Obesity and COVID-19: A Virchow's Triad for the 21st Century

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-strand β-RNA virus which causes coronavirus disease-2019 (COVID-19).[1] The majority of infected subjects remain asymptomatic or experience mild disease but many require hospitalization including intensive care admission and have substantial morbidity and mortality.[2]

Early COVID-19 characterization identified significant numbers of (often younger) patients without significant pre-existing medical disorders that developed a severe clinical phenotype characterized by rapid cardiorespiratory deterioration that was attributed to a "cytokine storm."[3] This hyperinflammatory syndrome with high mortality and apparent stochastic nature has been particularly alarming to clinicians and remains incompletely understood.

Recent reports have also highlighted that many younger subjects hospitalized with COVID-19 are overweight. In a large series of 5,700 patients hospitalized in New York, the rate of mechanical ventilation was 12.2% and the death rate of those ventilated was 88%. The overall rate of obesity in this series was 41%.[4] Obesity is associated with well-recognized deleterious effects on pulmonary mechanics and ventilation including lower lung volumes, lower respiratory muscle strength, and impaired gas exchange.[5] Strategies that have been adopted to overcome these anomalies and improve oxygenation include prone ventilation. In other types of pneumonia, including acute respiratory distress syndrome (ARDS), an "obesity paradox" has been previously observed where the risk of death is decreased in those with higher body mass index.[6] The mechanisms responsible for this paradox are speculative but its existence contrasts with the severity of COVID-19 respiratory failure where precipitous decline in clinical course of a subset of critically ill patients with COVID-19 cannot be explained by deterioration in pulmonary parameters alone.

A minority of COVID-19 patients evolve a rapid inflammatory syndrome with an ARDS-like clinical phenotype (~30%)[7] and multiorgan failure approximately 8 to 9 days after symptom onset.[8] In a second shunt phenotype (>60%) patients show well-preserved lung mechanics but severe hypoxia, high respiratory compliance, and high shunt fraction.[7] While direct lung injury due to SARS-CoV-2 infection plays a central role in the pathophysiology of all COVID-19 patients, it does not explain the differential severity of the disease between lean and overweight subjects, nor the profound mismatch between hypoxia and ventilatory compromise in some patients. Disease severity is significantly mediated by multifaceted host responses and obesity may be one "hidden driver" of the heterogeneous host response and hyperinflammatory COVID-19. We posit that adipose tissue acts as a powerful inflammatory reservoir for SARS-CoV-2 viral replication in overweight subjects with more adipose tissue generating a larger inflammatory response than in lean subjects.[9] This inflammatory disorder in subjects with obesity may drive heterogeneity in vascular injury,[10] in situ thrombosis events, and thromboembolic complications in the systemic[11] and pulmonary vascular system (►**Fig. 1**).[12]

SARS-CoV-2 enters human cells by binding to the angiotensin-converting enzyme 2 (ACE2) on the plasma membrane,[13] which is widely expressed in lung alveolar cells, cardiomyocytes, and vascular endothelium.[14] ACE2 is also expressed in adipocytes, smooth muscle cells, and myofibroblasts, and its expression has been found to be significantly upregulated in obesity.[15] Enhanced ACE2-mediated viral access and replication in local organ adipose tissue very likely leads to significant paracrine/endocrine elaboration of proinflammatory cytokines and adipokines that mediate inflammation in COVID-19.[9] This activation may include inter alia elements of the complement system[16,17] and an unbalanced renin–angiotensin system (RAS), whereby RAS is activated and the counterregulatory ACE2/MAS receptor system is downregulated.[18] Patients with severe COVID-19 show higher plasma levels of interleukin (IL)-2, IL-6, and IL-7, with IL-6 being an independent predictor

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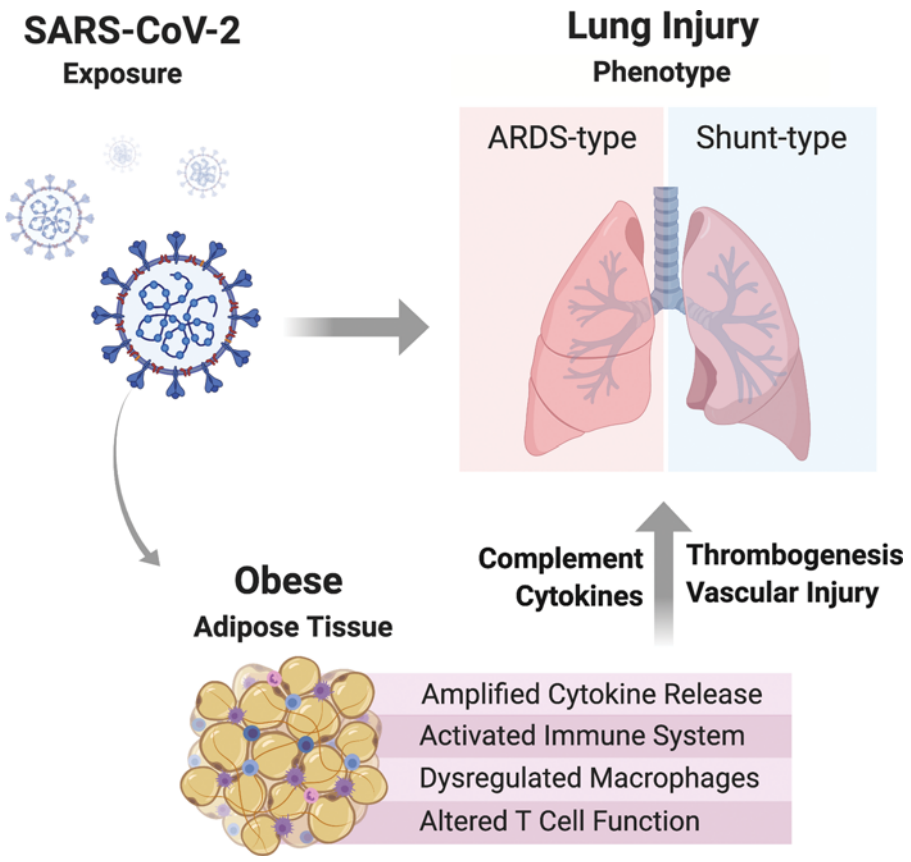

Fig. 1 Schematic of direct and indirect effects of SARS-CoV-2 manifesting two phenotypes of lung injury.[1,2,7,8] Hyperimmune adipose tissue in subjects with obesity may contribute to increased activation of inflammatory cells, cytokines,[3] complement,[17] local and systemic coagulation,[11,12] and vascular injury.[19] ARDS, acute respiratory distress syndrome.

of mortality.[2,3] Inflammatory cytokines released from visceral and perivascular adipose tissue include IL-6, IL-2, granulocyte colony-stimulating factor, interferon-γ, monocyte chemotactic protein-1, and tumor necrosis factor-α, and these same cytokines are primarily responsible for recruitment of monocytes and T-lymphocytes to infected and inflamed organs.[9] Magro et al recently reported COVID-19 pneumonitis without classic ARDS features including complement activation, septal capillary injury, and mural and luminal fibrin deposition, in addition to neutrophil infiltration.[17] Moreover numerous emerging studies indicate COVID-19 association with elements of disseminated intravascular coagulation[17] and regional pulmonary intravascular coagulopathy.[12] Activation of the immune,[19] complement,[16] and coagulation[20] systems already exists in obesity and may contribute to augmented tissue injury seen in organs directly impacted by SARS-CoV-2 tissue damage, such as the lungs (►**Fig. 1**).

Furthermore, SARS-CoV-2-mediated inflammation via these pathways may occur in other "pockets" of adipose tissue in the heart, kidney, liver, and vasculature, explaining some of the more unexpected clinical phenomena seen in younger subjects with COVID-19, such as stroke, acute kidney injury, and apparent myocardial infarction.[21] Cases of ST-elevation myocardial infarction (STEMI) without demonstrable coronary occlusion have been widely reported and remain unexplained.[22] These "STEMIs" have been speculated to represent SARS-CoV-2 myocarditis or acute coronary syndrome secondary to sepsis or hypoxia. It is also conceivable that lung-associated SARS-CoV-2-mediated inflammation of epicardial white adipose tissue may masquerade as a STEMI with the epicardium and adjacent adipose tissue known to share a common microcirculation.

Beyond local effects, systemic release of inflammatory cytokines/adipokines from adipose tissue may promote a Virchow's triad of events including vascular thrombosis, endothelial dysfunction, and blood flow stasis through reactive oxygen species and vasoconstriction (►**Fig. 2**). Such an inflammatory thrombogenic vasculopathy may in part explain the precipitous multiorgan failure and also the variability of clinical course and treatment response in some patients.

The role of obesity and the potentially deleterious impact of adipose tissue in COVID-19 warrant significant worldwide attention. Recognition of enhanced risk in overweight subjects should be at the forefront of clinical decision-making in COVID-19. Stratification based on traditional risk scores (APACHE, SAPS, SOFA, and MPM), lung injury phenotype, and circulating inflammatory markers, such as soluble urokinase plasminogen activator receptor (suPAR), known to be elevated in obesity at baseline and to predict poorer clinical course in COVID-19, may guide earlier intervention in these groups.[10] In parallel we need to gain a deeper understanding of the biology of inflammation and thrombotic vasculopathy in these patients, in particular how adipose tissue plays a role in this aspect of disease amplification. While awaiting successful vaccines, preemptive strategies to lessen the severity of the

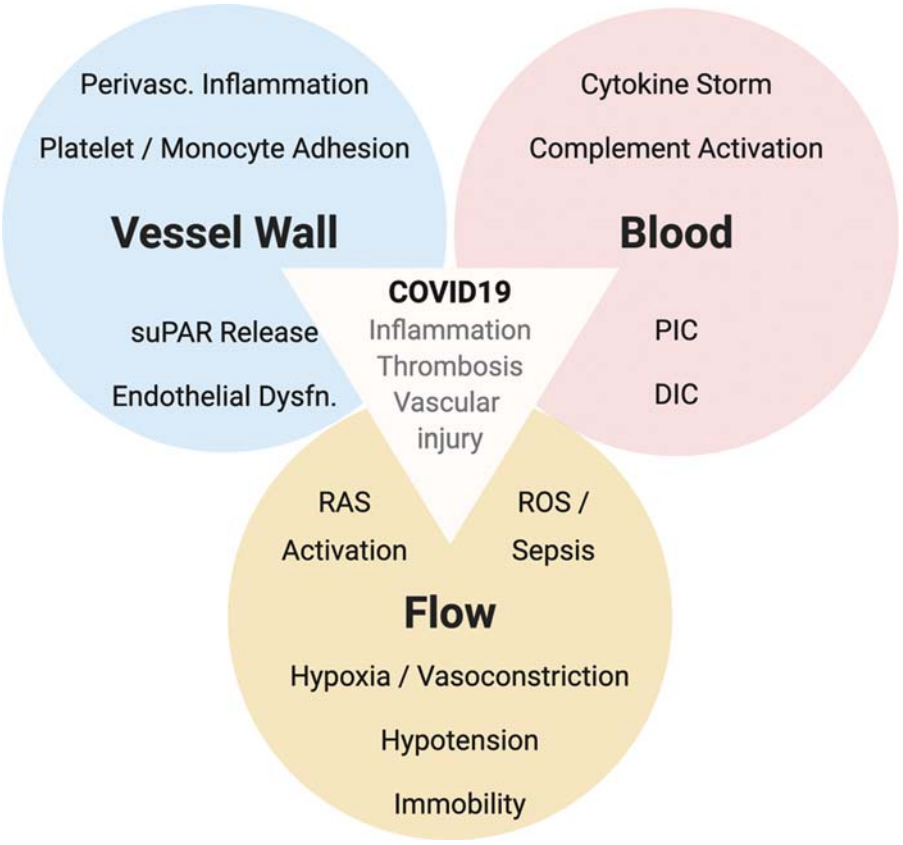

Fig. 2 Virchow's triad revisited. Potential for multiorgan involvement in COVID-19 with heterogeneous presentation depending on predominance of sepsis, inflammation,[3] coagulation,[11,12,17] hypoperfusion,[9,10] or vasculopathy.[10,17,21] DIC, disseminated intravascular coagulation; PIC, pulmonary intravascular coagulation; RAS, renin–angiotensin system; ROS, reactive oxygen species; suPAR, soluble urokinase plasminogen activator receptor.

inflammatory, thrombogenic, and vasculopathic phenotypes in COVID-19 will prove important. These may involve monoclonal antibodies against pivotal cytokines in the inflammatory cascade.[23] In addition, prospective targeting of downstream elements of complement activation (monoclonal antibodies) and thrombophilia (thrombin inhibitors) in obese subjects from a preventive and therapeutic aspect may be useful with clinical trial results of such approaches eagerly awaited.

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Conflict of Interest
None declared.

References

1 Zhu N, Zhang D, Wang W, et al; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(08):727–733
2 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506
3 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–1034
4 Richardson S, Hirsch JS, Narasimhan M, et al; and the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323(20):2052–2059
5 Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med 2018;12(09):755–767
6 Nie W, Zhang Y, Jee SH, Jung KJ, Li B, Xiu Q. Obesity survival paradox in pneumonia: a meta-analysis. BMC Med 2014;12:61
7 Rello J, Storti E, Belliato M, Serrano R. Clinical phenotypes of SARS-CoV-2: implications for clinicians and researchers. Eur Respir J 2020;55(05):2001028
8 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;201(10):1299–1300
9 Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread, immune activation, and cytokine amplification in coronavirus disease 2019? Obesity 2020;28(07):1191–1194
10 Rovina N, Akinosoglou K, Eugen-Olsen J, Hayek S, Reiser J, Giamarellos-Bourboulis EJ. Soluble urokinase plasminogen activator receptor (suPAR) as an early predictor of severe respiratory failure in patients with COVID-19 pneumonia. Crit Care 2020;24(01):187
11 Bikdeli B, Madhavan MV, Jimenez D, et al; Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for

prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(23):2950–2973
12 Fogarty H, Townsend L, Ni Cheallaigh C, et al. More on COVID-19 coagulopathy in Caucasian patients. Br J Haematol 2020;189(06): 1060–1061
13 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(02):271–280
14 Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res 2020;126(10):1456–1474
15 Shoemaker R, Tannock LR, Su W, et al. Adipocyte deficiency of ACE2 increases systolic blood pressures of obese female C57BL/6 mice. Biol Sex Differ 2019;10(01):45
16 Vlaicu SI, Tatomir A, Rus V, et al. The role of complement activation in atherogenesis: the first 40 years. Immunol Res 2016;64(01):1–13
17 Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 2020;220:1–13
18 Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med 2020;382(17): 1653–1659
19 Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest 2017;127(01):1–4
20 Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. Curr Opin Hematol 2013;20(05):437–444
21 Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 2020;382(20):e60
22 Mahmud E, Dauerman HL, Welt FG, et al. Management of acute myocardial infarction during the COVID-19 pandemic. J Am Coll Cardiol 2020. Doi: 10.1016/j.jacc.2020.04.039
23 ClinicalTrials.gov. NCT04322773: Anti-il6 treatment of serious COVID-19 disease with threatening respiratory failure (TOCIVID). 2020; Available at: https://clinicaltrials.gov/ct2/show/NCT04322773. Accessed May 5, 2020