When the Flu Is Not the Flu

by

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Part I – From Nurse to Patient

After another long shift at the hospital, 32-year-old Jamie collapsed into bed exhausted, achy, and with a worsening dry cough. He awoke in the middle of the night with a low-grade fever. It was not unusual for him to have bouts of mild illness. After all, Jamie had been working as a nurse in the emergency department (ED) for seven years and was in frequent contact with sick patients, especially during flu season. Fortunately he had the next few days off and hoped to kick these symptoms by the time he was scheduled to return to work.

Within the next week, however, Jamie's fever spiked over 102 °F, and his breathing became labored and quite painful. At 24 breaths per minute, his ventilation rate was double his normal rate. He was struggling to catch his breath, and antipyretic medicines had little effect on reducing his fever. After testing negative for influenza and showing signs of a developing lower respiratory infection, Jamie returned to the ED, this time as a patient. By now, a few of Jamie's patients from the previous week had gotten their test results and were found to be positive for the SARS-CoV-2 virus, which was rapidly spreading coronavirus disease (COVID-19) within his hospital and across the globe. Jamie's colleagues were concerned about the severity and rapid progression of his respiratory symptoms and immediately isolated him in the COVID-19 ward where he awaited his test results. An arterial blood gas sample was taken and revealed the results in Table 1.

Table 1. Arterial blood gas lab results.

	Jamie's results	*Normal range**
pH	7.32	7.35–7.45
PaO_2	55 mmHg	75–100 mmHg
$PaCO_2$	54 mmHg	35–45 mmHg
$[HCO_3^-]$	27 mEq/L	22–26 mEq/L
SaO_2	88%	95–100%

*Castro, D., and M. Keenaghan. 2020. Arterial blood gas. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK536919/>.

Questions

1. Identify the abnormalities in Jamie's arterial blood gas results and list how these differ from normal values (e.g., elevated, reduced).

2. The equation below depicts the relationship between carbon dioxide and acid in the body, catalyzed by the carbonic anhydrase enzyme (CA). Based on LeChatelier's principle and the Henderson-Hasselbalch equation, how would you explain Jamie's pH value given his $PaCO_2$ result from Table 1? (Assume that his $PaCO_2$ is stable at this value.)

$$CO_2 + H_2O \overset{CA}{\longleftrightarrow} H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

3. What can you infer about Jamie's $[HCO_3^-]$ level based upon his blood pH and $PaCO_2$? Which organ system is primarily responsible for regulating bicarbonate levels in the blood?

4. The acid-base nomogram (Figure 1) depicts acid-base disturbances based on arterial blood lab results. Based on Jamie's lab results, which of the following best describes his acid-base status? Please explain your answer.
   a. Uncompensated metabolic acidosis
   b. Partially compensated metabolic acidosis
   c. Uncompensated respiratory acidosis
   d. Partially compensated respiratory acidosis

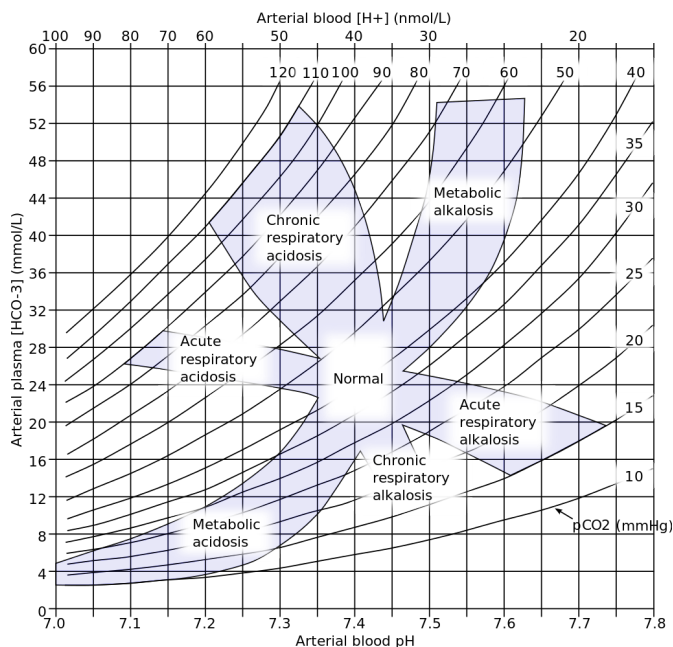*Figure 1.* An acid-base nomograph of human serum. *Credit:* Huck-finne, PD, <https://commons.wikimedia.org/wiki/File:Acid-base_no-mogram.svg#filelinks>

Part II – Acute Respiratory Distress Syndrome

After two days in the hospital, Jamie grew increasingly anxious that he was not getting any better. Until this point, Jamie had been a relatively young and healthy person; he expected that he would recover from such an infection without much intervention, aside from intravenous fluids and perhaps oxygen to make his breathing easier as his immune system fought the infection. However, Jamie's symptoms worsened. His ventilation rate increased to 33 breaths per minute, and his breathing became shallower. He was diagnosed with bilateral pneumonia (i.e., in both lungs) and put on supplemental oxygen. Although there are several causes that can trigger the inflammation and accumulation of fluid in the alveoli that is characteristic of pneumonia, Jamie had tested negative for the most common infectious agents that trigger pneumonia. So when his test results came back positive for COVID-19, the attending physician began to worry about the severe complications that she had been seeing in other patients in the COVID-19 ward.

SARS-CoV-2 infects the lung epithelium and triggers an innate immune response that can lead to acute respiratory distress syndrome (ARDS). ARDS is characterized by a rapid onset of widespread inflammation and the accumulation of protein-rich fluid and cellular debris, called a hyaline membrane, inside of the damaged alveoli. It is a serious complication of the respiratory insufficiency associated with COVID-19 that contributes significantly to mortality rates. Alveoli that are damaged in ARDS also have greatly reduced compliance (i.e., ability to stretch and expand), in part due to a loss of functional surfactant. Figure 2 depicts a normal, healthy alveolar wall and capillary diffusion barrier.
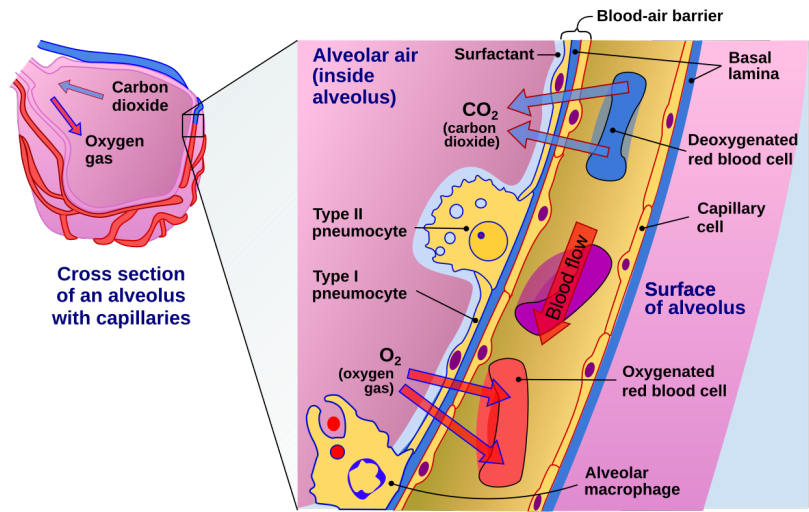

Figure 2. Cross section of an alveolus and capillaries showing diffusion of gases. *Credit:* Delmalani18, CC BY-SA 4.0, <https://commons.wikimedia.org/wiki/File:Cross_section_of_an_alveolus_and_capillaries_showing_diffusion_of_gases.svg>

Given Jamie's positive COVID-19 test result and worsening symptoms, the attending physician ordered a chest radiograph. Figure 3 shows Jamie's x-ray (right) compared with that of normal, healthy lungs (left).
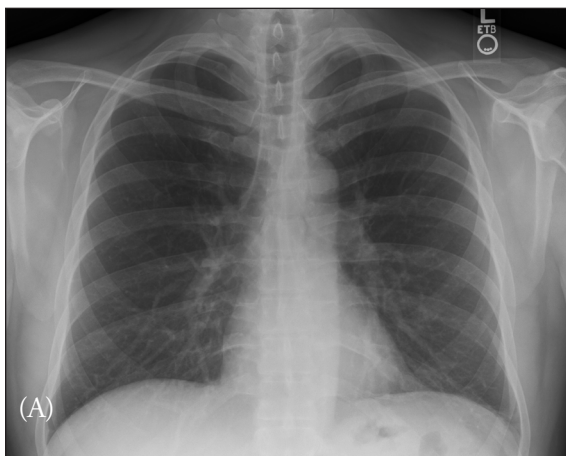

Figure 3. Radiographs of normal lungs (A) and what Jamie's lungs look like (B).
Credits: (A) Stillwaterising, PD, <https://commons.wikimedia.org/wiki/File:Chest_Xray_PA_3-8-2010.png>. (B) James Heilman, MD, CC BY-SA 4.0, <https://commons.wikimedia.org/wiki/File:ARDSSevere.png>.

Questions

5. Jamie's radiograph shows the characteristic bilateral "ground glass opacities" observed in ARDS patients. Healthy, air-filled lungs have extremely thin alveolar membranes and appear dark in a radiograph whereas the lighter color of Jamie's lungs suggest an abnormality. Based on the changes to the alveolar environment in ARDS patients discussed above, explain how the body's response to SARS-CoV-2 infection in COVID-19 could cause the appearance of this abnormal radiograph. (Consider the effect that alveolar wall damage, inflammation, and protein-rich fluid accumulation would have on the appearance of lung tissue on a radiograph.)

6. The equation below shows the diffusion rate for gas across the alveolar wall. Explain how Jamie's complication of COVID-19 with ARDS affects gas exchange in his lungs. Be sure to identify which variables in the equation are likely to change and explain why the change would occur.

P_AO_2 = partial pressure of oxygen in alveolar gas
P_cO_2 = partial pressure of oxygen in capillary blood (40 mmHg)
Area = surface area of alveolar wall for gas exchange
Solubility = how well the gas dissolves in the fluid
Thickness = alveolar membrane thickness
MW = molecular weight of the gas

$$\text{Diffusion} = \left[\frac{k * (\text{area} * \text{solubility})}{\text{thickness} * \sqrt{MW}} \right] * (P_AO_2 - P_cO_2)$$

Part III – Oxygenation

As Jamie's condition continued to deteriorate, he was put on mechanical ventilation to improve the oxygenation of his blood. The partial pressure of a particular gas depends on the barometric pressure and the fraction of air occupied by that gas (i.e., percentage of the barometric pressure made up of a particular gas). The fraction of atmospheric air for oxygen is 0.21.

Questions

7. Using the following equation, calculate the partial pressure of inspired oxygen for the fractions in the table below. Assume sea level atmospheric pressure (760 mmHg) and P_{H_2O} for normal humidified inspired air (47 mmHg).

$$PO_2 = F_IO_2 * (P_B - P_{H_2O})$$

PO_2 = partial pressure of inspired oxygen entering the alveoli
F_IO_2 = fraction of inspired oxygen (normal = 0.21)
P_B = barometric (atmospheric) pressure
P_{H_2O} = partial pressure of water vapor for inspired air in the lungs

F_IO_2	PO_2
0.21	
0.45	
0.60	
1.00	

8. Henry's gas law states that the amount of dissolved gas in a liquid is proportional to its partial pressure above that liquid. Based on Henry's law and the diffusion equation in Part II, how would increasing the fraction of inspired oxygen (F_IO_2) improve Jamie's arterial blood gas levels (e.g., dissolved oxygen in his arterial blood)?

9. ARDS is classified by the ground glass opacities seen in Jamie's radiograph in Part II and a P_aO_2/F_IO_2 ratio of less than 200 mmHg. This ratio allows for the assessment of blood oxygenation in the presence of supplemental oxygen treatment. Based on the blood gas values in Table I, what was Jamie's P_aO_2/F_IO_2 ratio upon arriving at the ED? What would the P_aO_2/F_IO_2 ratio be for a healthy person? How did Jamie's initial P_aO_2/F_IO_2 ratio compare with the ratio expected for a healthy person?

Part IV – Ventilator-Induced Lung Injury

Jamie had been put on a ventilator in an attempt to improve oxygen delivery. A major challenge in ARDS is the frequency with which damaged alveoli collapse as air is expired. Re-inflating collapsed alveoli requires a significant increase in the work of breathing to generate the greater transmural pressure gradient that is required to re-open non-aerated alveoli, which is not likely to be achieved by normal breathing patterns in ARDS. Additionally, damaged alveoli in ARDS are extremely fragile and easily damaged during repeated collapsing and re-opening of alveoli. Mechanical ventilation helps to maintain air flow by decreasing the work of breathing. This is especially important for severely ill COVID-19 patients who struggle to breathe without assistance due to the changes COVID-19 causes to their alveolar environment.

One potential complication of mechanical ventilation in COVID-19 ARDS patients is ventilator-induced lung injury (VILI). Two methods that can help to prevent the occurrence of VILI include: (1) the use of applied positive end-expiratory pressure (PEEP), which helps to keep damaged or edematous (fluid-filled) alveoli from collapsing during expiration by maintaining a positive alveolar air pressure at functional residual capacity; and (2) high-frequency ventilation, which increases the respiratory rate and decreases the tidal volume to reduce the stress of stretching damaged alveolar walls.

Question

10. Based on your understanding of air flow, respiratory physiology, and lung function, brainstorm possible ways in which these two methods might help to prevent VILI in a COVID-19 ARDS patient. (As part of your answer, consider where air would flow if some alveoli are collapsed and what effect a normal tidal volume would have on the open alveoli during inspiration.)