The Role of Acute Respiratory Distress Syndrome (ARDS) in Cerebral Hypoperfusion and Delirium: Analysing the Pathophysiological Mechanisms of Persistent Cognitive Impairment

Abstract

Acute respiratory distress syndrome (ARDS) is an inflammatory lung condition characterised by impairment to the capillary and alveolar endothelial lining of the lungs, causing acute respiratory failure following the accumulation of inflammatory mediators within the parenchyma tissue. (Diamond M, Peniston HL, Sanghavi D, et al.) Accordingly, Covid-19 carries the potential to induce pathological changes and necrosis to the alveolar epithelium by introducing sepsis, in which the lung endothelium adopts a pro-inflammatory phenotype that stimulates a cytokine storm to enter the bloodstream. Therefore hypoxemic respiratory failure occurs in response to the viral proteins from SARS-CoV-2 accompanied by enhanced blood-brain barrier permeability that enables cytokine entrance within the cerebrospinal fluid, initiating neuronal damage and cerebral hypoperfusion. Furthermore, the inflammatory cascade comprised of pro-inflammatory immune cells including alveolar macrophages and neutrophils causes damage to the lung interstitial lining following exudation, proteinaceous fluid flooding and pulmonary oedema prior to hyaline membrane formation and fibroblast proliferation to repair the disrupted alveolar endothelium. (Saguil, 2012) Therefore, interstitial thickening following the fibrotic phase of ARDS disrupts efficient gas exchange, inducing hypoxemia and hypoxia within the patient ((Gibson, Qin and Puah, 2020).

Pathophysiology of ARDS

ARDS arises from acute injury to lung tissue and is characterised by bilateral lung infiltrates in which fluid consisting of neutrophils and cytokines enters the parenchyma of the lungs as a result of pulmonary vascular endothelial cell semi-permeability accompanied by hypoxemic Respiratory failure that begins within 7 of the initial offending cause of the lung tissue damage. (Gonzales, J. N., Lucas, R., & Verin, A. D. 2015). Accordingly, the severity of ARDS is dependent on the PaO2/FiO2 ratio, in which a result of 300 or less when dividing the patient's arterial oxygen partial pressure (PaO2) by the fraction of inspired oxygen (FiO2) indicates acute lung injury. (Diamond M, Peniston HL, Sanghavi D, et al.) Furthermore, the process of progressing diffuse alveolar damage (DAD) accompanied by disrupting the pulmonary capillary endothelial membranes within the lung due to ARDS can be divided into three primary stages that vary in severity for each patient. The pulmonary endothelial barrier of a healthy lung is characterised by its exposure to the partial pressure of oxygen and its role in modulating vascular homeostasis and anti-platelet activity after recognising intracellular and extracellular stimuli, as endothelial cells bind the anti-coagulant proteins known as tissue factor pathway inhibitors (TFPI) (Gonzales and Verin, 2018).

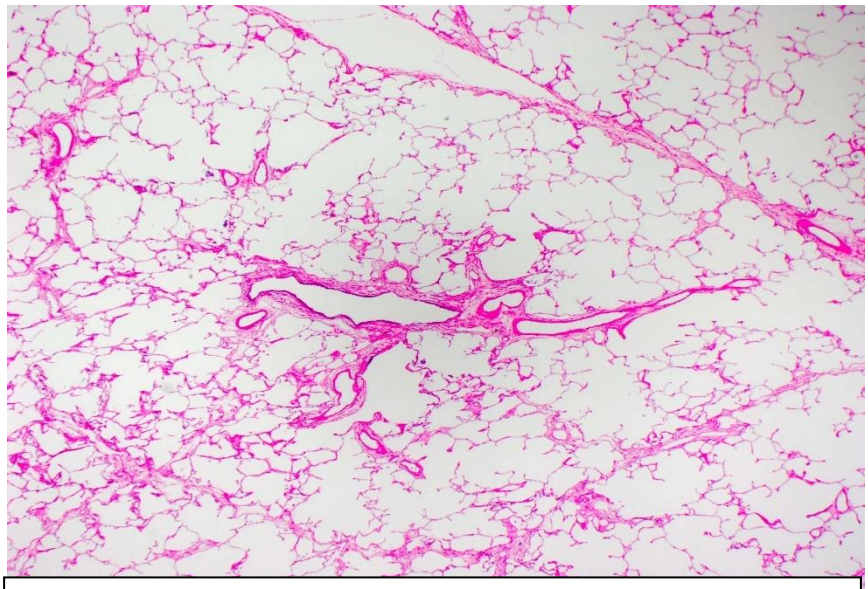

Figure 1: Histological image of normal lung specimen revealing open alveolar ducts covered by type 1 alveolar cells (Yoshikawa and Bychkov, 2022).

The anti-inflammatory phenotype of the lung endothelium is recognised as a critical mediator in controlling inflammation to regulate various functions such as signal transduction, fluid transport, intravascular coagulation, leukocyte transfer and many other processes (Millar et al., 2016). Accordingly, ARDS introduces complex interactions between various pro-inflammatory and anti-inflammatory cells that disrupt the critical functions of the lung endothelium. The beginning phase of exudation in the progression of ARDS occurs within a few days following lung injury, in which an inflammatory cascade comprised of alveolar macrophages and neutrophils is stimulated to infiltrate the lung interstitium to repair lung endothelial damage and prevent leakage of plasma, protein-rich oedema and proteinaceous fluid.

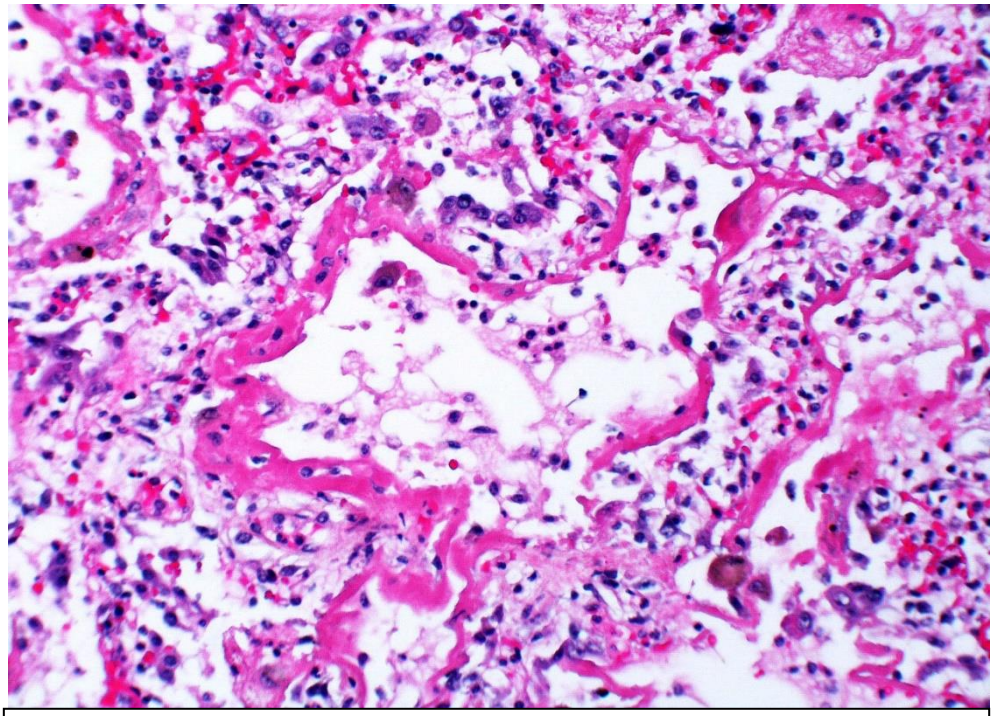

Figure 2: Histological image of prominent hyaline membranes within the lungs during the beginning exudative phase of ARDS (Yoshikawa and Bychkov, 2022).

The diffuse alveolar damage and necrosis of alveolar epithelial type I cells are prioritised for repair within the second phase of proliferation, in which granulation tissue is comprised of proliferating type II alveolar cells, fibroblasts and myofibroblasts produce a collagen-rich extracellular matrix to remodel the lung endothelium within the parenchyma.

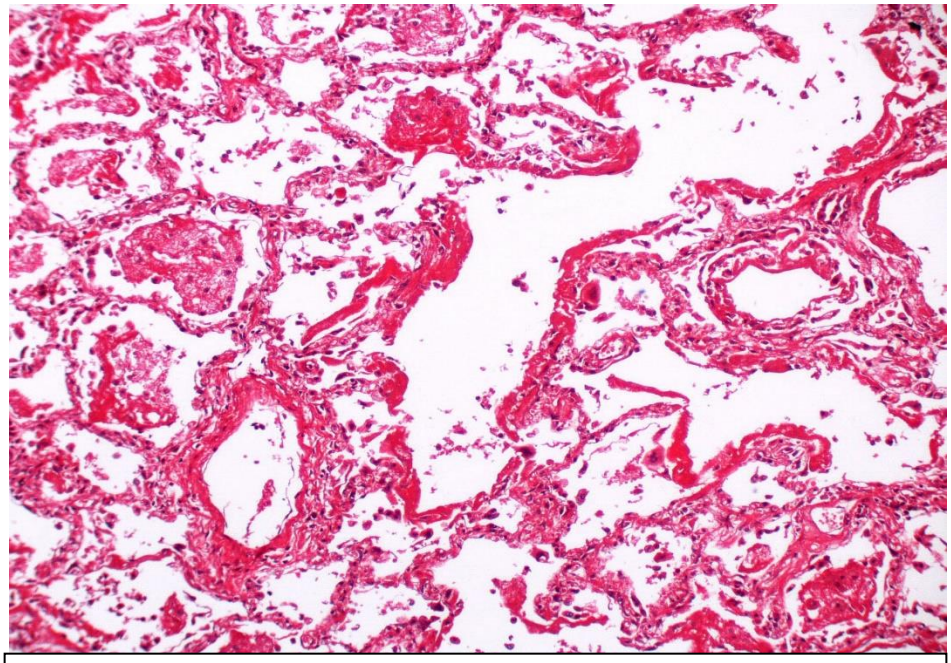

Figure 3: Histological image of alveolar walls during fibrotic phase of ARDS with eosinophilic hyaline membranes (Yoshikawa and Bychkov, 2022).

The progression of ARDS ends with fibrosis in which fibrillar collagens I and III stimulate collagen deposition and the production of microcysts to replace the alveolar-capillary membrane, creating a thick endothelium that inhibits efficient gas exchange (Spadaro et al., 2019).

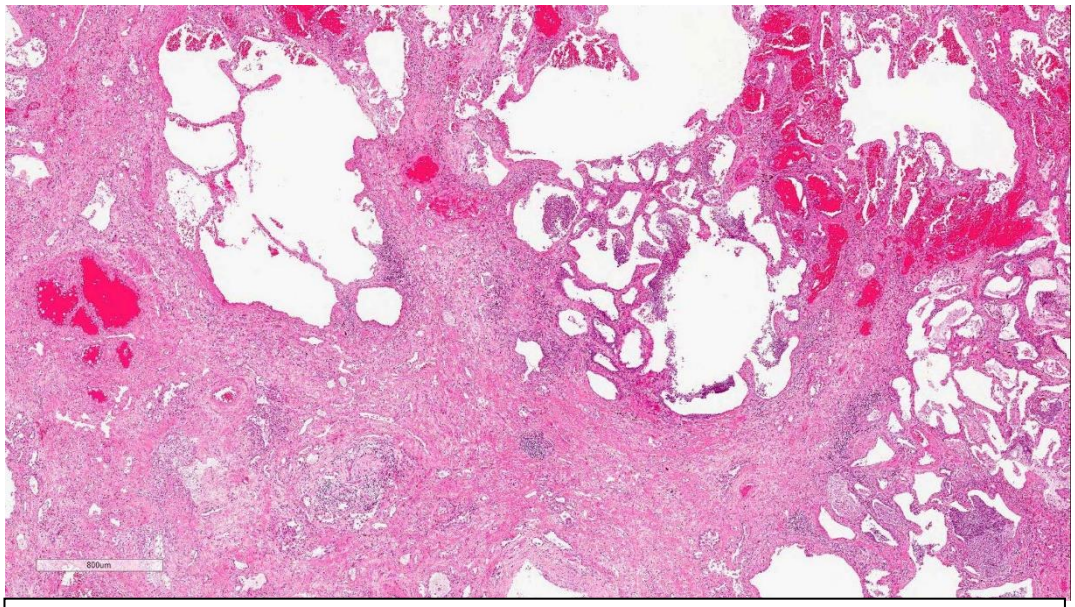

Figure 4: Histological image of thick, dense, collagen-rich alveolar walls during fibrotic phase of ARDS (Yoshikawa and Bychkov, 2022).

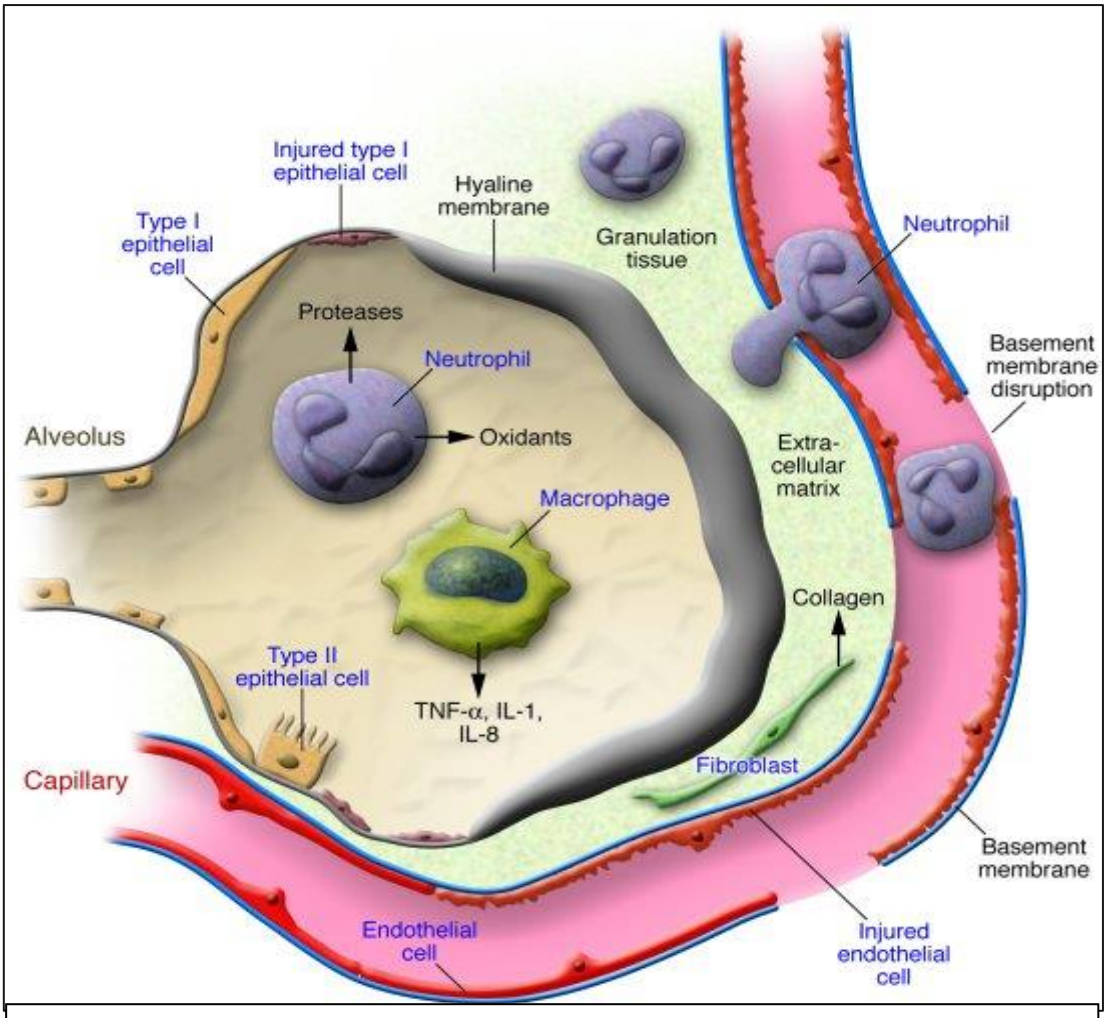

Figure 5: Diagram representing infiltration of cytokines and inflammatory cells into lung interstitium to repair damaged endothelium.

Covid-19 and sepsis-induced ARDS

Sepsis is caused by an excessive inflammatory response to infectious pathogens, in which the body's immune response induces further damage to cells, tissues and organs. Accordingly, viral proteins from SARS-CoV-2 introduce the infectious condition known as covid-19, in which septic shock and multiple organ failure may arise in response to the damaging and excessive pro-inflammatory cascade of cytokines entering the bloodstream. ARDS is diagnosed in 42% of patients experiencing covid-19 as the individual meets the Berlin 2012 ARDS diagnostic criteria (Gibson, Qin and Puah, 2020).

Clinical Symptoms of ARDS

The clinical hallmarks that characterise ARDS as a result of disrupted gas exchange include tachypnoea, hypoxemia and hypoxia. Accordingly, Proteinaceous fluid flooding into the elastic alveoli within the lungs occupies the parenchyma and prevents the organ from filling with air, depriving the bloodstream of receiving enough oxygen and manifesting into hypoxemia (Mayo Clinic. 2020). Hypoxemia may induce hypoxia, a condition in which oxygen fails to reach tissues to support necessary organ functions, thus increasing the respiratory rate of the patient in which they will experience rapid and shallow breathing. (Brinkman JE, Toro F, Sharma S.)

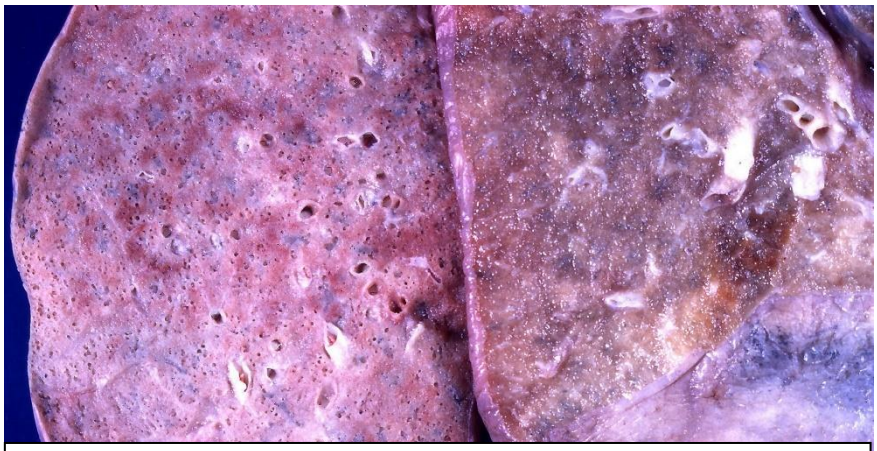

Figure 6: Specimen on left represents pale zones of diffuse alveolar damage whereas the specimen on the right shows no abnormality (Yoshikawa and Bychkov, 2022).

Effect of Arterial PO2 and PCO2 on Cerebral Blood flow

Central and peripheral chemoreceptors within the lungs recognise the inefficient gas exchange in response to hypoxemia and hypoxia, in which they transmit sensory signals to the brain to stimulate respiratory drive. Accordingly, carotid and aortic bodies are peripheral chemoreceptors that monitor arterial blood oxygen and carbon dioxide levels. Aortic bodies are located within the aortic arch and transmit signals via the vagus nerve to the brain whereas carotid bodies are located at the carotid sinus at the burification of the common carotid arteries in which they convey signals via the glossopharyngeal nerve (Brinkman JE, Toro F, Sharma S.). Hypoxic ventilatory depression in response to the lack of oxygen supplying bodily tissues

varies in severity based on the intensity of Co2 partial pressure, specifically the processes of hypocapnia and acidosis. Accordingly, a low hypocapnia state characterised by the decrease in alveolar carbon dioxide results in a non-existent ventilatory response to hypoxia. However, a high hypercapnia state accompanied by metabolic acidosis causes an increase in the sensitivity of the peripheral mechanoreceptors, stimulating a hypoxic ventilatory response.

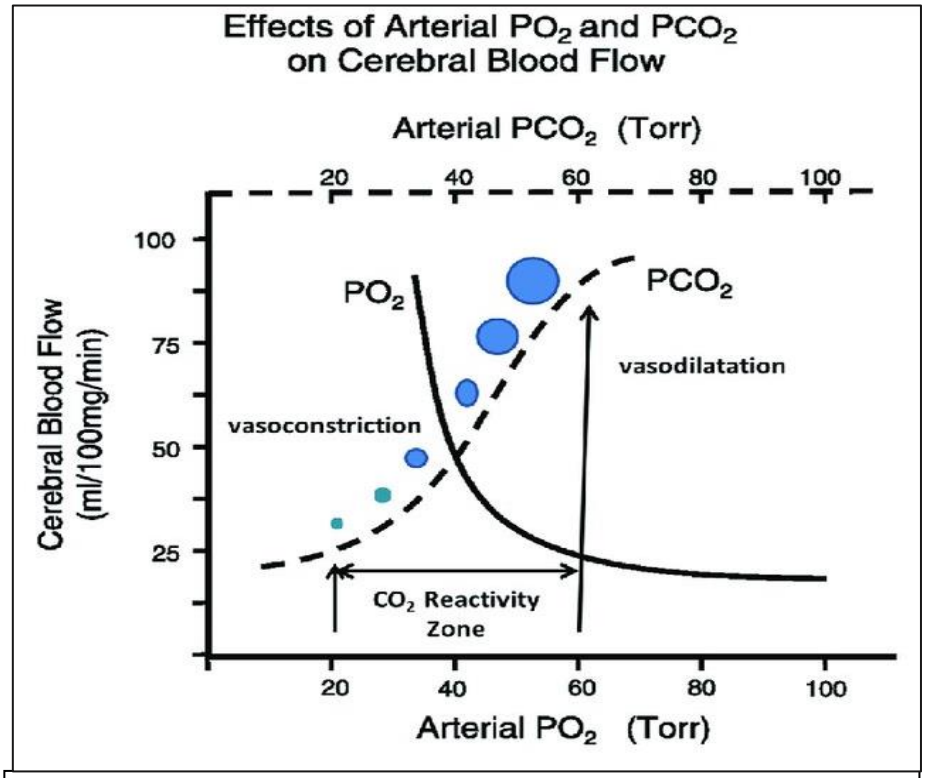

Figure 7: Graphical representation of effects of arterial partial pressure of oxygen (PO2) and partial pressure of carbon dioxide (PCO2) on cerebral blood flow (Godoy D, Seifi A, Garza D, et al.)

Furthermore, central chemoreceptors located within the retrotrapezoid nucleus below the medulla ventrolateral surface adopt a dissimilar response to a drop in arterial PCO2 and a high hypocapnia state, in which they sense the alkalotic pH state of the cerebrospinal fluid that results from the decrease of H+ ions in the bloodstream and transmit sensory input signals through the afferent vagus nerve to the brainstem, stimulating hypoventilation. Contrastingly, high levels of Co2 increase the concentration of H+ ions within the bloodstream, stimulating a

state of acidosis within the cerebrospinal fluid that is recognised by the central chemoreceptors, inducing hyperventilation. (Patel S, Miao JH, Yetiskul E, et al).

ARDS: Cerebral Hypoperfusion and Delirium

ARDS has been associated with inducing neuronal injury following the hyperinflammatory cytokine release during the exudative phase of the disease progression. Accordingly, a 1996 clinical trial published in the European respiratory journal conducted by H Schutte discovered significantly increased concentrations of inflammatory cytokines IL-8, IL-6, and TNF-α within the bronchoalveolar lavage (BAL) fluid of patients diagnosed with severe ARDS, cytokines released by adipocytes that stimulate the production of the highly inflammatory C-reactive plasma protein. ((Schütte et al., 1996))

The pathogenesis of ARDS following a Covid-19 diagnosis is enhanced following the expression of pattern recognition receptors (PRRs) upon pulmonary epithelial cells that recognise damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), activating transcription factor Nuclear factor-kappa B (NF-*κ*B) as varying stimuli stimulate multi-subunit IκB kinase (IKK) to phosphorylate IκBα, inducing degradation within the proteasome to prompt nuclear translocation of NF-κB (Liu, Zhang, Joo and Sun, 2017). As a result, NF-*κ*B stimulates the gene expression of varying pro-inflammatory cytokines including interleukins IL-1*α*, IL-1β, IL-6, IL-2, IL-8, IL-10, and TNF-α, to activate natural killer (NK) cells, macrophages and basophils, inducing their arrival to the site of lung endothelial injury (Bauer, 2000). Furthermore, the gene transcription of inflammatory IFN-*γ*, TNF and Th1 cells induces a state of cytotoxicity in which they release granulocyte colony-stimulating factors (GCSF) and Granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate $CD14^+$ and $CD16^+$ monocytes into the bloodstream. The high concentration of circulating cytokines lingering in the bloodstream further induces the proliferation of

endothelial cells and smooth muscle cells of the vascular lining by growth factors including PDGF and VEGF (Chen et al., 2021). The 2014 in vivo trial conducted by Dr Brian P. Daniels discovered enhanced blood-brain barrier permeability accompanied with the disrupted tight junction functioning within mice infected with the West Nile Virus as a result of attenuated type 1 interferon (IFN-I) signalling (Daniels et al., 2014**).**

Therefore, the direct transport of cytokines across the blood-brain barrier into the cerebrospinal fluid is linked to activating astrocytes and microglia to further recruit chemical mediators of

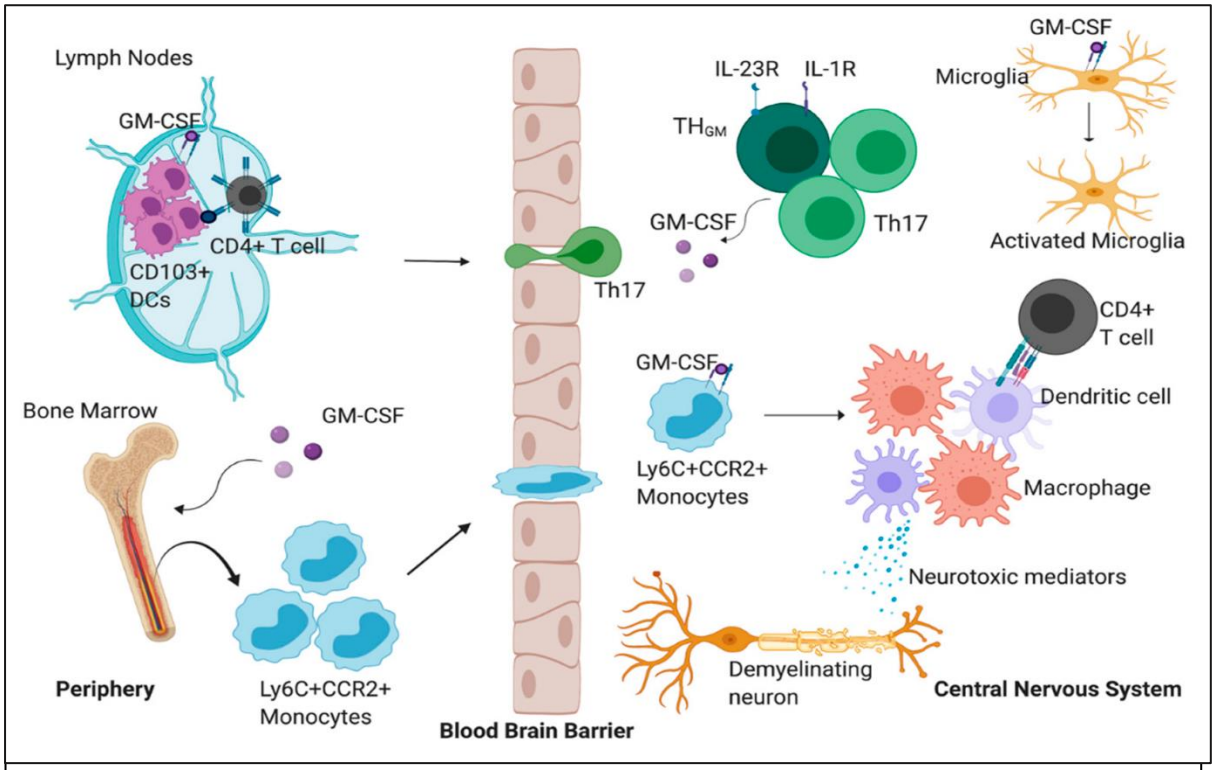

Figure 8: Diagram representing granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulate $CD14^+$ and $CD16^+$ and other pro-inflammatory cells to enter bloodstream in order to cross blood brain barrier, activating microglia. (Monaghan and Wan, 2020)

inflammation such as glutamate and quinolinic acid, in which N-methyl-D-aspartate (NMDA) receptors adopt a state of hypofunction following up-regulation (Boldrini, Canoll and Klein, 2021). Therefore, neuronal damage results from excitotoxic brain injury, altered memory and learning functions and disrupted neuroplasticity (Albaiceta et al., 2021).

Accordingly, a 2006 clinical investigation conducted by Ramona Hopkins underwent an observational cohort study in which 15 patients of 66 total patients diagnosed with ARDS received a brain CT, in which it was discovered that 53% of the subjects had significant brain atrophy, neurological damage and ventricular enlargement. Therefore, it is essential to recognise the devastating effects of losing respiratory function in response to lung endothelial damage or viral antigens of SARS-CoV-2 upon cognitive function (Hopkins, Gale and Weaver, 2006).

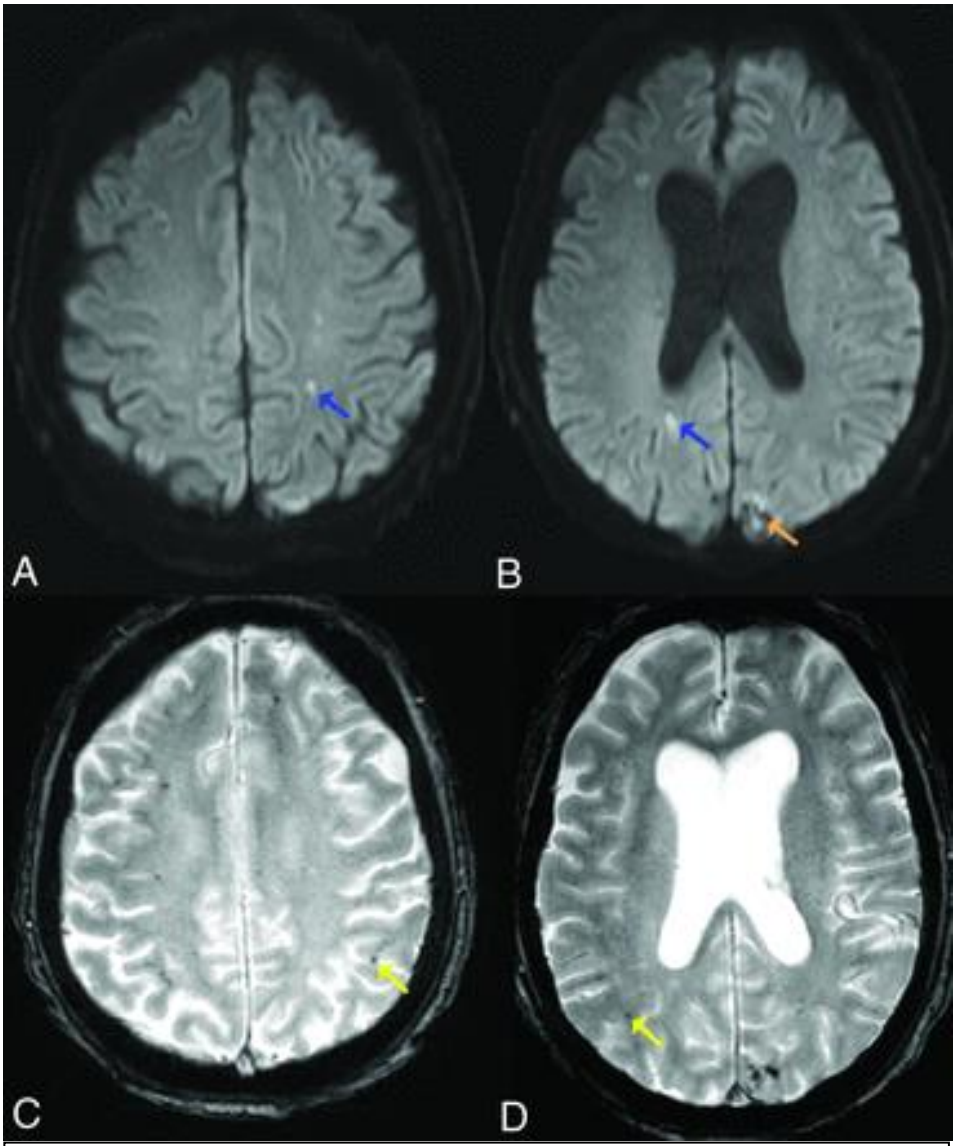

Figure 9: Axial CT (A,B) and gradient-echo scan (C, D) of 61-year-old man with Covid-19. The blue arrows reveal localised region of dead tissue in the cerebral white matter whereas the orange arrows indicate haemorrhagic and dead tissue in the left occipital region. Yellow arrow reveals further haemorrhagic within cerebral hemisphere (Gulko et al., 2020).

Bibliography

Kamuf, J., Garcia Bardon, A., Ziebart, A., Ruemmler, R., Schwab, J., Dib, M., Daiber, A., Thal, S. and Hartmann, E., 2021. Influence of rosuvastatin treatment on cerebral inflammation and nitro-oxidative stress in experimental lung injury in pigs. BMC Anesthesiology, [online] 21(1). Available at: <https://bmcanesthesiol.biomedcentral.com/articles/10.1186/s12871-021-01436-0#citeas> [Accessed 27 May 2022].

National Institute for Health and Care Research, 2018. Statins are of no benefit in acute respiratory distress syndrome. [online] Available at: <https://evidence.nihr.ac.uk/alert/statins-are-of-no-benefit-in-acute-respiratory-distress-syndrome/> [Accessed 27 May 2022].

Diamond M, Peniston HL, Sanghavi D, et al. Acute Respiratory Distress Syndrome. [Updated 2022 Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK436002/

Saguil, A., 2012. Acute Respiratory Distress Syndrome: Diagnosis and Management. American Family Physician, [online] 85(4). Available at: <https://www.aafp.org/afp/2012/0215/afp20120215p352.pdf> [Accessed 27 May 2022].

Gibson, P., Qin, L. and Puah, S., 2020. <scp>COVID</scp> -19 acute respiratory distress syndrome (<scp>ARDS</scp>): clinical features and differences from typical pre- <scp>COVID</scp> -19 <scp>ARDS</scp>. Medical Journal of Australia, [online] 213(2), p.54. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361309/#:~:text=ARDS%20is%20underdiagnosed%20in%20intensive,of%20those%20requiring%20intensive%20care> [Accessed 27 May 2022].

Gonzales, J. N., Lucas, R., & Verin, A. D. (2015). The Acute Respiratory Distress Syndrome: Mechanisms and Perspective Therapeutic Approaches. Austin journal of vascular medicine, [online] 2(1), 1009. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4786180/

Diamond M, Peniston HL, Sanghavi D, et al. Acute Respiratory Distress Syndrome. [Updated 2022 Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK436002/

Gonzales, J. and Verin, A., 2018. Pulmonary Vascular Endothelial Cells. Endothelial Dysfunction - Old Concepts and New Challenges, [online] Available at: <https://www.intechopen.com/chapters/61198> [Accessed 27 May 2022].

Millar, F., Summers, C., Griffiths, M., Toshner, M. and Proudfoot, A., 2016. The pulmonary endothelium in acute respiratory distress syndrome: insights and therapeutic opportunities. Thorax, [online] 71(5), pp.462-473. Available at: <https://thorax.bmj.com/content/71/5/462> [Accessed 27 May 2022].

Spadaro, S., Park, M., Turrini, C., Tunstall, T., Thwaites, R., Mauri, T., Ragazzi, R., Ruggeri, P., Hansel, T., Caramori, G. and Volta, C., 2019. Biomarkers for Acute Respiratory Distress syndrome and prospects for personalised medicine. Journal of Inflammation, [online] 16(1). Available at: <https://journal-inflammation.biomedcentral.com/articles/10.1186/s12950-018-0202-y> [Accessed 27 May 2022].

Yoshikawa, A. and Bychkov, A., 2022. ARDS / DAD. [online] Pathologyoutlines.com. Available at: <https://www.pathologyoutlines.com/topic/lungnontumordiffusealveolardamage.html> [Accessed 27 May 2022].

Gibson, P., Qin, L. and Puah, S., 2020. <scp>COVID</scp> -19 acute respiratory distress syndrome (<scp>ARDS</scp>): clinical features and differences from typical pre- <scp>COVID</scp> -19 <scp>ARDS</scp>. Medical Journal of Australia, [online] 213(2), p.54. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361309/#:~:text=ARDS%20is%20underdiagnosed%20in%20intensive,of%20those%20requiring%20intensive%20care> [Accessed 27 May 2022].

Mayo Clinic. 2020. ARDS - Symptoms and causes. [online] Available at: <https://www.mayoclinic.org/diseases-conditions/ards/symptoms-causes/syc-20355576> [Accessed 27 May 2022].

Brinkman JE, Toro F, Sharma S. Physiology, Respiratory Drive. [Updated 2022 Apr 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482414/

Godoy D, Seifi A, Garza D, Lubillo-Montenegro S, Murillo-Cabezas F. (2017). Hyperventilation Therapy for Control of Posttraumatic Intracranial Hypertension. Frontiers in Neurology. 8. 10.3389/fneur.2017.00250 [Accessed 27 May 2022].

Patel S, Miao JH, Yetiskul E, et al. Physiology, Carbon Dioxide Retention. [Updated 2022 Jan 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482456/

Schütte, H., Lohmeyer, J., Rosseau, S., Ziegler, S., Siebert, C., Kielisch, H., Pralle, H., Grimminger, F., Morr, H. and Seeger, W., 1996. Bronchoalveolar and systemic cytokine profiles in patients with ARDS, severe pneumonia and cardiogenic pulmonary oedema. European Respiratory Journal, [online] 9(9), pp.1858-1867. Available at: <https://erj.ersjournals.com/content/9/9/1858?ijkey=2581da16fa1956454e4d17432214398988305b30&keytype2=tf_ipsecsha> [Accessed 27 May 2022].

Bauer, T., 2000. Comparison of systemic cytokine levels in patients with acute respiratory distress syndrome, severe pneumonia, and controls. Thorax, [online] 55(1), pp.46-52. Available at: <https://thorax.bmj.com/content/55/1/46> [Accessed 27 May 2022].

Daniels, B., Holman, D., Cruz-Orengo, L., Jujjavarapu, H., Durrant, D. and Klein, R., 2014. Viral Pathogen-Associated Molecular Patterns Regulate Blood-Brain Barrier Integrity via Competing Innate Cytokine Signals. mBio, [online] 5(5). Available at: <https://pubmed.ncbi.nlm.nih.gov/25161189/> [Accessed 27 May 2022].

Boldrini, M., Canoll, P. and Klein, R., 2021. How COVID-19 Affects the Brain. JAMA Psychiatry, [online] 78(6), p.682. Available at: <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2778090> [Accessed 27 May 2022].

Albaiceta, G., Brochard, L., Dos Santos, C., Fernández, R., Georgopoulos, D., Girard, T., Jubran, A., López-Aguilar, J., Mancebo, J., Pelosi, P., Skrobik, Y., Thille, A., Wilcox, M. and Blanch, L., 2021. The central nervous system during lung injury and mechanical ventilation: a narrative review. British

Journal of Anaesthesia, [online] 127(4), pp.648-659. Available at: <https://www.bjanaesthesia.org/article/S0007-0912(21)00434-7/fulltext> [Accessed 27 May 2022].

Liu, T., Zhang, L., Joo, D. and Sun, S., 2017. NF-κB signaling in inflammation. Signal Transduction and Targeted Therapy, [online] 2(1). Available at: <https://www.nature.com/articles/sigtrans201723#citeas> [Accessed 27 May 2022].

Minamino, T. and Komuro, I., 2006. Regeneration of the endothelium as a novel therapeutic strategy for acute lung injury. Journal of Clinical Investigation, 116(9), pp.2316-2319.

Monaghan, K. and Wan, E., 2020. The Role of Granulocyte-Macrophage Colony-Stimulating Factor in Murine Models of Multiple Sclerosis. *Cells*, [online] 9(3), p.611. Available at: <https://www.mdpi.com/2073-4409/9/3/611/htm> [Accessed 27 May 2022].

Hopkins, R., Gale, S. and Weaver, L., 2006. Brain atrophy and cognitive impairment in survivors of acute respiratory distress syndrome. Brain Injury, 20(3), pp.263-271.

Gulko, E., Oleksk, M., Gomes, W., Ali, S., Mehta, H., Overby, P., Al-Mufti, F. and Rozenshtein, A., 2020. MRI Brain Findings in 126 Patients with COVID-19: Initial Observations from a Descriptive Literature Review. American Journal of Neuroradiology, 41(12), pp.2199-2203.