The authors describe molecular pathways involved in the immune response to COVID-19, focusing on the cytokine response. In some patients, this inflammatory response results in cardiac injury, as manifested by elevated levels of circulating cardiac biomarkers. Troponin release in COVID-19 patients with underlying cardiovascular risk factors has been shown to be highly predictive of requirement for intensive care unit admission, mechanical ventilation, and death.[4] Although the cytokine response is the host's ammunition against the virus, the inflammatory response that ensues may result in collateral damage to host tissues and organs.

Understanding the molecular pathways involved in COVID-19 pathogenesis is critical for the development of diagnostic and therapeutic tools. As the authors explain, the virus has been sequenced and its nonstructural and structural proteins have been described. Some of these will likely be targets for a vaccine in the future. Yet with more than 6 million confirmed cases and 370,000 deaths as of June 1, 2020,[5] we remain in dire need of therapeutics for the disease. It is likely that insight into the basic science of COVID-19 will translate into treatment options in the future.

References

1. Krumholz H. Where have all the heart attacks gone? *The New York Times*. April 6, 2020.
2. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol*. March 27, 2020 [Epub ahead of print].
3. Thankam FG, Agrawal DK. Molecular chronicles of cytokine burst in patients with coronavirus disease 2019 (COVID-19) with cardiovascular diseases. *J Thorac Cardiovasc Surg*. 2021;161:e217-26.
4. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. March 27, 2020 [Epub ahead of print].
5. World Health Organization coronavirus disease 2019 (COVID-19) dashboard. Available at: https://covid19.who.int/. Accessed June 1, 2020.

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Commentary: Evolving understanding of coronavirus disease 2019: Molecular biology, immunology, and surgery

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CENTRAL MESSAGE

Understanding molecular mechanisms of COVID-19 disease is crucial for cardiothoracic surgeons.

The global pandemic of coronavirus disease 2019 (COVID-19) has major implications for cardiothoracic surgeons. It has influenced all aspects of our lives. Resources that previously seemed unlimited have become scarce. The COVID-19 pandemic has not only resulted in dramatically increased need for urgent mechanical cardiorespiratory support in the epicentres of disease outbreaks but also put significant pressure on perioperative management of patients—ranging from congenital heart disease to organ transplantation—everywhere in the world. Thus, the

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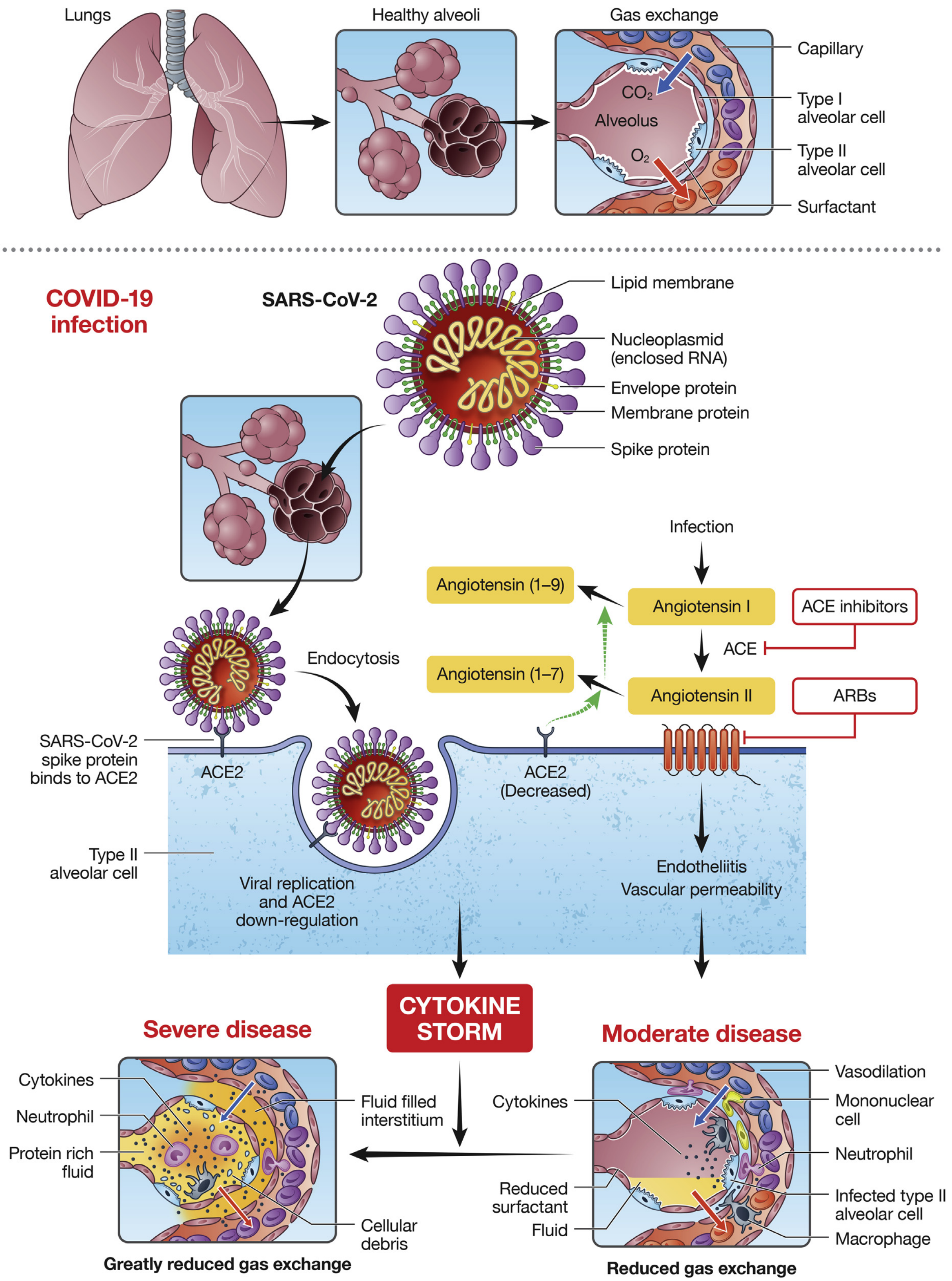

FIGURE 1. Pathophysiology of coronavirus 2019 (*COVID-19*) disease. Coronavirus enters cells by binding to angiotensin-converting enzyme 2 (*ACE2*). Resultant decreased ACE2 availability translates into activation of the angiotensin signaling that causes increased vascular permeability, which, in its turn, facilitates extravasation of mononuclear cells and neutrophils leading to a generalized endotheliitis in response to ongoing viral infection. A cytokine storm in susceptible individuals contributes to further progression of diseases from moderate to severe. *CO_2*, Carbon dioxide; *O_2*, oxygen; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2; *ARB*, angiotensin receptor blocker.

importance of mechanistic understanding of the molecular and cellular pathophysiology of COVID-19 disease cannot be overemphasized. In this context, Thankam and Agrawal[1] explored the mechanistic basis of COVID-19 disease. Their comprehensive review focuses on the interaction between COVID-19 infection, cardiovascular disease, and the angiotensin signaling pathway. Coronavirus binds to the angiotensin converting enzyme (ACE) 2 molecule and enters cells where it triggers a series of signaling pathways (Figure 1). Decrease in ACE2, an enzyme with its own anti-inflammatory effect, appears to unbalance the angiotensin system. Excessive angiotensin pathway stimulation increases vascular permeability and as such, contributes to mononuclear cell and neutrophil extravasation as well as generalized endotheliitis.[2] The frequently used cardiovascular drugs, ACE inhibitors, and angiotensin receptor blockers interact in the angiotensin pathway, but their effect, if any, on disease progression remains unclear. A cytokine storm caused by viral infection in susceptible patients results in rapid disease progression from mild or moderate to severe.

Among the most intriguing aspects of COVID-19's viral interaction with the immune system is an exceptionally low rate of severe disease in children, a seemingly most-vulnerable population. Emerging evidence suggests this may be related to important differences in immune response in children compared with adults, in particular in the circulating levels of T-regulatory cells and interleukin-17 producing T-helper cells.[3] Despite the paucity of severe respiratory disease in the vast majority of children, an outbreak of severe Kawasaki-like disease in children has been reported from the Italian epicenter of COVID-19 infection.[4] Thus, generalized virus-induced endotheliitis combined with immature immune response in children may result in similar outbreaks of Kawasaki-like disease in the countries influenced by COVID-19 epidemics.[4]

The role of extracorporeal life support (ECLS) in patients with severe adult respiratory distress syndrome was established following a landmark randomized controlled trial and reinforced through experience in supporting patients with adult respiratory distress syndrome in the influenza pandemic of 2009.[5,6] Early reports of ECLS for patients with COVID-19 demonstrate 30% to 50% mortality rates and prolonged duration of support, with many patients still remaining on ECLS at the time of publication.[7,8] The Extracoporeal Life Support Organization has provided guidance on the use of ECLS to support COVID-19 patients.[9]

Heart and lung transplantation in context of a global pandemic poses a special set of challenges due to the substantial resource consumption and the additive risk of COVID-19 infection to immunosuppressed patients. The International Society of Heart and Lung Transplantation suggests that heart and lung transplantation services should focus on those patients in most urgent need to fulfill our obligation to provide transplant to candidates while maintaining capacity for COVID-19 patients.[10] As expected, the initial reports of COVID-19 infection in solid organ transplantation recipients demonstrated higher mortality rates compared with the general population,[11] an important consideration for patients awaiting transplantation.

The late sequelae of COVID-19 infection are not yet fully appreciated. The acute cytokine storm and endotheliitis seen at the time of infection may result in accelerated cardiovascular disease. For instance, outbreaks of Kawasaki-like disease may cause coronary aneurysm, which necessitates coronary artery bypass in childhood. Time will tell. The COVID-19 pandemic is not over. A thorough understanding of the mechanism of COVID-19 will make us prepared for whatever comes.

References

1. Thankam FG, Agrawal DK. Molecular chronicles of cytokine burst in patients with coronavirus disease 2019 (COVID-19) with cardiovascular diseases. *J Thorac Cardiovasc Surg*. 2021;161:e217-26.
2. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020; 395:1417-8.
3. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol*. 2010;40:1830-5.
4. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395: 1771-8.
5. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374:1351-63.
6. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Bailey M, Beca J, Bellomo R, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302:1888-95.
7. Jacobs JP, Stammers AH, St Louis J, Hayanga JWA, Firstenberg MS, Mongero LB, et al. Extracorporeal membrane oxygenation in the treatment of severe pulmonary and cardiac compromise in COVID-19: experience with 32 patients. *ASAIO J*. 2020;66:722-30.
8. Li X, Guo Z, Li B, Zhang X, Tian R, Wu W, et al. Extracorporeal membrane oxygenation for coronavirus disease 2019 in Shanghai, China. *ASAIO J*. 2020; 66:475-81.
9. Bartlett RH, Ogino MT, Brodie D, McMullan DM, Lorusso R, MacLaren G, et al. Initial ELSO guidance document: ECMO for COVID-19 patients with severe cardiopulmonary failure. *ASAIO J*. 2020;66:472-4.
10. Holm AM, Mehra MR, Courtwright A, Teutebrg MD, Sweet S, Potena L, et al. Ethical considerations regarding heart and lung transplantation and mechanical circulatory support during the COVID-19 pandemic: an ISHLT COVID-19 task force statement. *J Heart Lung Trans*. April 25, 2020 [Epub ahead of print].
11. Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. *Am J Transplant*. 2020;20:1800-8.