A PERSONAL VIEW

Opportunistc physiology: inserting physiology and pathophysiology content into virtually delivered clinical rotations

Thad E. Wilson, Minal Mulye, and Samina Akbar
Division of Biomedical Sciences, Marian University College of Osteopathic Medicine, Indianapolis, IN

Submitted 16 June 2020; accepted in final form 28 July 2020

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an opportunistic single-stranded RNA virus and the causative agent of COVID-19, has wreaked havoc on human life, daily liberties, our economies, and how we educate students. In this COVID-19 world, clinical medical education involving patient contact has needed to take a less prominent role for the protection of clinical trainees, as well as to direct resources to and focus on the protection and care of patients. Our medical school officially reassigned year 3 and year 4 students from their in-person clinical rotations on March 17, 2020. Fortunately, we had clinical content normally delivered in the summer as part of a colloquium that was restructured for virtual delivery to provide uninterrupted didactics. However, once the extended duration of a virtually delivered medical curriculum owing to COVID-19 was apparent, our major focus was to identify best and most effective ways to continue educating these medical trainees in the absence of traditional clinical rotation settings.

Since most of our medical partners are not directly affiliated with academic health centers or other educational entities, we took this opportunity to capitalize on student interest (1, 2), as well as provide students with information that they could subsequently share with their preceptors and clinical rotation sites. This type of knowledge distribution (i.e., student to practicing physician) is more analogous to an agriculture extension of a large land grant university delivering new techniques to farmers and farmer cooperatives in field settings. Such service-learning experiences (21) should allow for additional recall, integration, and teaching opportunities for the student to solidify learning (3); and 2) provide additional “value” for the clinical host, as it helps health care workers with less exposure to current infectious disease and cellular and molecular physiology concepts to fill in some gaps left due to practice focus. Our solution was to create a public health elective virtual clinical rotation utilizing the COVID-19 pandemic as the underlying health care theme. Although other disorders would not be excluded, the focus would be on the World Health Organization denotation of severe acute respiratory infections, or SARI (9). The SARI classification includes SARS-CoV-2 and can lead to pneumonia, acute respiratory distress syndrome (ARDS), septic shock, systemic inflammation, and multiple-organ dysfunction, including cardiac dysfunction and acute kidney injury (24, 25). This is where opportunistic physiology started to invade the course, to intertwine with the other strands of information, and finally to be expressed in this new course.

Course Design and Structure

We began with defining the learning outcomes and then the physiology learning objectives of the course (Table 1). We decided that this geographically dispersed group of advanced students, who already have the required background knowledge, could work in online small groups such that week 1 of this 2-wk rotation (i.e., clerkship) would be faculty-guided self-study in nature. One principle we applied to the self-study portion was to provide as much guidance as possible, as only experts appear to benefit from partial or no guidance (4). To that end, students were provided with faculty-vetted potential resources, along with both discrete and open-ended focus question for each physiology learning objective. We also utilized an open-source training course on “Mechanical Ventilation for COVID-19,” which was developed for general physicians to step into situations where they would oversee
Table 1. Example learning objectives and focus questions to direct physiology and pathophysiology self-studies

| Learning Objective | Focus Questions |
|--------------------|-----------------|
| Explain why individuals with diabetes mellitus, hypertension, and severe obesity (BMI ≥ 40 kg/m²) are more likely to be infected and are at a higher risk for complications and death from SARS-CoV-2 (COVID-19). | To better appreciate the risk of COVID-19, identify incidence rates of diabetes mellitus, hypertension, and severe obesity (BMI ≥ 40 kg/m²) in the US population. |
| Explain the role of ARDS pathophysiology in SARI. | How does one classify acute respiratory failure, and which type does COVID-19 patients most likely present with? |
| Explain the role of sepsis pathophysiology in SARI. | How do chest X-rays and computer tomography change across early to late phases of ARDS? |
| Explain the role of pneumonia pathophysiology in SARI. | How do interstitial and alveolar edema develop? |
| Describe how COVID-19 can lead to acute renal/kidney injury and cardiac dysfunction. | What are the causes of AKI, and which of these causes is most likely for COVID-19? |

ACE, angiotensin converting enzyme; AKI, acute kidney injury; ANG, angiotensin; ARDS, acute respiratory distress syndrome; BMI, body mass index; FIO₂, fraction of inspired oxygen; FRC, functional residual capacity; ICU, intensive care unit; PaO₂, partial pressure of oxygen in arterial blood; RAA.S, renin-angiotensin-aldosterone system; SARI, severe acute respiratory infections; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO₂, pulse oximetry; TMPRSS2, transmembrane protease, serine 2.

ventilated patients (36). This hybrid (internally and externally generated) content approach forms an interesting union of information between institution-specific needs and strengths, and the expertise of the global community (8). We inserted various discussion points in the form of a handout and developed a formative quiz to emphasize the physiology correlates in addition to the very clinical aspects of mechanical ventilation.

Synchronous online learning was conducted with panel and clinical case studies during week 2 of the virtual rotation. This provided an opportunity for knowledge recall and probing conceptual understanding, both of which are known to improve long-term retention (3). Students received various cases and content to investigate and present the following day, incorporating the knowledge from the previous week whenever possible. We believed structuring the course to include recall, peer teaching, and targeted knowledge expansion would maximize students’ ability to meet our learning outcomes and allow for multiple recall opportunities of the physiology content. Additionally, since the primary focus was clinical and public health related, expert panelists included public health specialists, physicians, and biomedical scientists. The Doctor of Medicine/Doctor of Osteopathic Medicine panelists who participated were actively treating COVID-19 patients in the emergency department, intensive care unit, obstetrics, and primary care (follow-up) settings.

Course Content

Physiology topics on which we were able to expand and directly apply with our COVID-19 focus began with the renin-angiotensin (ANG)-aldosterone system (RAAS). In our pre-clerkship integrated grouped organ system curriculum, students encountered RAAS during the cardiovascular, renal, and endocrine sections. However, this coverage exclusively focused on the ANG-converting enzyme (ACE) isotype that
converts ANG I to ANG II, known as ACE1. SARS-CoV utilizes another isoform of ACE (i.e., ACE2) to bind and facilitate translocation into cells. ACE2 facilitates the conversion of ANG II to ANG-(1–7), and the more minor pathway of ANG I to ANG-(1–9) as substrate and product, respectively (31). Membrane-bound ACE2 is expressed in different parts of the body (e.g., oral and nasal mucosa, gastrointestinal system, immune-related organs, testes, heart, kidney, brain, and lung), with particularly abundant surface expression in type 2 pneumocytes of the lung epithelia (11). The spike proteins of SARS-CoV bind to a non-ANG binding site of ACE2 (22), followed by serine proteases [e.g., transmembrane protease, serine (TMPRSS2) and furin] priming and then cleaving the spike protein S1/S2 domains, which then facilitates endocytosis into the cell (12). Once replicating within a cell, SARS-CoV downregulates expression of ACE2. The upregulation of ACE2 in hypertension and diabetes mellitus patients could be a potential reason for COVID-19 disproportionately affecting these patients (24, 25). Once liberated from endocytic vesicles, the virus then hijacks normal cellular machinery to replicate and then eventually be shed. Because of the prominent role of the respiratory epithelia, this topic allowed many recall opportunities for physiological roles of pulmonary surfactants and the role of pneumocytes in the air-blood interface and gas exchange. It also allowed for integration with the immune responses to COVID-19 (e.g., impaired neutrophil recruitment, macrophage activity, and antigen presentation), thus allowing for a multi-disciplinary and integrated view of the topic.

The ACE2 content allowed for another physiological review of the RAAS pathway, including functional comparisons of the beneficial effects of ANG-(1–7) (via Mas-R signaling) and ANG II (via ANG II type 2 receptor signaling), as well as potential harmful effects of ANG II (via ANG II type 1 receptor signaling) in tissues and organ systems (10, 14, 31). There is currently no cure for COVID-19, and the push for therapeutics is on the forefront for scientists, clinicians, and even political figures. Current recommendations for patients on therapy that involves ACE inhibition or ANG II receptor blockers are to maintain the therapy during COVID-19 but not to start a new course of these agents (7). We were able to have students predict and theorize how agonizing and antagonizing these receptors, as well as up- or downregulating enzyme concentrations, might affect outcomes. We were partially successful in encouraging group discussions related to the following: 1) ACE2 blockade and downregulation; 2) ACE2 upregulation; 3) TMPRSS2 inhibition; and 4) ANG-(1–7) augmentation and Mas-R stimulation. ACE2 blockade and downregulation in theory could reduce SARS-CoV-2 entry but then also decrease tissue protective products ANG-(1–7). TMPRSS2 inhibition may allow continued conversion of ANG II to ANG-(1–7), but yet not virus translocation (13). ANG-(1–7) and Mas-R agonists might be able to retain tissue protective effects of these pathways (17, 33), even if ACE2 was blocked. In this exercise, theoretical combinations of treatments to minimize viral entry and retain tissue protective effects were also encouraged. Using various Bloom’s taxonomy tools (6, 32), this type of prediction and hypothesis generation (i.e., synthesis) is aligned with higher order thinking and appears to aid learning, whether the original prediction/hypothesis was accurate or not (18).

In week 2, the physiology topics on which we expanded and directly applied to COVID-19 discussion focused around various aspects of ARDS treatment and pathophysiology. COVID-19–related hypoxemia was a common case theme; this allowed for the review of the five primary types of hypoxemias (hypoventilation, decrease in fraction of inspired oxygen, diffusional limitation, right-to-left shunt, and ventilation/perfusion inequality) and corresponding physiological mechanisms. The primary reason for hypoxemia in ARDS (and with pneumonia) are altered ventilation-perfusion ratios (35). Because one mechanism of treatment involves placing the patient in the prone position (15, 16), it allowed review of positional (upright, supine, and prone) effects on ventilation and perfusion. Other pulmonary physiology concepts discussed were chemoreflexes, hypoxic vasoconstriction, and both the hypercapnic and hypoxic ventilatory responses. This is especially the case, as many of the presenting physicians discussed “happy hypoxic” patients, who have a low arterial PO2 or pulse oximetry, but are not dyspneic (5). Lung compliance/elastance is a major issue in ARDS, which allowed for recall and review of respiratory mechanics. Finally, with mechanical ventilation being a potential, the cardiovascular effects of mechanical ventilation and additional respiratory mechanics could be reviewed.

The physiology content complemented the immunology content describing the development of a “cytokine storm” in COVID-19 patients. SARS-CoV-2 infection leads to lymphocytopenia, which, coupled with innate immune cell-mediated excessive inflammatory cytokine production, results in a “cytokine storm” (27, 29), subsequently leading to the systemic inflammatory response. This eventually progresses to multiple-organ dysfunction, failure, and mortality in COVID-19 patients (34). In our pre-clerkship curriculum, we use multiple-organ system dysfunction and failure as an integrative physiology teaching tool (30) after respiratory, cardiovascular, hematology, and renal systems presentation. The associated pathophysiology seen in systemic inflammatory response syndromes allows for clinical correlations of organ-to-organ cross talk as we review both physiology and immunology concepts that were presented in sepsis and septic shock (20).

Instructor Reflections

We received very positive feedback from the students and adjunct clinicians regarding both format and content. The students showed enthusiasm and interest in discussing various aspects of COVID-19. Having clinicians and basic scientists present during these discussions proved beneficial to emphasize the importance of basic science knowledge in making clinical choices or decisions. Traditionally in medical education, we teach what is known and vetted (i.e., we often wait for scientific verification before teaching material to professional school learners). This approach was not possible with SARS-CoV-2 and COVID-19, as new information is being published daily. This information overload can feel chaotic to an educator. There is even a term for this, “infodemic,” which is an overabundance of information (with accuracy to be determined later) that occurs during an epidemic or pandemic (19, 26). One piece of advice from Kevin Patton that we found useful is that there are no “inside-the-box” or “outside-the-box” approaches, because there currently is “no box” in pandemic teaching (28);
only hindsight will provide us with the “box” or context. In subsequent iterations of this new virtually delivered clinical rotation course, we plan to assess the learning outcomes dealing with both knowledge gained by the student and the success of student-mediated information distribution to our clinical partners.

Conclusions

It is important to include additional physiology and pathophysiology content in clinical rotations to thwart the 2–8% decline observed in physiology discipline scores from US Medical Licensing Examination Step 1 to 2 (23). Opportunistic physiologists need to team up with other biomedical and clinical scientists to make virtual clinical rotations successful during the COVID-19 pandemic. We encourage you to replicate this opportunistic approach in your host institution to reinforce our discipline’s content and further medical trainee experiences, even if it mutates based on your environment.

ACKNOWLEDGMENTS

Authors thank Dr. Kristen Metzler-Wilson for constructive comments regarding the manuscript. T. E. Wilson thanks the American Journal of Physiology—Lung Cellular and Molecular Physiology special call, The Pathophysiology of COVID-19 and SARS-CoV-2 Infection, Letters to Editors [e.g., Covid-19 infection and mortality: a physiologist’s perspective enlightening mechanisms of physiology and pathophysiology. *Physiol Rev* 98: 1627–1738, 2018. doi:10.1152/physrev.00038.2017].

REFERENCES

1. Ainley M, Hidi S, Berndorff D. Interest, learning, and the psychological processes that mediate their relationship. *J Educ Psychol* 94: 545–561, 2002. doi:10.1037/0222-0663.94.3.545.
2. Allchin D, Hooks, lines, & sinks. *Am Biol Teach* 77: 718–720, 2015. doi:10.1097/ACM.0b013e318183e2fc.
3. Brown PC, Roediger HL, McDaniel MA. *Make It Stick: The Science of Successful Learning*. Cambridge, MA: Belknap Press, 2014.
4. Clark RE, Kirschner PA, Sweller J. Putting students on the path to learning: the case for fully guided instruction. *Am Educ 36*: 6–11, 2012.
5. Couzin-Frankel J. The mystery of the pandemic’s ‘happy hypoxia’. *Science* 368: 455–456, 2020. doi:10.1126/science.368.6490.455.
6. Crowe A, Dirks C, Wenderoth MP. Biology in bloom: implementing Bloom’s Taxonomy to enhance student learning in biology. *CBE Life Sci Educ* 7: 386–381, 2008. doi:10.1187/cbe.08-05-0024.
7. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. *Hypertension* 75: 1382–1385, 2020. doi:10.1161/HYPERTENSIONAHA.120.15082.
8. Emanuel EJ. The inevitable reimagining of medical education. *JAMA* 323: 1127, 2020. doi:10.1001/jama.2020.1227.
9. Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, Brown C, Clark S, Duenger E, Gross D, Hauge S, Hirve S, Jorgensen P, Katz MA, Mafi A, Malik M, McCarron M, Meерhoff T, Mori Y, Mott J, Olivera MTDC, Ortiz JR, Palekar R, Rebello-de-Andrade H, Soetens L, Yahaya AA, Zhang W, Vandemaele K. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. *Bull World Health Organ* 96: 122–128, 2018. doi:10.2471/BLT.17.194514.
10. Forrester SJ, Booz GW, Sigmund CD, Coffman TM, Kawai T, Rizzo V, Scalia R, Eguchi S. Angiotensin II signal transduction: an update on mechanisms of physiology and pathophysiology. *Physiol Rev* 98: 1627–1738, 2018. doi:10.1152/physrev.00038.2017.
11. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 203: 631–637, 2004. doi:10.1002/path.1570.
12. Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. *Mol Cell* 78: e5779–784, 2020. doi:10.1016/j.molcel.2020.04.022.
13. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181: e271–280, 2020. doi:10.1016/j.cell.2020.02.052.
14. Iwai M, Horiiuchi M. Devil and angel in the renin-angiotensin system: ACE-angiotensin II-AT1 receptor axis vs. ACE2-angiotensin-(1–7)-Mas receptor axis. *Hypertens Res* 32: 533–536, 2009. doi:10.1038/hr.2009.74.
15. Jiang LG, LeBaron J, Bodnar D, Caputo ND, Chang BP, Chiricolo G, Flores S, Kenny J, Melville L, Sayan OR, Sharma M, Shemesh A, Suh E, Farmer B. Conscious proning: an introduction of a proning protocol for non-intubated, awake, hypoxic Emergency Department COVID-19 patients. *Acad Emerg Med* 27: 566–569, 2020. doi:10.1111/acem.14035.
16. Kallet RH. A comprehensive review of prone position in ARDS. *Respir Care* 60: 1660–1687, 2015. doi:10.4187/respcare.04271.
17. Klein G, Gerhardts F, Supé S, Kaestle SM, Nickles H, Erfinand M, Lei X, Yin J, Wang L, Mertens M, Szaszki K, Walther T, Kuebler WM. Angiotensin-(1–7) protects from experimental acute lung injury. *Crit Care Med* 41: e334–e343, 2013. doi:10.1097/CCM.0b013e3182ba6688.
18. Lang JM. Small Teaching: Everyday Lessons from the Science of Learning. San Francisco, CA: Jossey-Bass, 2016.
19. Larson HJ. A call to arms: helping family, friends and communities navigate the COVID-19 infodemic. *Nat Rev Immunol* 20: 449–450, 2020. doi:10.1038/s41577-020-0380-8.
20. Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. *Nat Rev Nephrol* 14: 417–427, 2018. doi:10.1038/s41577-018-0005-7.
21. Levesque-Bristol C, Knapp TD, Fisher BJ. The effectiveness of service-learning: it’s not always what you think. *J Experiential Educ* 33: 208–224, 2011. doi:10.11177/0885290011300302.
22. Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science* 309: 1864–1868, 2005. doi:10.1126/science.1116480.
23. Ling Y, Swanson DB, Holtzman K, Buckad SD. Retention of basic science information by senior medical students. *Am J Med* 83: Suppl: S82–S85, 2008. doi:10.1016/j.ajmmed.2008.03.001.
24. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 142: 68–78, 2020. doi:10.1161/CIRCULATIONAHA.120.047549.
25. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* 318: E736–E741, 2020. doi:10.1152/ajpendo.00124.2020.
26. Moro Y, Gott J, Olivaer MTDC, Ortiz JR, Palekar R, Rebello-de-Andrade H, Soetens L, Yahaya AA, Zhang W, Vandemaele K. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. *Bull World Health Organ* 96: 122–128, 2018. doi:10.2471/BLT.17.194514.
27. Preston RR, Wilson TE. Systems failure. In: Lippincott Illustrated Reviews: Physiology. Philadelphia, PA: Wolters Kluwer, 2019.
28. Santos RAS, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ. The ACE2/angiotensin-(1–7)
32. Semsar K, Casagrand J. Bloom’s dichotomous key: a new tool for evaluating the cognitive difficulty of assessments. *Adv Physiol Educ* 41: 170–177, 2017. doi:10.1152/advan.00101.2016.

33. Supé S, Kohse F, Gembardt F, Kuebler WM, Walther T. Therapeutic time window for angiotensin-(1–7) in acute lung injury. *Br J Pharmacol* 173: 1618–1628, 2016. doi:10.1111/bph.13462.

34. Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. *Am J Emerg Med* 26: 711–715, 2008. doi:10.1016/j.ajem.2007.10.031.

35. Weinberger SE, Cockrill BA, Mandel J. *Principles of Pulmonary Medicine*. Philadelphia, PA: Elsevier, 2019.

36. Wilcos S, Piraino T. *Mechanical Ventilation for COVID-19*. edX Inc. https://online-learning.harvard.edu/course/mechanical-ventilation-covid-19 [8 May 2020].