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Case Studies in Physiology: The Case of the Giant Giraffe

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This issue of the journal marks the first Case Study article we have published (15). These articles are the physiological equivalent of clinical case reports, showcasing unusual or extreme physiology in single experimental subjects. Our vision is simple - we wish to encourage studies of rarely available subjects, not because they are rare, but when they have the potential for clarifying important concepts thanks to some unusual structural or functional feature they uniquely possess. Thus a key component of a Case Study article must be to clarify an important, general physiological mechanism; a simple description of unusual physiology will not suffice. A risk in such reports is of course presenting data from just a single subject, such that the outcome is not robust, because the subject is not reflective of the population. That challenge must be reasonably met by the authors by comparing signal to noise in their analysis, and by the reader in recognizing the limitations of the data.

A case study might evaluate an individual world champion athlete; an astronaut who has been at the International Space Station for a year; a climber able to ascend Everest without supplemental oxygen; a wild animal whose physiology is unique and rarely accessible. This case study evaluates the gas exchange properties of a giraffe. Yes, the giraffe is rarely available for study, but that alone does not justify publication. Here, the large lungs lend themselves to exploration of the effects of gravity on ventilation and blood flow distribution; the long neck raises the question of a likely large conducting airway deadspace volume and how that may alter ventilation. In this case, there is also the opportunity to evaluate the effect of anesthesia on pulmonary gas exchange compared to other species, given the large lung size.

Nyman et al (15) used the multiple inert gas elimination technique (MIGET) to evaluate pulmonary gas exchange in a young giraffe. This opportunity arose because the animal underwent anesthesia for veterinary care. The study is notable, in part, since conducting MIGET in the presence of inhalational anesthesia is technically demanding: MIGET gases are present in parts per million while the concentrations of volatile anesthetics required for anesthesia are orders of magnitude higher, interfering with the measurement of MIGET gases with chromatography. However, with care these constraints can be overcome.

Perhaps one of the most interesting applications of MIGET is in evaluating the comparative physiology of gas exchange allowing the ability to study the relationship between lung structure

and function. Across species, lung structure varies markedly - from the simple unicameral sac-like structures for some reptiles, to the bird lung where ventilation and gas exchange are served by different structures (16) to the alveolar lung of mammals. Remarkably, ventilation-perfusion matching is similar across species such as reptiles (7), birds (19) and mammals (18) and the difference between species is less than the differences between humans with normal lungs and patients with lung diseases (18). Nyman et al adds to this body of literature by furthering a comparison of ventilation-perfusion matching across lungs of markedly different sized animals from the rat (~400g) to the giraffe which at ~400 kg is 1000 times larger. Based on this case report and other work the take home message is clear –the extent of ventilation-perfusion mismatch varies little with lung size; the giraffe is not worse than a rat. Why this is the case is not clear. Much larger gravitational effects are expected on the large lungs of the giraffe than on the small lungs of a rat. That it is not seen may be because gravity affects ventilation and perfusion similarly or because ventilation and blood flow distributions are dominated by vascular and airway structure rather than by gravity –still an area of ongoing controversy (2)!

Larger animals have larger alveoli than smaller animals (11) and in humans CT scanning studies show that lung tissue density is not constant as lung size increases (1). Rather, individuals with larger lungs have lower lung density, implying that the alveolar structures are also larger. What implications does this variation in alveolar size have for gas exchange? Comparative MIGET studies may shed light on this issue as well: Diffusion limitation of gas transport potentially occurs both at the level of the blood gas barrier and also within the alveolar gas phase, where incomplete gas mixing between inspired and alveolar gas may predispose to diffusion limitation. Gas phase diffusion limitation is detected by differences in retention and excretion between cyclopropane, which has the lowest molecular weight of any gas used in MIGET and enflurane, which has the highest. This results in a systematic error and high residual sum of squares in the MIGET analysis. Gas-phase diffusion limitation is expected in situations where the diffusion distances are larger, and has been reported in resting spontaneously breathing varanid lizards (7), and in anesthetized alligators (17) both of which have larger gas exchanging air spaces than mammals. Gas-phase diffusion limitation is seen in dogs that have recently undergone pneumonectomy (8) where alveolar size is larger because of compensatory hyperinflation and in horses (6) which have a large lung. Gas-phase diffusion limitation might also be expected when dead space is smaller and the homogenizing effects of deadspace may

82 be less. For all of these reasons one would predict gas-phase diffusion limitation in the giraffe
83 but this is not seen in the present work. This case study adds another piece of information to
84 understanding this issue but does not resolve it.

85 This work also allows the evaluation of the effect of anesthesia on a large lung. Humans show
86 the rapid development of shunt and marked ventilation-perfusion mismatch under anesthesia
87 (3, 4, 12), which arises from atelectasis (5) and is worse in the lateral position (10). Horses, a
88 species noted for very tight ventilation-perfusion matching in conscious adult animals, also
89 develop marked ventilation-perfusion mismatch, and in particular shunt, with anesthesia (13).
90 With the giraffe one might postulate that the very large lung, which is larger than that of the
91 horse, would develop atelectasis in the dependent regions, resulting in a large shunt. Significant
92 shunt did not develop in the giraffe, and may reflect unique characteristics of the species. The
93 lack of shunt may be because of the short duration of the anesthesia, but, arguing against this,
94 humans typically develop shunt within 15 minutes of induction of anesthesia (5). Other
95 potential reasons include lack of breathing hyperoxic gas, the semi-lateral recumbent posture
96 and the fact that the animal was spontaneously ventilating. Alternately perhaps some structural
97 feature of the giraffe lung is protective against the development of shunt, but this is unclear.

98 One final notable aspect is the low deadspace in this animal. The giraffe with its very long neck
99 is expected to have a large deadspace, but this is not the case. Giraffes have a low deadspace-
100 tidal volume ratio that is explained on the basis of a relative large tidal volume combined with a
101 narrow trachea (9, 14, 20). As this study confirms, the physiologic deadspace is ~ 700 ml, which
102 is much lower than expected for an animal of this size. For comparison the physiologic
103 deadspace in healthy humans with an order of magnitude smaller body size is ~150 ml.

104 The present study is therefore much more than a simple description of giraffe gas exchange. It
105 poses questions regarding the influence of lung size on gas exchange, and remarkably, shows
106 that for this critical function, size may *not* matter. It is a nice illustration of the purpose and
107 vision underlying Case Reports in Physiology – to go beyond mere description of physiology in
108 unusual subjects to address basic physiological principles across species and circumstances.

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