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Review Article

Understanding dead space in giraffes, and its application to critically ill COVID-19 patients

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Abstract: Giraffes have long been a subject of study for scientists due to the physiological anomaly their anatomical design can present. The study of the species helps aid in understanding of clinically relevant processes. The long trachea of a giraffe presents the dilemma of exaggerated dead space; however, this physiological problem is surmounted by a narrow trachea when compared to mammals of similar size, thus decreasing potential dead space. As COVID-19 patients in the hospital and ICU can develop COVID-19 associated acute respiratory distress syndrome, limiting excess dead space in COVID-19 patients is favorable. Removing additional tubing for a patient with an endotracheal tube in a ventilator circuit could help lower the patient's $PaCO_2$ and raise their pH.

Keywords: Dead space, giraffe, COVID-19, acute respiratory distress syndrome (ARDS), COVID-19 acute respiratory distress syndrome, ventilation

Introduction

The use of comparative anatomy can be helpful to physicians when applied to clinically relevant concepts, such as the importance of understanding dead space in COVID-19 patients with Acute Respiratory Distress Syndrome (ARDS). The physiology of dead space can be better appreciated and easier understood when using the giraffe as a comparative subject. Giraffes have long been of interest in scientific study due to their unique and anatomical challenges related to their long neck. In this paper, we will discuss our current understanding of the respiratory difficulty of giraffes, namely dead space from unused ventilation, as a platform for discussion of dead space in human disease with the example of COVID pneumonia, where infection leads to ARDS and respiratory failure. Furthermore, we will examine current technology used to manipulate respiratory physiological parameters and how comparative anatomy can help in the understanding of modifying treatment.

Dead space and giraffes

The anatomy and physiology of giraffes has been a source of scientific interest for hundreds of years, owing to the unique feature of its long neck. In 1787, a French scientist, Vosamer, studied the anatomical features of a giraffe and correctly hypothesized that the diaphragm would be the primary muscle for inspiration [1]. The evolution of giraffes' characteristic long neck is still debated. Jean-Baptiste Lamark believed that the adaptation was to reach food at higher branches, and since then, many scientists have looked for a concrete answer [2]. The evolutionary cause, whether being from sexual selection or for better thermoregulation, has posed an added physiological dilemma for the species, due to the length of the trachea and the height of the brain relative to the heart [2].

The part of tidal volume that does not participate in gas exchange is referred to as dead space. The nose, pharynx, and conduction airways that do not contribute to gas exchange are considered anatomical dead space, as these structures lack alveolar or gas exchange surface features [3]. Physiological dead space encompasses the anatomical dead space as well as the alveolar dead space, in which there is ventilation but no perfusion, preventing gas exchange [4]. In a healthy individual, alveolar dead space is minimalized allowing for anatomical and physiological dead space to be con-

sidered equal. In humans, dead space is about 150 mL [5]. A majority of the volume of dead space in mammals, including humans and giraffes, is from their trachea. The length of an adult giraffe's trachea is about 2 meters long, which would suggest that their dead space is an obstacle to overcome in order to replenish their lungs with new air [1]. In the second half of the twentieth century, physiologists began to theorize and study giraffes as an aid to understanding how this anatomical hurdle is surmounted. An early, accurate account was in 1978 when a team was able to record breathing measurements of a single giraffe in the London Zoo. They used a Fleisch pneumotachograph to make recordings through a single nostril of the giraffe and then applied the method of Fowler to determine anatomical deadspace. At the time, they went against the current literature, which suggested that the dead space of a giraffe would be abnormally large for an animal of its relative body mass [1]. Hugh-Jones P, Barter CE, Hime JM and Rusbridge MM determined the ratio of dead space to tidal volume (V_D/V_T) to be 0.36, which is surprisingly similar to the 0.30 = V_D/V_T in humans [6]. Hugh-Jones P, Barter CE, Hime JM and Rusbridge MM concluded that the extent of the dead space in a giraffe was reduced by the narrow trachea. When the diameter of the trachea is related to its length, the other mammals in the study-a horse, ox, red deer, sheep and human-had a consistent linear relationship [6]. The giraffe was an outlier, with its trachea being of lesser diameter than expected. While the narrow trachea itself decreases the total volume of air, it does pose another problem for giraffes. The mean flow velocity was calculated to be 180 cm/sec, yielding a Reynold's number of 1800 [6]. A lower Reynold's number is associated with laminar flow, as is the case in a quiet breathing human where Reynold's number is approximately 1000, but when Reynold's number is over 2000 turbulent flow ensues. A giraffe's narrow trachea limits exercise capability as they have a small window to increase their breathing rate without allowing the airflow in their trachea to become turbulent with the resultant increase in airway resistance [6].

Over thirty years later, a study was carried out with 46 giraffes in Zimbabwe to further study lung volumes in giraffes. This study was much more extensive than the singular recording of one giraffe in the London Zoo. The Mitchell study found that the dead space volume of one 775 kg giraffe was significantly increased compared to similar weighted mammals at a volume of 2.24 Liters, but that it was balanced by a larger than expected tidal volume of 8.18 Liters (resultant V_D/V_T was calculated to be 0.28), which is still lower than it would be without the adaptation of a narrow trachea [1]. In the study, the anatomical dead space was assumed to be the same as the volume of the trachea. They acknowledged the underestimation, because their measurements did not include the extensive bronchial tree [1]. The lung size in a giraffe was determined to be smaller than expected for a mammal of a similar size, and as giraffes gain mass, the lung mass size will decrease in relation to the body mass increase [1]. Even so, giraffes have a large tidal volume, which helps offset the large amount of dead space and preserves the V_D/V_T fraction at an expected amount. Mitchell also noted the larger tidal volume was achieved by a slower and more prolonged respiratory pattern in the giraffe at rest. The relatively large tidal volume compared to the total lung volume reduces the inspiratory reserve capacity, and the ability of the giraffe to adjust the tidal volume with activity. Instead, with exercise, giraffes have to increase their respiratory rate to increase ventilation volumes [1]. This, and the resultant increased airway resistance, are theorized to explain the observed limits of giraffes to exercise beyond short bursts of maximal activity. The slower and prolonged respiratory pattern allowing for a larger tidal volume, and the narrow trachea that mitigates the larger than expected dead space, allows giraffes to have a similar V_D/V_T ratio as a human.

Anatomical dead space in the mechanically ventilated patient is extended to include portions of the ventilator tubing and the endotracheal tube [3]. Physiological dead space includes anatomical dead space as well as the dead space that is made up of alveoli that are well ventilated, yet receive minimal or no blood flow [3]. When estimating pulmonary dead space in a clinical setting, the V_D/V_T ratio is most commonly used, and with an increased ratio, there is a diminished ability to exhale CO_2. A high V_D/V_T ratio is also associated with an increased risk of death in patients with ARDS [3]. A study done in 2017 determined that an

increased alveolar dead space fraction is associated with a prolonged ICU and hospital length of stay and duration of mechanical assistance [7]. When caring for a patient, adjusting the ventilation settings can manipulate the amount of dead space to excrete more CO_2, including increasing the minute ventilation and tidal volume, as well as optimization of the positive end-expiratory pressure [5].

Clinical case of an ICU patient with suspected increase in dead space ventilation

A 48-year-old man with no significant past medical history was admitted to an urban academic center in late March 2020 with cough, fever and acute hypoxic respiratory failure. A nasal swab revealed evidence of SARS-CoV-2 infection. A chest radiograph confirmed patchy alveolar infiltrates consistent with COVID-19 pneumonia. Laboratory studies were significant for normal serum creatinine and electrolytes, mild transaminitis, a mildly elevated lactate (2.3 mmol/L which did not resolve with crystalloid fluid infusion), lymphopenia, elevated CRP 10.70 mg/dL, normal procalcitonin 0.14 ng/mL, elevated ferritin 917 ng/mL, and elevated D-Dimer 471 ng/mL.

The patient had increasing oxygen requirements over the first several days of admission, ultimately requiring ICU transfer. He was intubated on hospital day five. He required proning and intermittent paralysis with rocuronium for refractory hypoxemia due to severe COVID-19 associated ARDS. On hospital day nine, the patient continued to deteriorate.

The blood gases collected at this time showed a pH of 7.48, pCO_2 of 46 mmHg and a PO_2 of 70 mmHg. The patient was receiving mechanical ventilation in the assist control mode with a tidal volume of 450 ml, a fraction of inspired oxygen of 60%, a rate of 24 and PEEP of 14 cmH_2O. The flow rate was 90 liters/minute and the plateau pressure was 25 mmHg. Neuromuscular blockade was continued. Despite these changes and prone positioning, the patient's condition deteriorated and the blood gas worsened with a fall in pH to 7.31, an elevation in $PaCO_2$ to 71 mmHg, and a PaO_2 of 71 mmHg suggesting worsening dead space ventilation.

Despite attempts to further increase the respiratory rate by increasing the tidal volume while maintaining plateau pressure, and continued use of prone positioning, the $PaCO_2$ did not respond consistent with high dead space physiology. The RESP score suggested an estimated survival on Extracorporeal Membrane Oxygenation (ECMO) of better than 70% [8]. The patient was cannulated for ECMO. While on ECMO, the new ventilation strategy allowed for ultra-low volume and pressure strategy to reduce biotrauma [9]. Treatment with ECMO continued for nine days with complications including ventilator associated pneumonia, excessive clotting and pulmonary thromboembolism despite treatment with therapeutic anticoagulation. Tracheostomy and PEG placement were performed. Throughout the hospitalization, COVID-19 treatment included a five day course hydroxychloroquine, dethomexasone, thiamine, zinc, and vitamin C (this case predated release of remdesivir). The patient was ultimately discharged to comprehensive inpatient rehabilitation and was able to return home recovered.

Dead space in the ICU

Challenging to directly assess; a conceptual understanding of dead space is essential to clinicians caring for patients in the critical care unit because of its correlation with mortality and the need to understand how various ventilator adjustments might influence $PaCO_2$ and, as a result, blood pH [3].

While not routinely measured in the ICU, worsening dead space can be a manifestation of microcirculatory changes and worsening in ARDS with clear prognostic implications [10]. The pulmonary dead space fraction is unique in its prognostic ability when compared to other clinical measurements [11]. Low tidal volumes consistent with a strategy to avoid "volutrauma", can contribute to further compromising the ratio of dead space to tidal volume and worsening CO_2 clearance.

In the patient presented, increasing dead space may have been accelerated because of microcirculatory changes in the pulmonary capillary bed as well as the occurrence of pulmonary thromboembolism. These microcirculatory changes have been noted as a hallmark of COVID-19 infection [12]. We point out that the course of patients with COVID-19 associated ARDS does appear to be different than traditional ARDS. Marini and Gattinoni have suggested

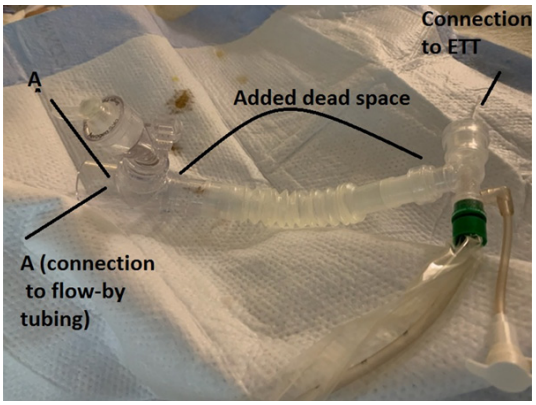

Figure 1. Tubing and Y connector show ex vivo. The tubing that bridges the Y connector to the connection point for the endotracheal tube (ETT) is labeled "added dead space". This portion of tubing will increase the amount of mechanical dead space by definition. "A" shows the connection point for the Y connector, and on the right is where the tubing will connect to the ETT.

that the course of COVID-19 ARDS is different from ARDS because of an "endothelial assault that mismatches perfusion to ventilation and may result in profound hypoxemia" [13]. We would add that this necessarily increases dead space ventilation as well and that recognizing this can help the clinician respond appropriately to clinical deterioration of COVID-19 patients in the ICU.

Astrom published findings in a pig model, which has biologic similarities to human respiratory physiology, that suggest the application of an end inspiratory pause (EIP) could lead to a reduced dead space volume and improvement in elevate PCO_2 [14]. This finding was later confirmed in ARDS by Aboab [15]. In addition, an EIP can decrease tidal volume, while still decreasing $PaCO_2$, allowing greater protection of the lung from excessive "volutrauma" [16]. This can represent one simple step the clinicians can take to improve CO_2 elimination in an effort to maintain a reasonable blood pH when using mechanical ventilation in the assist control mode.

Volumetric capnography (VCap) is a method to measure and graphically depict CO_2 elimination, including single breath measurements. This vital tool can provide an accurate estimate of mean alveolar pCO_2 (or $PACO_2$). This relatively easy-to-measure clinical tool can allow for an assessment of the efficiency of any specific ventilatory setting change as revealed by the directionality in alveolar PCO_2. Suarez-Sipmann HF, Bohm HS and Tusman HG have discussed the detail of this assessment in their important paper [17]. Because this estimate can also provide prognostic information, its value to the clinician is even greater, providing additional actionable data for clinicians in the ICU [17, 19-30].

In the COVID-19 case described, the failure of a variety of ventilatory methods in the setting of increasing dead space as revealed by rapidly rising $PaCO_2$ led to a decision to implement ECMO, which became lifesaving. An understanding of dead space can enhance the care of patients with ARDS, particularly in COVID-19 ARDS. It may be that early reports of improving survival as the pandemic progressed from April through July 2020, may have been in part due to greater understanding by clinicians of how to manage the unusual manifestations of COVID-19 in the ICU [18].

An additional aspect of managing dead space focuses on redundant tubing between the Y connector for the ventilator circuit and the endotracheal tube (ETT) as well as the length of the ETT itself (**Figures 1**, **2A**, **2B**). The redundant tubing that sits between the Y connector and the ETT adds mechanical dead space, and is directly analogous to the trachea in the neck of the giraffe. Just as the lengthened neck of a giraffe adds to their anatomical dead space, tubing that extends from the ETT to the ventilator adds extra mechanical dead space. This mechanical dead space represents the additional anatomic dead space beyond the patient's own trachea. The Y connector represents the source of fresh air (non-rebreathed) and the single column of tubing represents the giraffe's neck. Whereas the anatomy and physiology of the giraffe is modified appropriately to manage the additional dead space (such as constricting the diameter of the trachea), the extra tubing that connects the ventilator and the ETT can be removed to reduce additional mechanical dead space. In the figure provided, showing a patient with added tubing between the Y connector and the endotracheal tube, removal of the tubing led to a substantial reduction in $PaCO_2$ with improvement in the pH (**Table 1**).

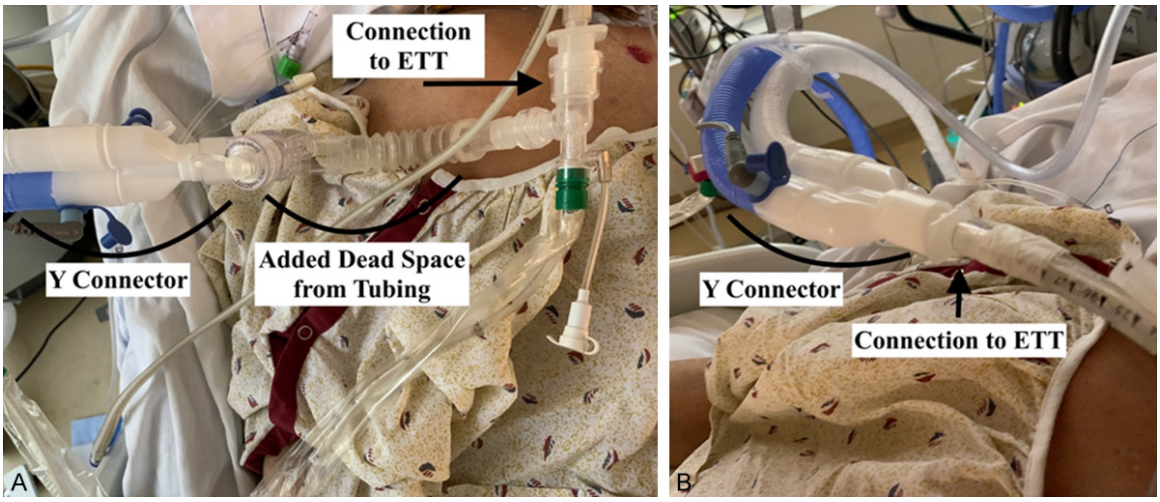

Figure 2. A and B. The image on the left displays the "added dead space from tubing" in clinical practice as described in **Figure 1**, oriented with a patient. In the image on the right, the middle tubing has been removed, so that the Y Connector will directly attach to the ETT, favorably removing additional mechanical dead space.

Table 1. Differences in laboratory findings after tubing removal

	pH	$PaCO_2$
Before tubing removal	7.32	75
After tubing removal	7.37	70

Conclusion

In summary, we present a detailed discussion about dead space in the giraffe and its physiologic adaptations which allow the giraffe to normalize dead space from what might be initially estimated by the casual observer. A working understanding of dead space is important to the ICU clinician for managing patients with severe respiratory failure and is particularly helpful in patients with COVID-19 associated ARDS, given the associated microcirculatory changes of this novel illness. As new diseases, like COVID-19, that affect the respiratory system emerge, it is important for clinicians to have a solid understanding of basic respiratory physiology, such as an understanding of dead space. An appreciation of comparative anatomy can lead to deeper comprehension of relational anatomical and physiological topics to aid physicians in modifying medical care plans, especially in an ICU setting. We discussed how in early cases of COVID-19, between March and July 2020, understanding of these concepts led to the enhanced care of patients as physicians adapted the management of these critically ill patients. Just as transitioning patients with failed dead space ventilation to ECMO and in other cases limiting extra tubing in the ventilatory circuit of mechanically ventilated patients; the savvy intensivist can use comparative anatomy to help explain why certain care adjustments can lead to improved physiological changes in patients.

Disclosure of conflict of interest

Dr. Kane is principal investigator of a grant addressing Lung Cancer Screening among vulnerable populations in Philadelphia. Dr. Kane is an officer (Treasurer) of the American College of Physicians, and the grant is from BMS foundation. Dr. Kane, Dr. Baram, and Michelle Schafer have no other conflicts of interest.

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