https://doi.org/10.1042/BCJ20220154>



Endothelial Pathology Leads to Tissue Hypoxia



Anomalous Clotting (Fibrin Amyloid Microdots)

+

Hyperactivated Platelets

+

Endothelial Damage and Dysfunction
From Spike



Vessel Damage/Subtotal Occlusion



Local Tissue Hypoxia and Hypoperfusion



Consequences of Microcapillary Blockage by Micro-Clots

- RBC cannot penetrate to tissues
- Ischemia
- Hypoxia
- Fatigue
- Damage to any tissue undergoing hypoxia
- → Ischemia-reperfusion injury



Microcapillary blockage by MICRO-CLOTS

Areas Now Use the Dissolved Oxygen(PP Oxygen) in Serum not Red Blood Cells

Partial pressure of oxygen in humans

Table 1. References values of PtO₂ measurements using different techniques

PtO ₂ (mmHg)	Organ and Tissue	Reference
108 mmHg	Alveoulus	Guyton [4]
30 mmHg	Brain	Meixensberger [51], Hoffman [52], Ortiz-Prado [3]
30 mmHg	Vestibular System (Balance)	
30.6 mmHg	Cornea	Bonanno [64]
28.9 mmHg	Skeletal Muscle fibers	Beerthuizen [58], Carreau [53]
29.6 mmHg	Myocardium	
22 mmHg	The Eye	Bonanno [64]
8 mmHg	Skin epidermis	Wang [35], Carreau [53]
24 mmHg	Dermal papillae	
55 mmHg	Liver	Leary [56]
72 mmHg	Superficial cortex of the kidney	Muller [57], Carreau [53]
90 ± 5 mmHg	Arterial PO ₂	Mah and Cheng [20], Guyton [4]
40 ± 5 mmHg	Venous PO ₂	Mah and Cheng [20], Guyton [4]

Ortiz-Prado E, Dunn JF, Vasconez J, Castillo D, Viscor G. Partial pressure of oxygen in the human body: a general review. Am J Blood Res. 2019 Feb 15;9(1):1-14. PMID: 30899601; PMCID: PMC6420699.



Triple Therapy

Combined triple treatment of fibrin amyloid microclots and platelet pathology in individuals with Long COVID/ Post-Acute Sequelae of COVID-19 (PASC) can resolve their persistent symptoms

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Treatment of Long COVID symptoms with triple anticoagulant therapy

Gert J Laubscher

Mediclinic Stellenbosch

M Asad Khan

Directorate of Respiratory Medicine, Manchester University Hospitals <https://orcid.org/0000-0003-1838-9002>



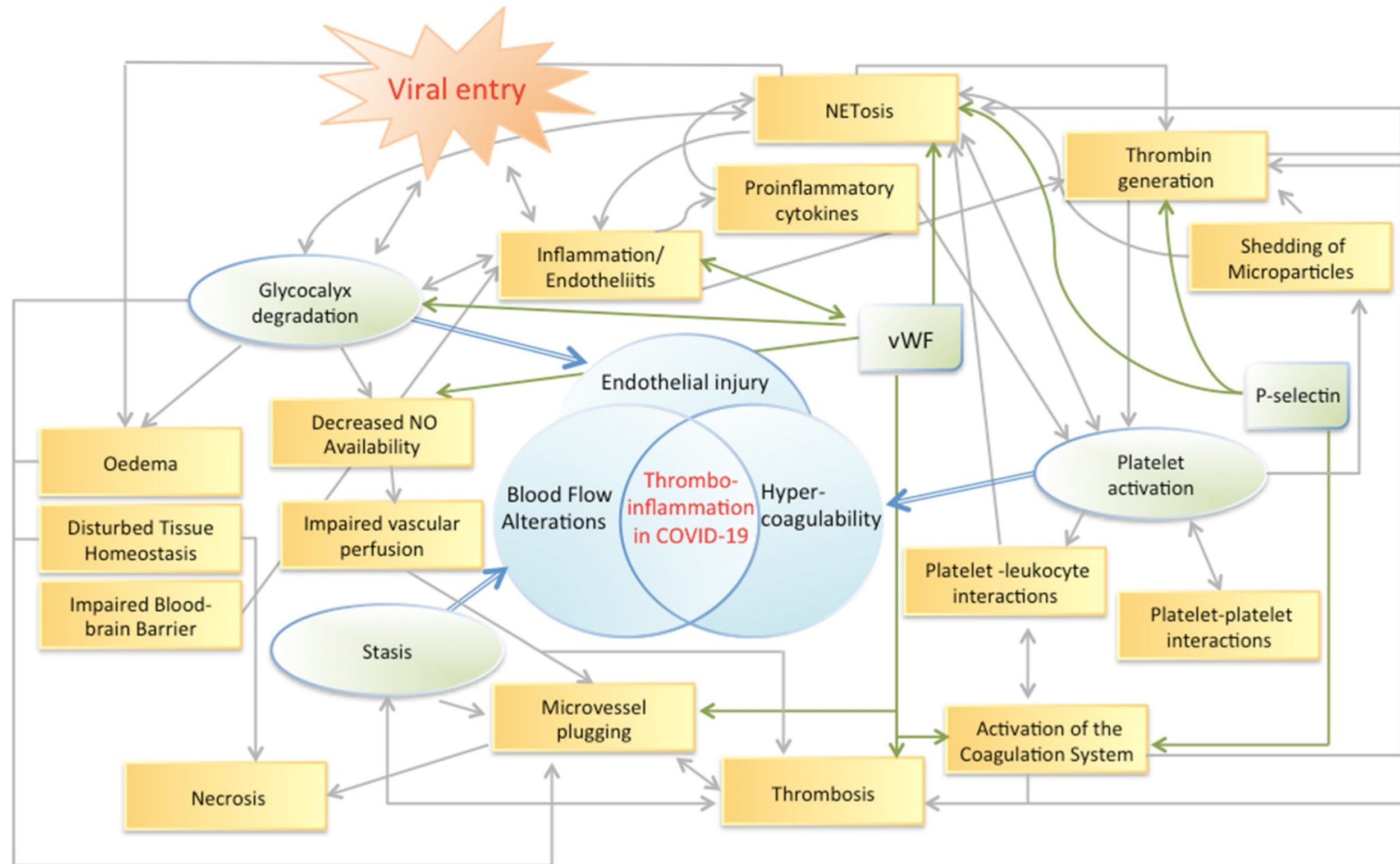
Why Triple Therapy?

Remember They are Resistant NOT Impervious

- Aspirin stops platelets from sticking to each other
- Plavix stops platelets from sticking to the endothelium
- Direct Oral Anticoagulant (DOAC) stops precipitation of fibrin from fibrinogen out of plasma to serve as mortar in micro-clot complex
- Famotidine for stomach protection and H2 blockage for mast cells

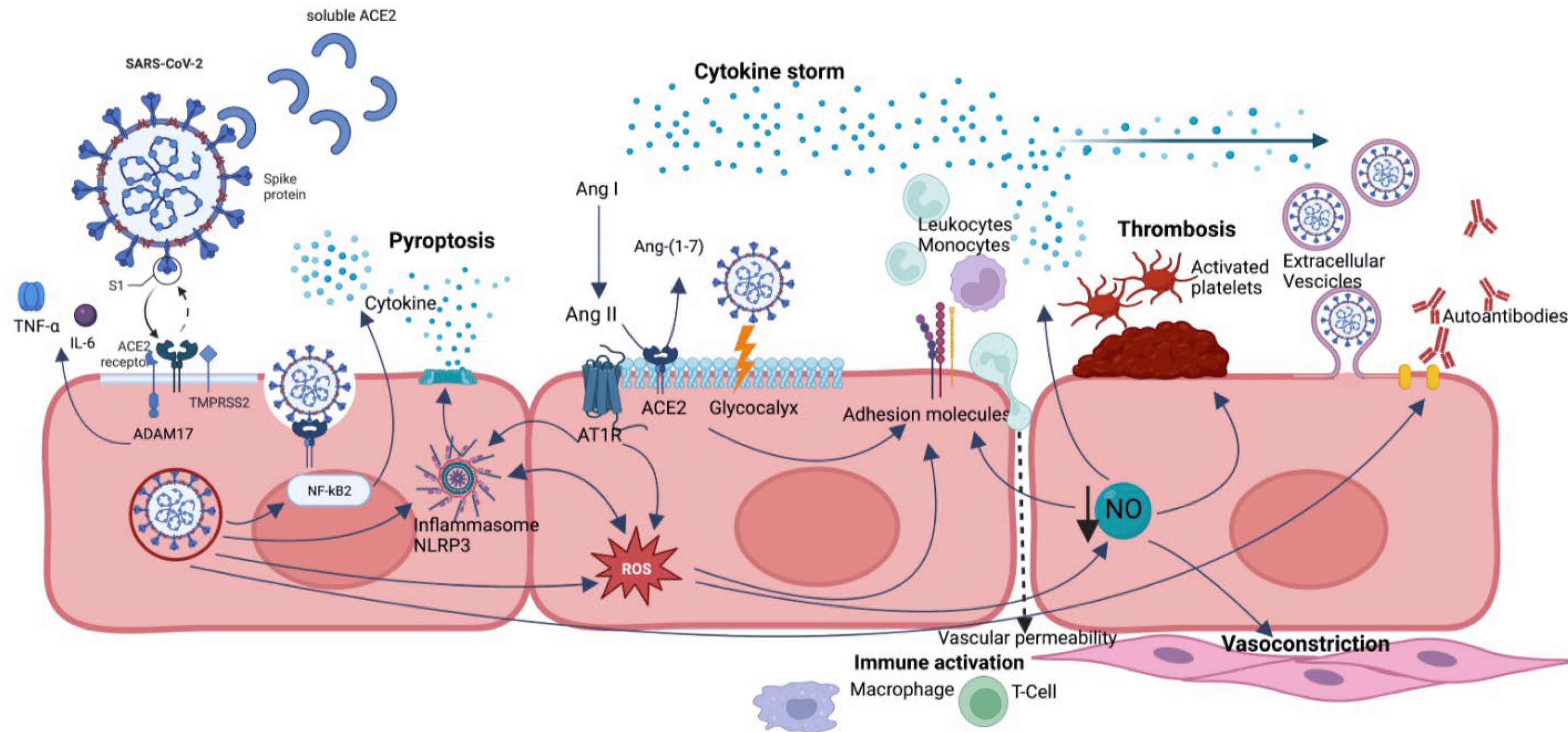


Endothelial Damage and Dysfunction



Wadowski, P.P.; Panzer, B.; Józkwicz, A.; Kopp, C.W.; Gremmel, T.; Panzer, S.; Koppensteiner, R. Microvascular Thrombosis as a Critical Factor in Severe COVID-19. *Int. J. Mol. Sci.* 2023, 24, 2492. <https://doi.org/10.3390/ijms24032492>

Endothelial Damage and Dysfunction

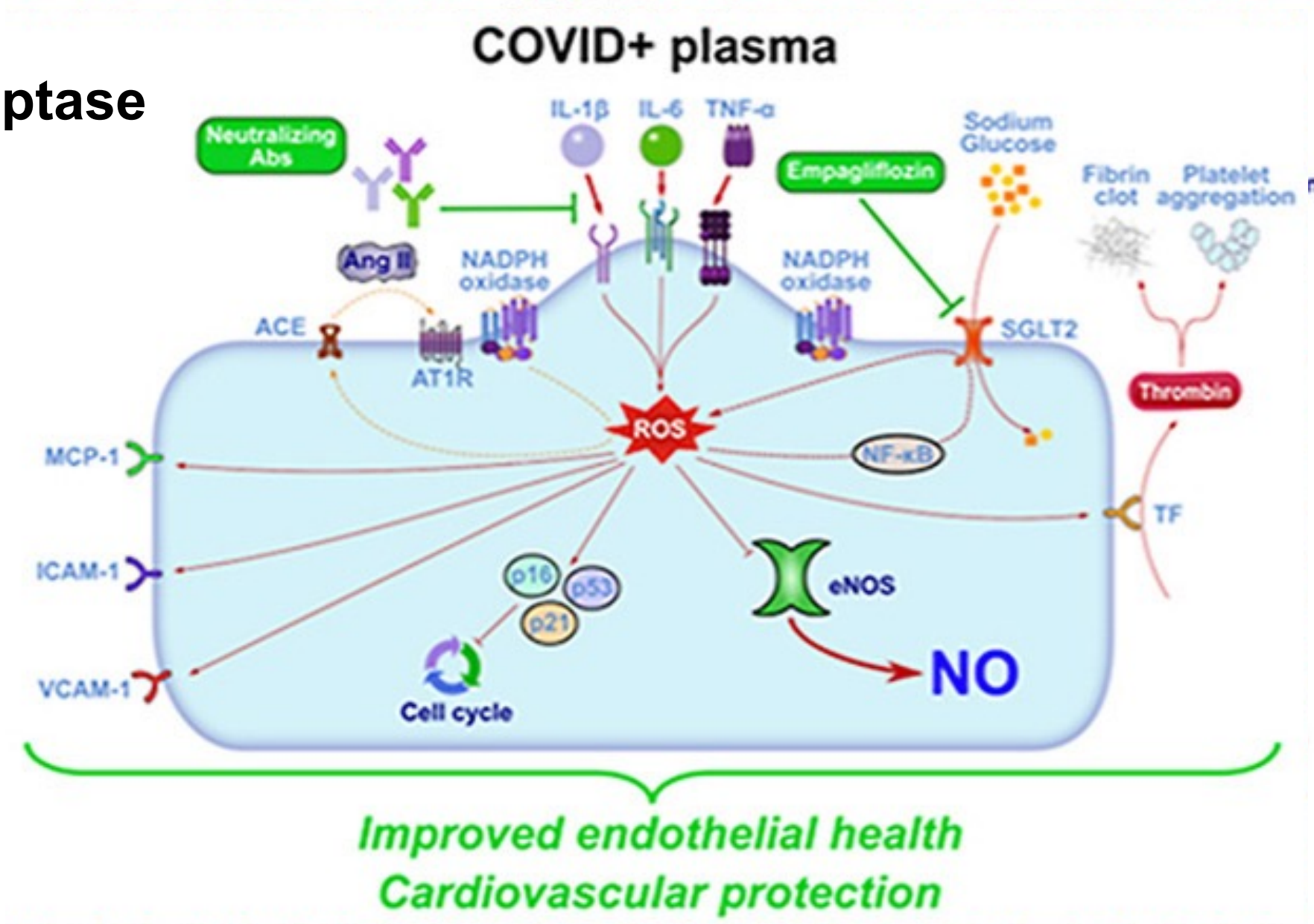


Santoro, L.; Zaccone, V.; Falsetti, L.; Ruggieri, V.; Danese, M.; Miro, C.; Di Giorgio, A.; Nesci, A.; D'Alessandro, A.; Moroncini, G.; et al. Role of Endothelium in Cardiovascular Sequelae of Long COVID. *Biomedicines* 2023, 11, 2239. <https://doi.org/10.3390/biomedicines11082239>

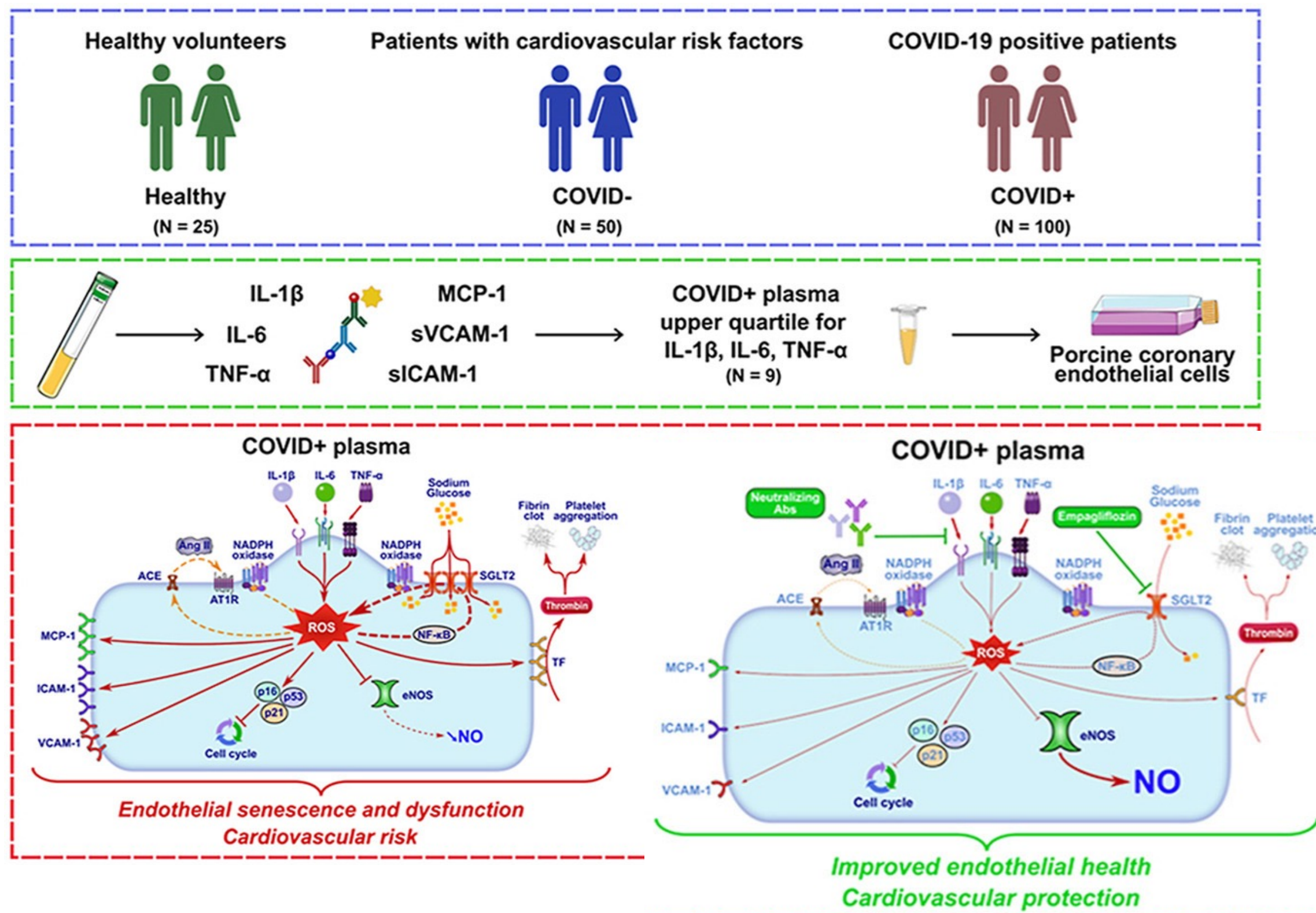
Endothelial Damage and Dysfunction

AGENTS TO ASSIST ENDOTHELIAL REPAIR

- Natural Things:
 - Nattokinase/Serrapeptase
- Aspirin
- Pentoxifylline
- SGLT-2i:
 - Empagliflozin



Mast Cell Activation



Mast Cell Activation Syndrome

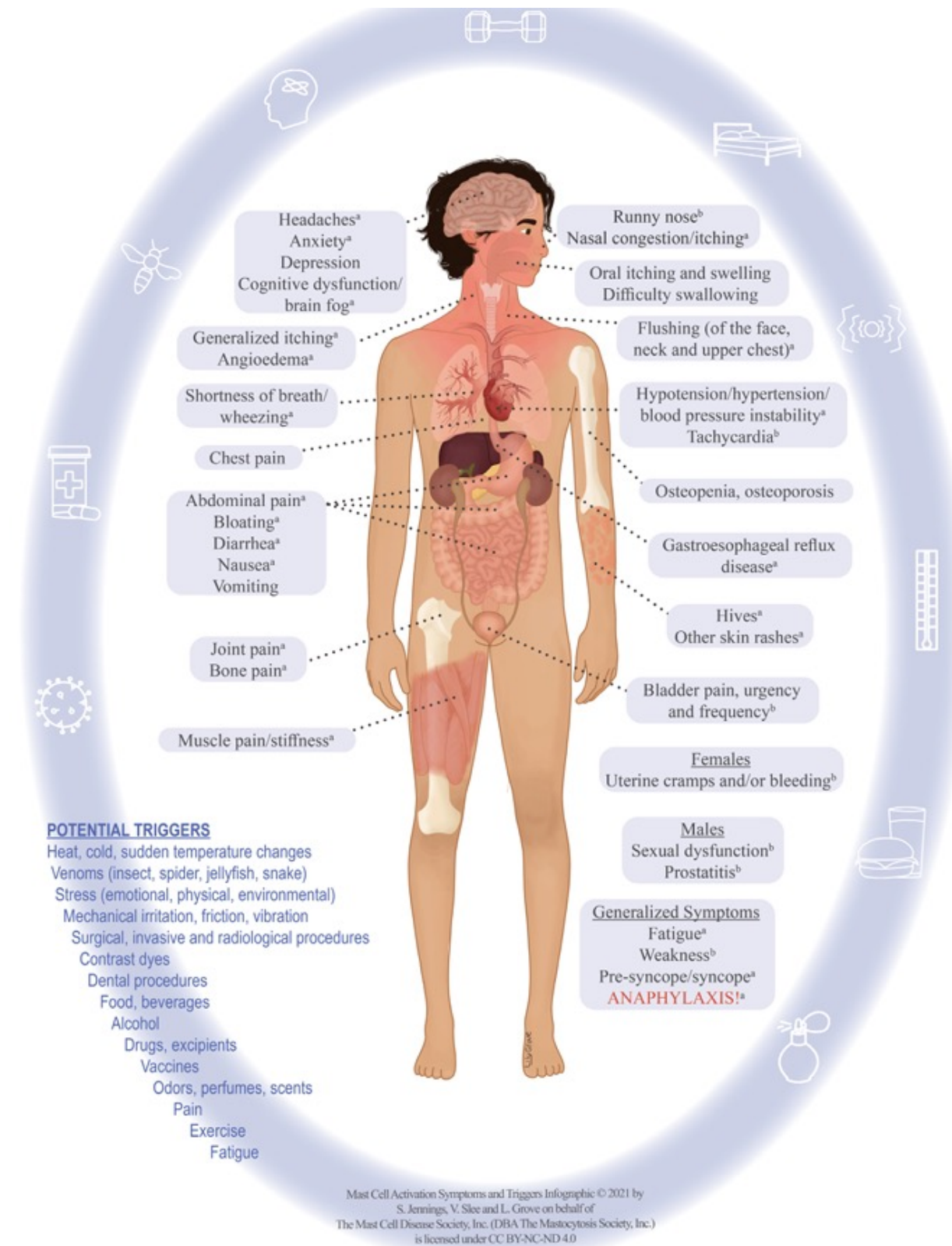
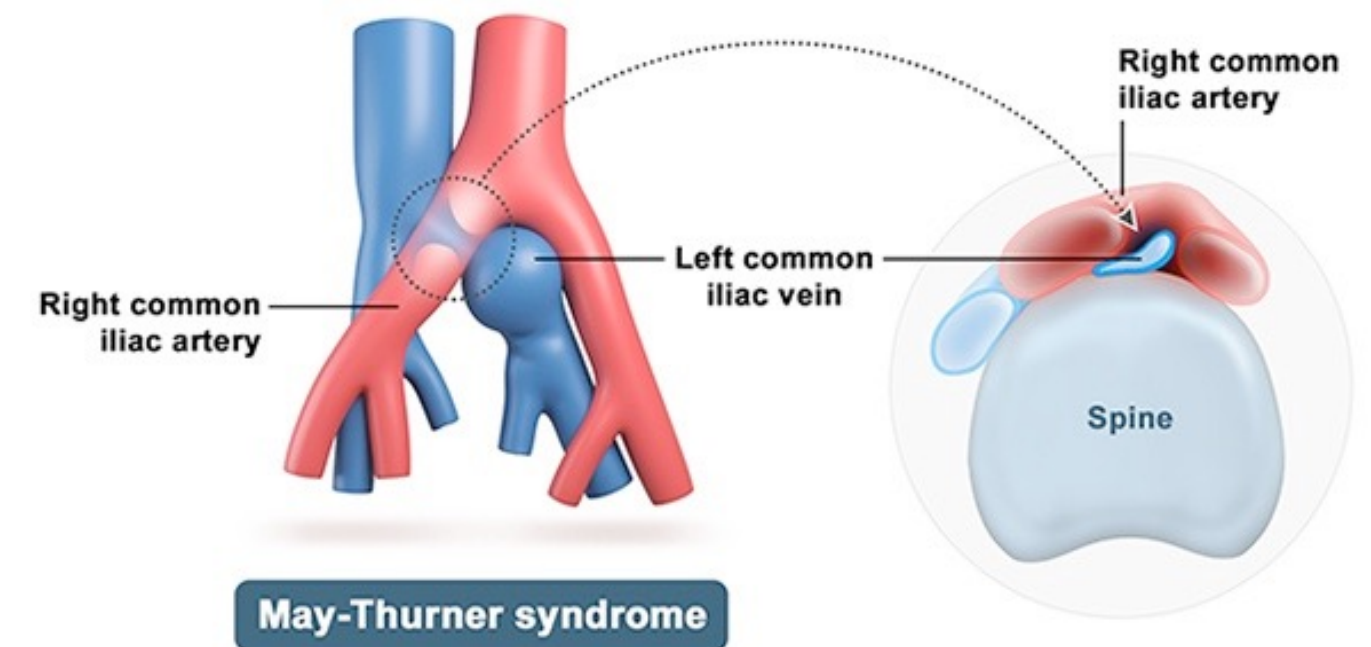


Figure 1. The most common presenting symptoms and potential triggers of mast cell activation.^{1,2,4} Symptoms and triggers are unique to the individual. Specific criteria, as noted in the article text, must be met to fulfill a diagnosis of MCAS. Not all patients react to each of the listed triggers or experience each of the listed symptoms. Mast Cell Activation Symptoms and Triggers Infographic 2021 printed with permission from The Mast Cell Disease Society, Inc (DBA The Mastocytosis Society, Inc). The superscript letter "a" indicates symptoms reported by more than 45% of TMS MCAS survey respondents as affecting them either moderately or severely in the course of their illness with MCAS.⁵ The superscript letter "b" indicates symptoms not queried in the TMS MCAS survey. DBA, doing business as; MCAS, mast cell activation syndrome; TMS, The Mast Cell Disease Society, Inc.



Another Phenotype: ILIAC VEIN COMPRESSION

- May-Thurner (Pelvic Venous Disease) plus MCAS and POTS following endothelial injury (spike protein) most are vaccine injury
- Common in:
 - Hypermobile: EDS or EDS like
 - Runners/cyclist/pelvic trauma
 - Multiparous women
 - Men with left scrotal testicle history including varicocele, torsion of the testes
- Vaccine injury results in lower extremity symptoms initially.
 - Most remember a TIME and DATE when things in their body were DIFFERENT
 - Many had mild issues prior including leg going to sleep when sitting for long times, etc.
- Initially symptoms are felt in the lower extremities and they feel heavy/lead-like or are swollen
- POTS and MCAS symptoms are increased
- Triple therapy (antiplatelet and anticoagulants) help but are not curative
 - Post thrombotic syndrome in this subset explains this



Another Phenotype: ILIAC VEIN COMPRESSION

Additional Issues:

- Urinary urgency or “frequent urinary tract infections” or Interstitial Cystitis
- Heavy menstrual cycles, pelvic pain, all issues are worse before and during cycle
- Hemorrhoids and irritable bowel symptoms
- Lower sacral back pain and sacral ileitis symptoms
- Boggy prostate and nocturia in younger men

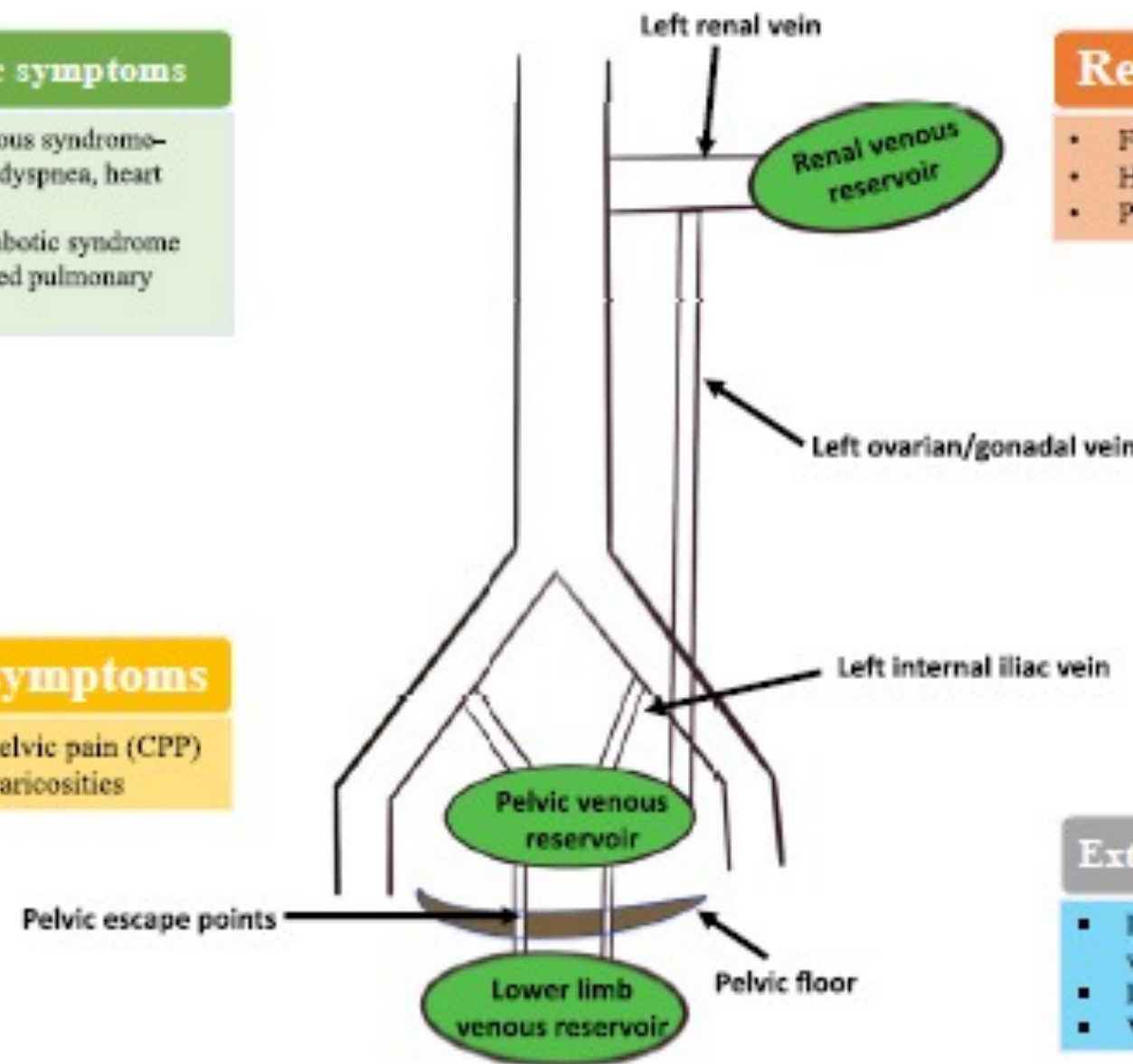


Another Phenotype: ILIAC VEIN COMPRESSION

Flank pain, hematuria, proteinuria

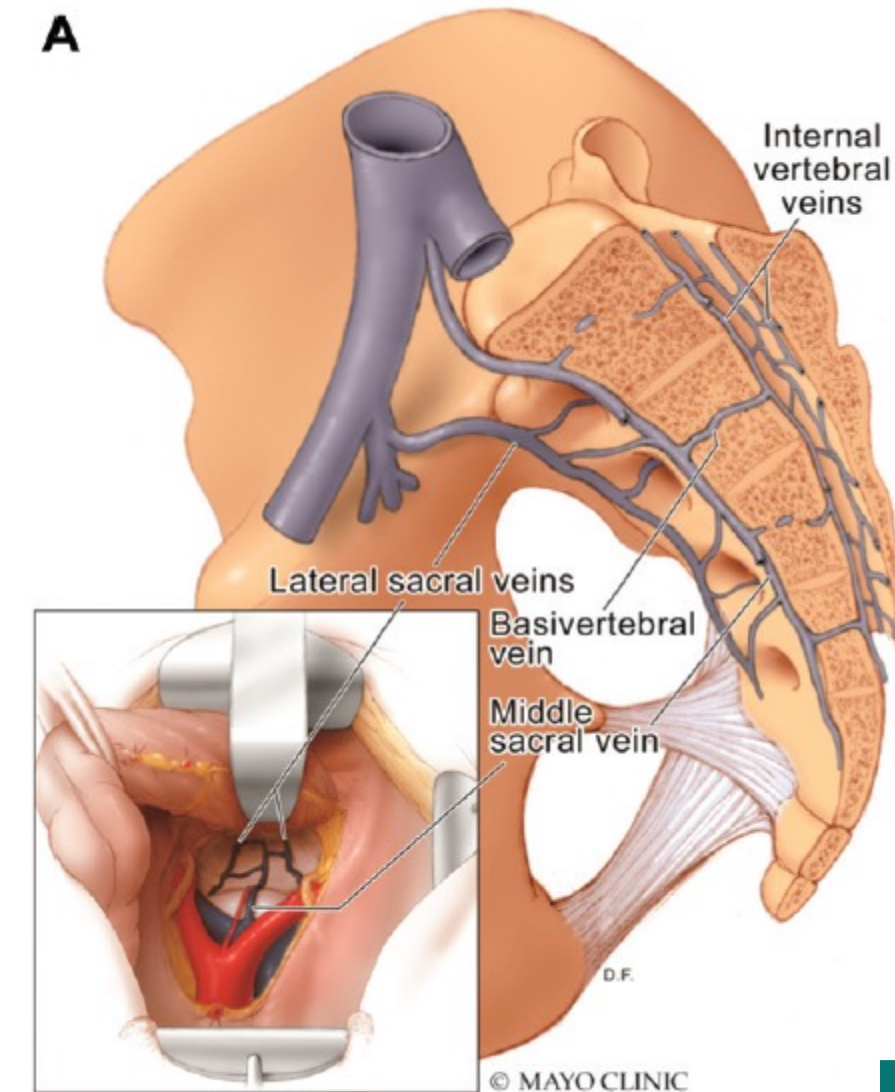
- Systemic symptoms**
- Cardiovenous syndrome—exertional dyspnea, heart failure
 - Post-thrombotic syndrome
 - Unexplained pulmonary emboli

- Pelvic symptoms**
- Chronic pelvic pain (CPP)
 - Perineal varicosities



- Renal symptoms**
- Flank pain
 - Hematuria
 - Proteinuria

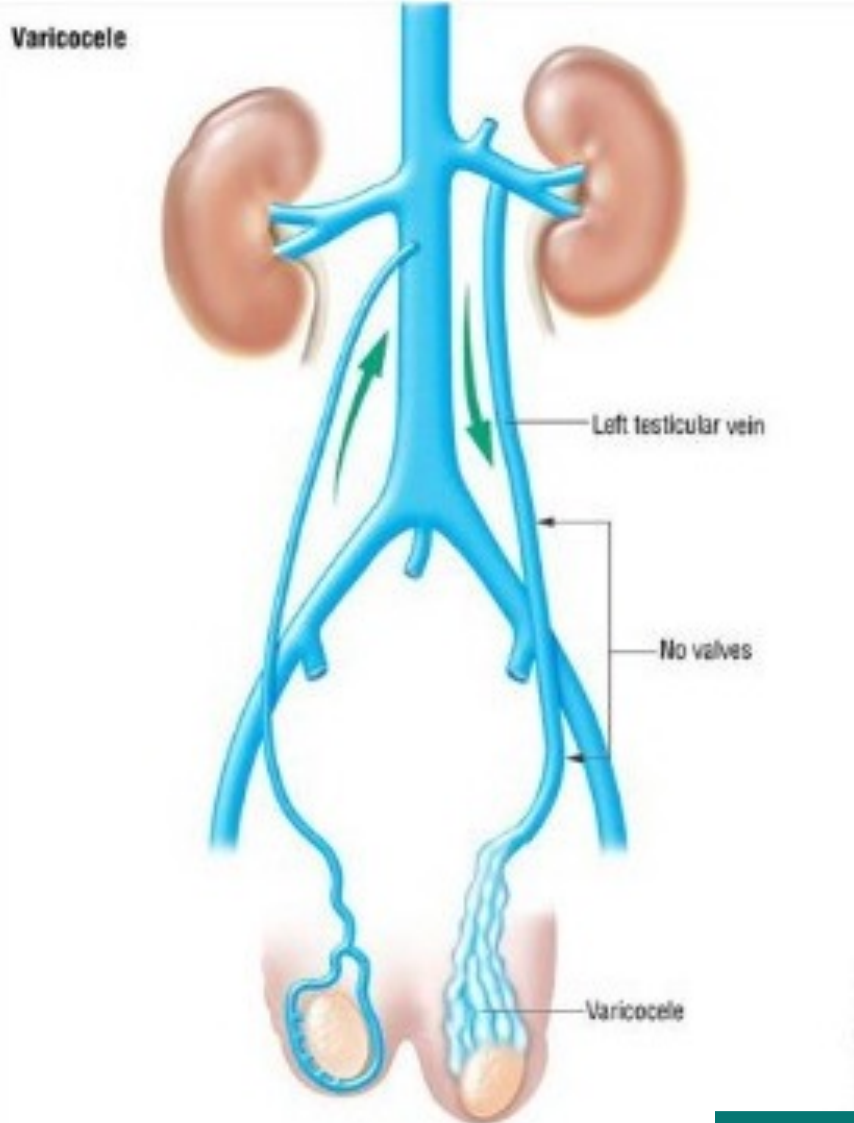
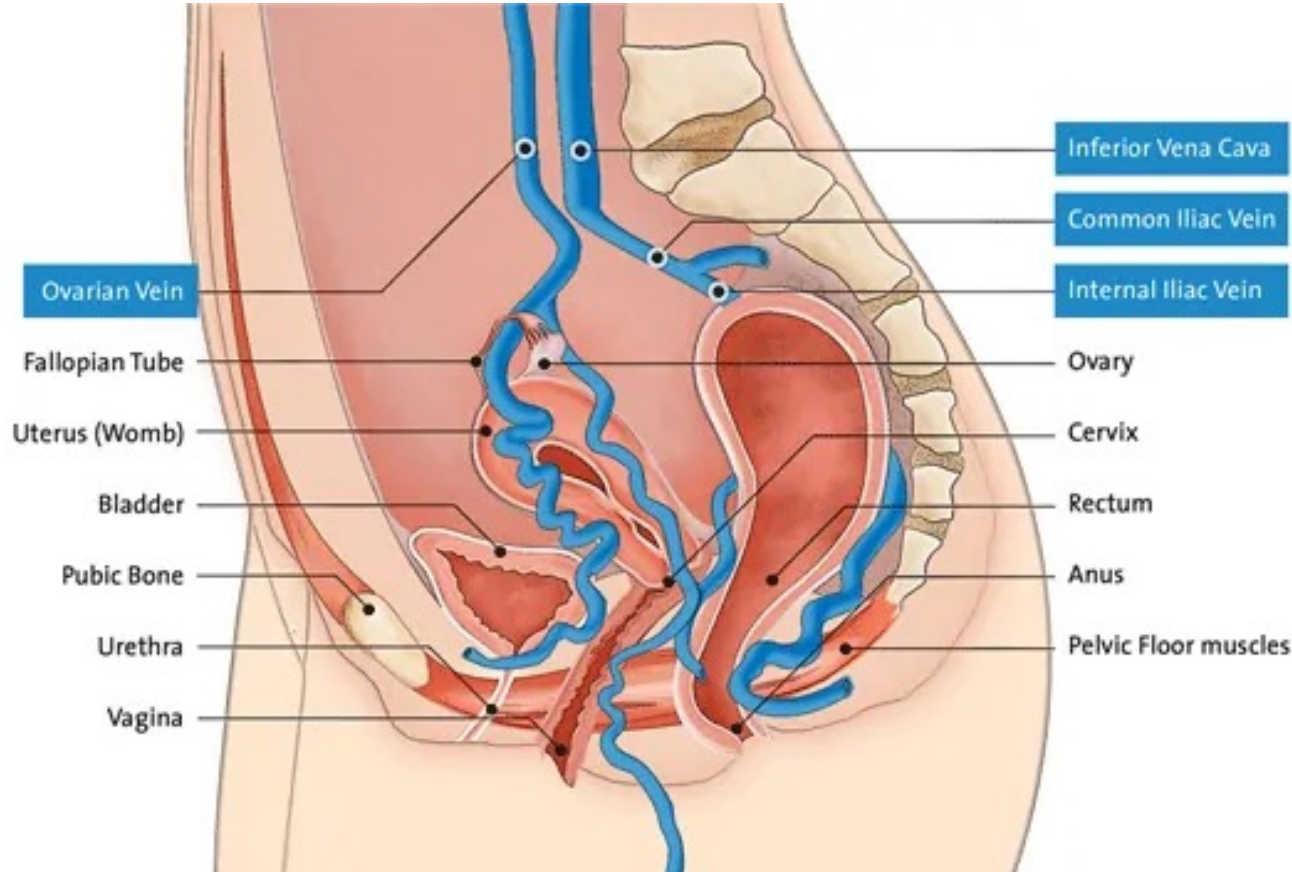
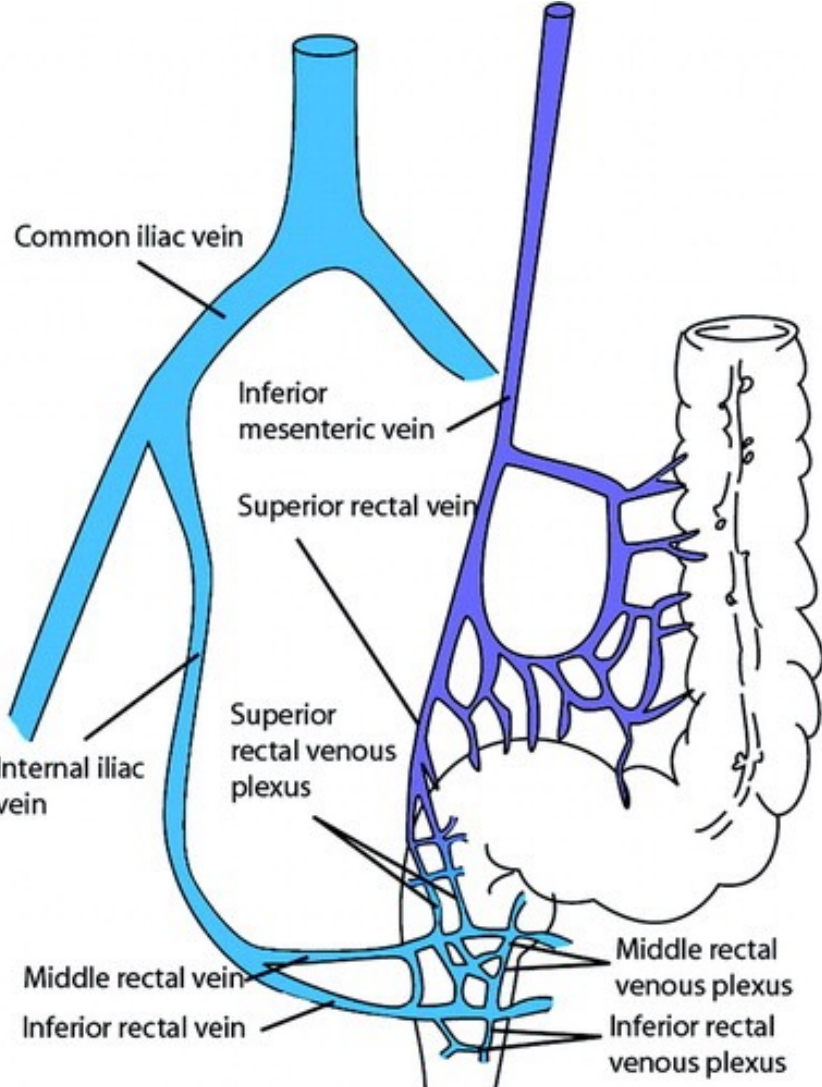
- Extra pelvic symptoms**
- Lower limb, vulvar varicosities
 - Lower limb swelling
 - Venous claudication



Sheikh AB, Fudim M, Garg I, Minhas AMK, Sobotka AA, Patel MR, Eng MH, Sobotka PA. The Clinical Problem of Pelvic Venous Disorders. *Interv Cardiol Clin.* 2022 Jul;11(3):307-324. doi: 10.1016/j.iccl.2022.03.003. PMID: 35710285.



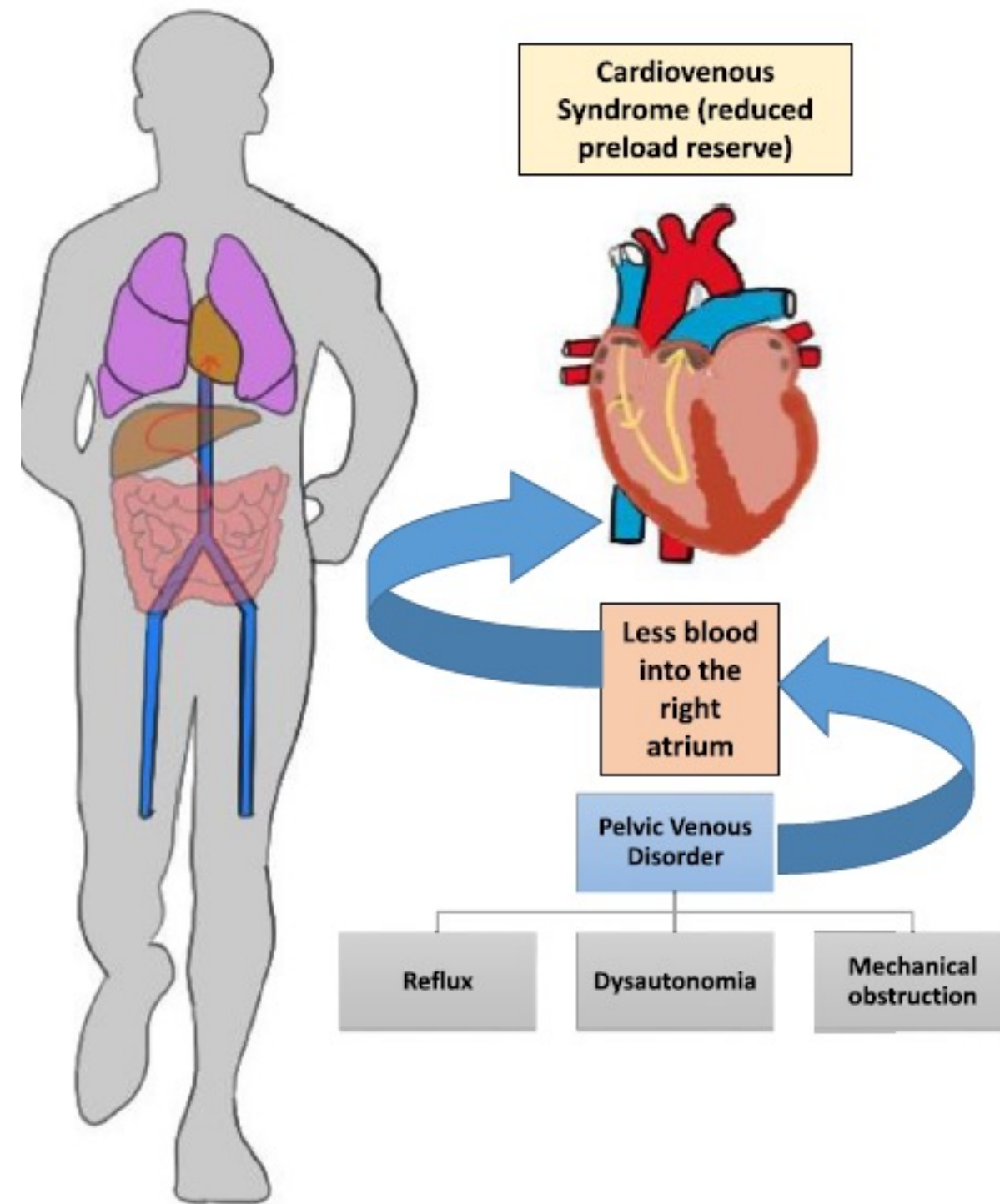
Another Phenotype: ILIAC VEIN COMPRESSION



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Another Phenotype: ILIAC VEIN COMPRESSION

Journal Pre-proof

Concentration of Inflammatory Markers in Plasma of Varicose Ovarian Veins in Women With Pelvic Venous Disorders: A Pilot Study

Marcin Czeczelewski, Eryk Mikos, Sara Moqbil, Maciej Szmygin, Hanna Szmygin, Krzysztof Pyra

PII: S1078-5884(23)00456-2

DOI: <https://doi.org/10.1016/j.ejvs.2023.06.011>

Reference: YEJVS 8824

To appear in: *European Journal of Vascular & Endovascular Surgery*

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Table 1. Comparison of blood counts and levels of inflammatory markers in samples from the antecubital vein and pelvic varicose vein of 25 patients of reproductive age referred for endovascular treatment of pelvic venous disorder.

Variable	Antecubital vein <i>n</i> = 25	Pelvic varicose vein <i>n</i> = 25	<i>p</i>
Erythrocytes – 10 ¹² /L	4.02 (3.17 – 4.91)	4.23 (3.30 – 4.86)	.002
Leukocytes – 10 ⁹ /L	4.62 (2.98 – 6.52)	5.21 (3.30 – 8.34)	.001
Platelets – 10 ⁹ /L	220.5 (163 – 279)	237 (196 – 302)	.005
Haemoglobin – g/dL	12.00 (9.70 – 15.20)	12.95 (10.80 – 15.40)	.001
D-dimer – pg/mL	9 884 (2 259 – 16 910)	13 330 (3 099 – 114 110)	.081
C-reactive protein – mg/L	0.15 (0.12 – 2.93)	0.24 (0.10 – 3.04)	.038
Fibrinogen – g/L	2.25 (1.7 – 4.50)	2.25 (1.60 – 3.60)	.410
Interleukin-6 – pg/mL	50.88 (36.58 – 87.16)	57.14 (40.03 – 79.38)	.038
von Willebrand – ng/mL	36.28 (21.15 – 168.6)	45.43 (20.68 – 89.00)	.442

Data are presented as median (range).



Another Phenotype: ILIAC VEIN COMPRESSION

Imaging Modality for Diagnosis MRV (MR Venography)



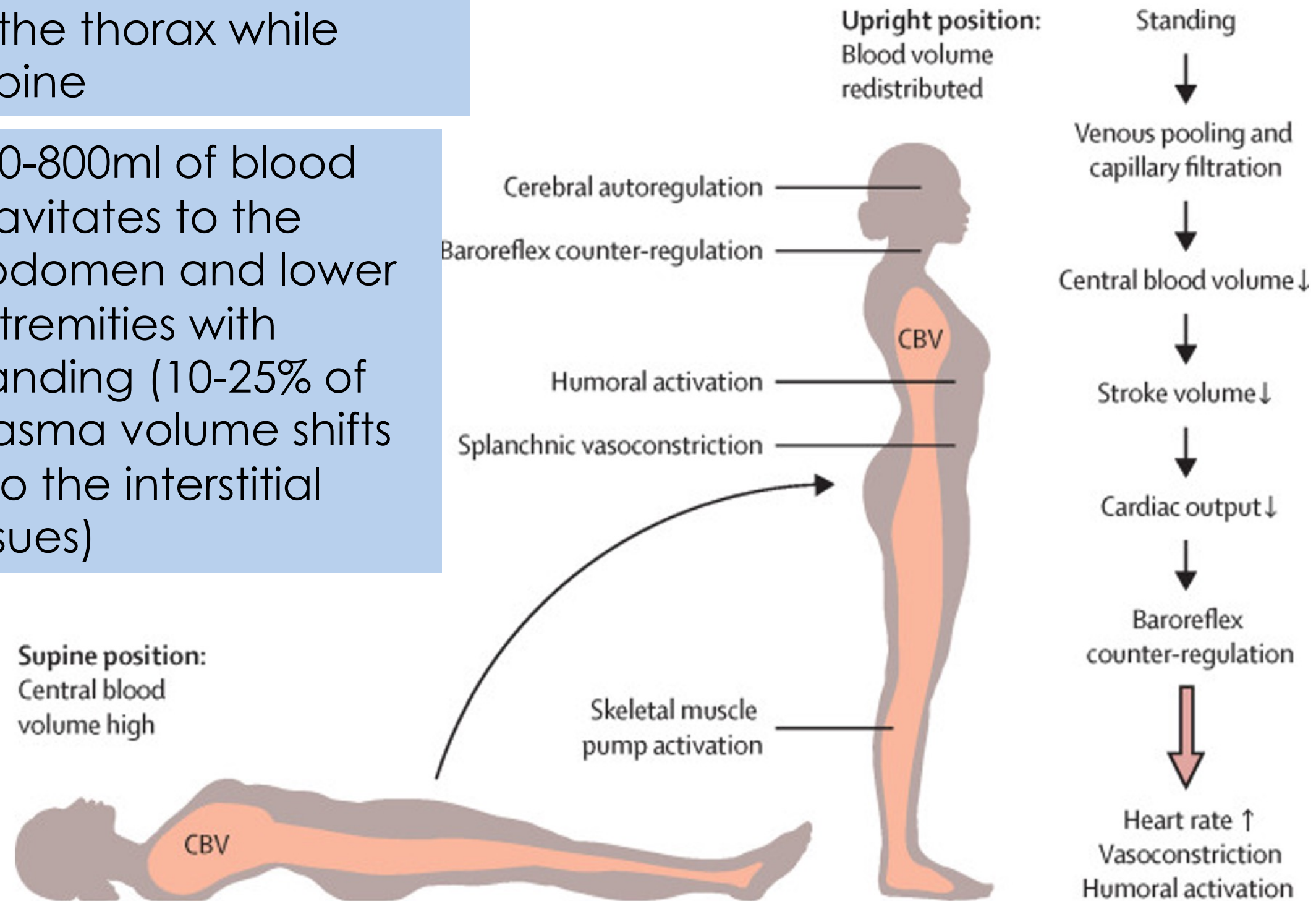
Venography of Iliac Vein and Intervention



OVERVIEW

30% of blood volume is in the thorax while supine

300-800ml of blood gravitates to the abdomen and lower extremities with standing (10-25% of plasma volume shifts into the interstitial tissues)

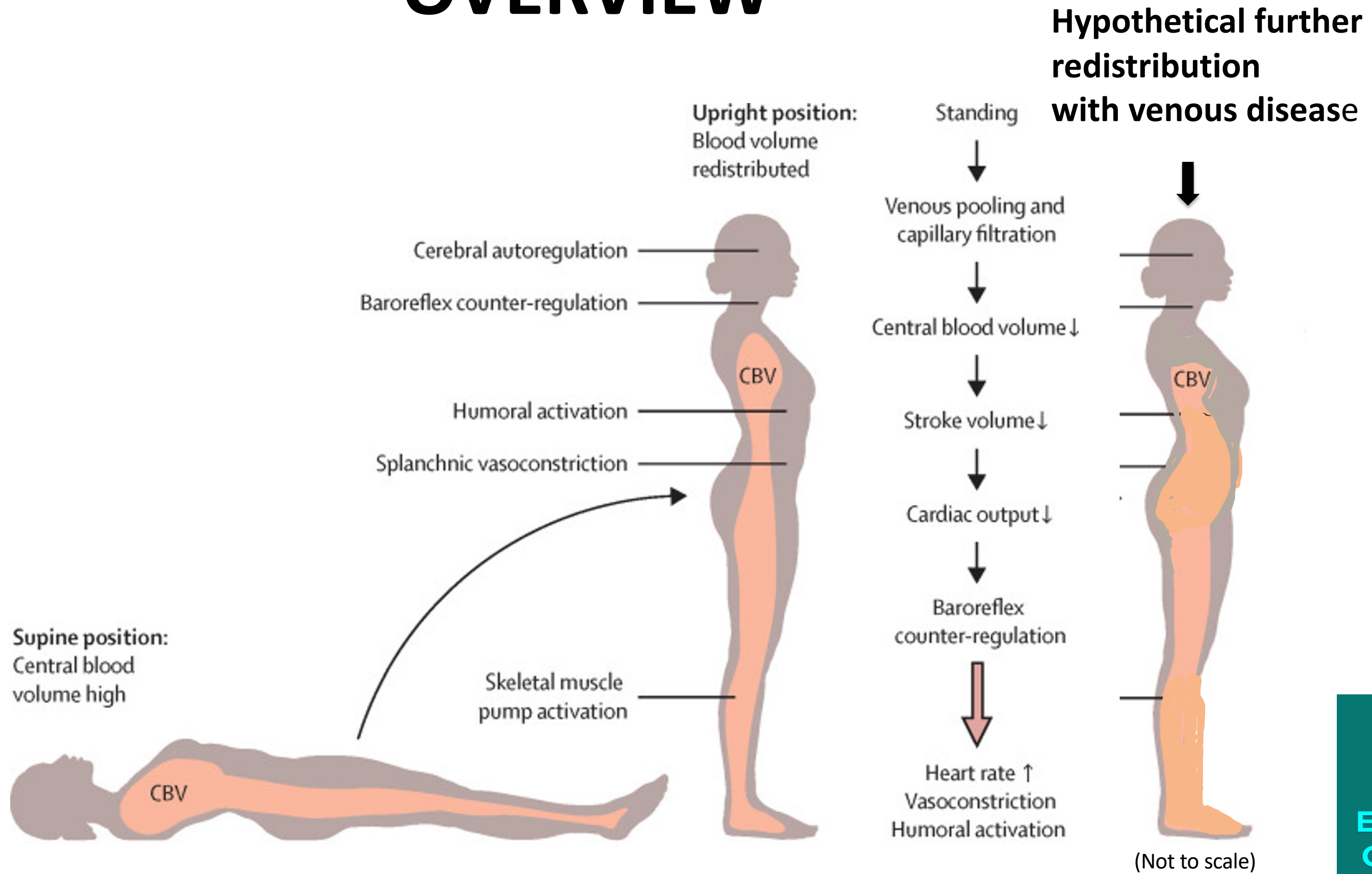


In normal patients this results in 10-15 bpm increase in HR and increase in diastolic BP of 5-10mmHg

W Weiling MD et al. Diagnosis and treatment of orthostatic hypotension. The Lancet Neurology. Volume 21, Issue 8, August 2022, Pages 735-746



OVERVIEW



Adapted from: W Weiling MD et al. Diagnosis and treatment of orthostatic hypotension. The Lancet Neurology. Volume 21, Issue 8, August 2022, Pages 735-746



Another Phenotype: ILIAC VEIN COMPRESSION

Non-Invasive Interventions and Medications:

- **Anticoagulation/Antiplatelet**
 - Low Dose Aspirin and DOAC (Eliquis)
 - Pentoxifylline (Increases Oxygen Delivery/Antithrombotic/Antiplatelet)
- **Mast Cell Stabilization:**
 - H1 and H2 blockade (Xyzal/Allegra plus Famotidine)
 - Mast cell stabilizers
 - Compounded oral ketotifen 1mg twice a day
 - Cromolyn sodium (best for MCAS with GI issues)
 - Quercetin(high dose 1 gram to 2 grams)
 - Turmeric/curcumin/black pepper)
- **Endothelial Repair:**
 - Diosmin 500 mg-750 mg daily; pycnogenol 50 mg twice a day
 - SGLT-2i (Jardiance, etc.)
- **Increase Intravascular Volume:**
 - Salt/hydration
 - Fludrocortisone



Another Phenotype: ILIAC VEIN COMPRESSION

Non-Invasive Interventions:

- **Physical Interventions: Venous System is LOW Pressure and w/o a PUMP**
- **Increase venous return by:**
 - **Lower extremity movement = venous pumping:**
 - Walking
 - Recumbent biking (body flat means lower pressures to work against IVC pressure lying down: 8-10mmhg versus standing up: 20-22mmhg)
 - Rowing
 - **Compression stockings**
 - **Intermittent compression devices especially prior to bedtime:**
 - Remember legs (aka venous pump) moves minimally during sleep
- **Current trial using soft wave technology directly on Iliac vein:**
 - Weekly treatment in those with mild to moderate compression
 - So far outcomes have been promising



FLC^CCC
ALLIANCE

**EDUCATIONAL
CONFERENCE**

