

STAYING CURRENT

The pulmonary physiology of exercise

 Paolo B. Dominelli¹ and  A. William Sheel²

¹Department of Kinesiology and Health Sciences, University of Waterloo, Waterloo, Ontario, Canada and ²School of Kinesiology, The University of British Columbia, Vancouver, British Columbia, Canada

Abstract

The pulmonary system is the first and last “line of defense” in terms of maintaining blood gas homeostasis during exercise. Our review provides the reader with an overview of how the pulmonary system responds to acute exercise. We undertook this endeavor to provide a companion article to “Cardiovascular Response to Exercise,” which was published in *Advances in Physiological Education*. Together, these articles provide the readers with a solid foundation of the cardiopulmonary response to acute exercise in healthy individuals. The intended audience of this review is level undergraduate or graduate students and/or instructors for such classes. By intention, we intend this to be used as an educational resource and seek to provide illustrative examples to reinforce topics as well as highlight uncertainty to encourage the reader to think “beyond the textbook.” Our treatment of the topic presents “classic” concepts along with new information on the pulmonary physiology of healthy aging.

NEW & NOTEWORTHY Our narrative review is written with the student of the pulmonary physiology of exercise in mind, be it a senior undergraduate or graduate student or those simply refreshing their knowledge. We also aim to provide examples where the reader can incorporate real scenarios.

control of breathing; exercise; gas exchange; respiratory; respiratory mechanics

INTRODUCTION

Whole body dynamic exercise using large muscle mass (e.g., running or cycling) places significant demands on the pulmonary system. Minute ventilation, pulmonary gas exchange, and the energetic requirements of the respiratory muscles increase many fold above resting values, yet the pulmonary system of healthy people is generally able to meet these demands. In this review, we detail how this impressive feat is accomplished. The intended audience for this review is instructors as well as students undertaking studies in advanced undergraduate or graduate-level exercise physiology. Our goal is to provide a companion to another article in *Advances in Physiological Education* (1), which details the cardiovascular response to exercise. We stress that our review is not intended to be comprehensive with respect to any one topic, as there are many other excellent resources available. Rather we provide a narrative review to ensure readers have a working knowledge surrounding the fundamentals behind the pulmonary response to exercise in healthy humans. With the above in mind, we focus on three interrelated themes: 1) how ventilation increases with exercise, 2) how we breathe, and 3) why we breathe. By structuring our approach as such we are able to summarize the control of exercise hyperpnea, respiratory mechanics, pulmonary gas exchange, and blood flow. We have focused our attention on the healthy adult human performing sea-level

exercise or the so-called “normal” response. We end by briefly highlighting some notable considerations to reemphasize physiological principles in, what we hope is, an interesting manner for inquisitive instructors and students alike.

Foundational Equations

As a starting point, we introduce two equations that are central to the field of exercise physiology. First, the Fick equation is a useful way to conceptualize the demand for oxygen during exercise:

$$\dot{V}O_2 = \dot{Q} \times a\bar{v}DO_2$$

The Fick equation describes how with increasing exercise intensity there are corresponding increases in O₂ uptake ($\dot{V}O_2$; in mL·min⁻¹), cardiac output (\dot{Q} ; in L·min⁻¹), and oxygen extraction ($a\bar{v}DO_2$; in mL) in the contracting locomotor musculature. An example of “typical” resting values would be $\dot{V}O_2 = 250$ mL·min⁻¹, $\dot{Q} = 5$ L·min⁻¹, and $a\bar{v}DO_2 = 50$ mL/L. The regulation of cardiac output and the cardiovascular system response to exercise is provided in a complimentary *Advances in Physiological Education* article (1). The “v” in the Fick equation represents mixed venous O₂ content and can be viewed somewhat as a surrogate for O₂ extraction at the level of the exercising musculature. For a comprehensive evaluation of the determinants of maximal O₂ uptake ($\dot{V}O_{2max}$), the interested reader is directed elsewhere (2, 3).



Here we focus on the “a” of the equation, which represents arterial O₂ content and is derived from the following equation:

$$Ca_{O_2} = (Hb \times 1.34 \times Sa_{O_2}) + Pa_{O_2} \times 0.003$$

where arterial O₂ content (Ca_{O₂}; in mL·dL⁻¹) is the sum of the O₂ bound and saturated (Sa_{O₂}; in %) to hemoglobin (Hb; in g·dL⁻¹) and that which is dissolved in the blood (Pa_{O₂} × 0.003). The “1.34” represents a constant where 1 g of Hb can bind with 1.34 mL of O₂. Typical or “textbook” examples for resting values used in the equation are Hb = 14 g·dL⁻¹, Sa_{O₂} = 98%, and Pa_{O₂} = 95 mmHg yielding a Ca_{O₂} of 18.7 mL·dL⁻¹. With these equations, one can now make use of Fig. 1, which shows the temporal response to many pulmonary system variables during progressive exercise. From a pedagogical standpoint, we recommend the reader revisit Fig. 1 throughout the rest of the article as the subsequent sections explain the “why” behind the changes presented within.

HOW VENTILATION INCREASES WITH EXERCISE

Consider a time when you last performed exercise, perhaps riding a bike or running to avoid being late for class. At the onset of exercise, your ventilation increased immediately with no conscious effort required. In this first section, we describe the control of exercise hyperpnea or more simply “how ventilation increases with exercise.” Despite the fundamental relationship between breathing and exercise, and with over a century of research there is no clear singular answer to the question: what makes us breathe during exercise? Rather, due to persistent researchers and creative experimental designs we now have a useful framework for understanding the mechanisms that contribute to the control of breathing during exercise. For an expanded treatment of the topic, the reader is directed to an authoritative review found elsewhere (4, 5). While there continues to be an incomplete

understanding of exercise hyperpnea, a model to begin with is the alveolar ventilation equation:

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{Pa_{CO_2}} \times K$$

where \dot{V}_A is alveolar ventilation (L·min⁻¹), \dot{V}_{CO_2} is carbon dioxide output (in mL·min⁻¹), and Pa_{CO₂} is arterial carbon dioxide tension (in mmHg). The term “K” is a constant and by convention when \dot{V}_A is in body temperature pressure saturated (BTPS), \dot{V}_{CO_2} is standard temperature pressure dry (STPD), and K = 0.863. A typical set of values at rest would be \dot{V}_{CO_2} = 300 mL·min⁻¹, Pa_{CO₂} = 40 mmHg, and \dot{V}_A = 6.5 L·min⁻¹. With exercise, metabolic CO₂ production increases as a function of skeletal muscle contraction and the associated energetic pathways, and alveolar ventilation initially increases proportionally to keep arterial carbon dioxide tension at (near) resting levels. With higher levels of exercise intensity (indicated by the shaded area in Fig. 1), ventilation increases in excess of metabolic demand and this point is often referred to as a “threshold.” Specifically, note in Fig. 1 that ventilation [both \dot{V}_A and minute ventilation (\dot{V}_E)] increases linearly until the threshold and thereafter increases curvilinearly. A variable that ties together ventilation and metabolism is the ventilatory equivalent of carbon dioxide (\dot{V}_E/\dot{V}_{CO_2}). The ventilatory equivalent for carbon dioxide can be thought of as how much air (often expressed in L) you are breathing for a unit (again, typically in L) of carbon dioxide production. For example, if ventilation was 60 L·min⁻¹ and \dot{V}_{CO_2} was 2.0 L·min⁻¹, the ventilatory equivalent for CO₂ would be 30. While this coupling of metabolism and ventilation is clear during (quasi) steady-state subthreshold exercise, other physiological mechanisms explain the immediate increase in ventilation observed upon initiation of exercise.

Consider ventilation when you first start to exercise. Your \dot{V}_{CO_2} does not increase immediately whereas ventilation rises nearly instantaneously. Clearly, something else must also be contributing to the onset of exercise hyperpnea in the absence of a metabolic linkage as detailed above. Like

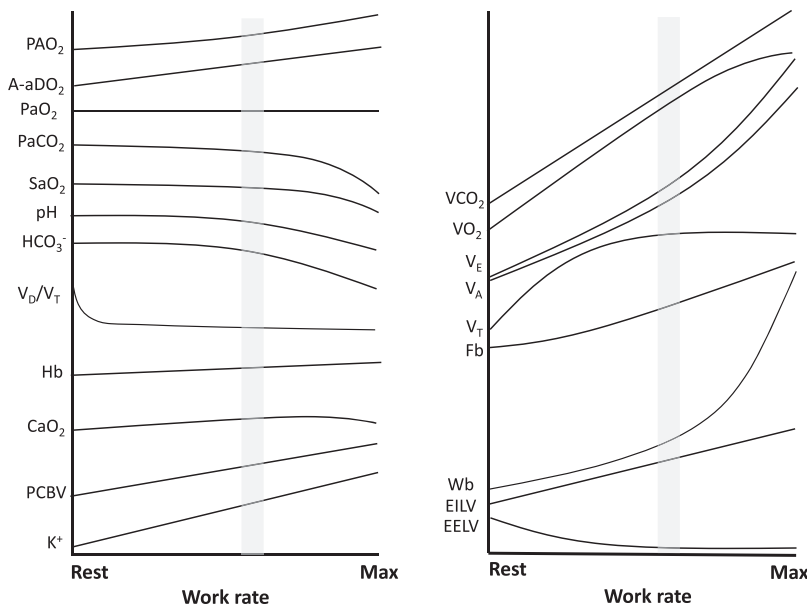


Figure 1. Temporal change in variables of interest from rest to maximal exercise. For teaching purposes, the x-axis could be expressed at any indication of metabolic rate (\dot{V}_{O_2} , \dot{V}_{CO_2} , work rate) as the result is unchanged. The y-axis is unitless and demonstrates the relative change in each variable, such that some variables show a dramatic change (e.g., work of breathing) while others are modest (e.g., saturation). The gray shaded area represents the threshold. PAO₂, alveolar oxygen tension; A-aDO₂, alveolar-to-arterial oxygen difference; PaO₂, arterial oxygen tension; PaCO₂, arterial carbon dioxide tension; SaO₂, arterial oxyhemoglobin saturation; pH, potential of hydrogen; HCO₃⁻, arterial bicarbonate concentration; V_D/V_T, dead space to tidal volume ratio; Hb, arterial hemoglobin concentration; CaO₂, arterial oxygen content; PCBV, pulmonary capillary blood volume; K⁺, arterial potassium concentration; \dot{V}_E , minute ventilation; \dot{V}_A , alveolar ventilation; V_T, tidal volume; Fb, breathing frequency; Wb, work of breathing; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; \dot{V}_{O_2} , oxygen uptake; \dot{V}_{CO_2} , carbon dioxide production.

the cardiovascular system, there is an element of central command influencing ventilation. Simply the act of generating the exercise patterns in the brain is sufficient to increase ventilation. This impressive feat of near instantaneous rise in ventilation was demonstrated in a landmark study whereby a decorticate unanaesthetised and paralyzed cat increased its ventilation when the hypothalamic locomotor region was stimulated producing fictitious locomotion (6). A decorticate model is where feedback is largely eliminated and being unanaesthetised means respiration would not be depressed by an aesthetic. The concept here is that a feed-forward mechanism (“central command”) originates in areas of the central nervous system that are responsible for movement. The “signal” from these areas is accompanied by parallel activation of respiratory areas in the brain and ventilation increases at the onset of exercise without feedback from the periphery. Evidence that activation of medullary respiratory neurons and motor pathways to limb locomotor muscles comes from a landmark study by Eldridge et al. (6). Using an experimental animal model, they clearly showed that there is a tight linkage between locomotion and ventilation that originates in the upper regions of the brain. Importantly, this was all accomplished in the absence of feedback thus isolating central command. The influence of central command is not isolated to just the initiation of exercise as it likely plays a role in mediating the rapid changes in ventilation that occur with changing muscle activation (as a surrogate for work). In addition to central command, there is often an “anticipatory” response to exercise that results in greater ventilation. For example, knowing one is about to exercise or even having an individual sit on a cycle ergometer will typically result in a rise in heart rate and ventilation, and this response is thought to prevent a lag in the response.

During subthreshold exercise, the ventilatory equivalents for carbon dioxide do not appreciably change, suggesting that ventilation and \dot{V}_{CO_2} are tightly linked. When the threshold is reached, however, ventilation rises over and above metabolic production (Fig. 1, gray bar). We have been purposely vague with respect to threshold terminology. There are a variety of thresholds (lactate, anaerobic, ventilatory, etc.) that have all been identified and used within the literature to reflect different biological constructs, although many occur at roughly similar times. For the sake of simplicity, we have not distinguished between the different thresholds, and we encourage the interested reader to review the work of Poole et al. (7) for a thorough treatment of the topic. The excessive increase in ventilation is, in part, an attempt to minimize the metabolic acidosis associated with supra-threshold exercise. Metabolic acidosis results in a lowering of arterial bicarbonate levels from the increasing levels of acids (from intense exercise) in the blood (Fig. 1, pH and HCO_3^-). Recall from the alveolar ventilation equation if \dot{V}_A increases out of proportion to \dot{V}_{CO_2} , then Pa_{CO_2} will fall. Lowering of Pa_{CO_2} helps to raise pH by depressing the bicarbonate-to- Pa_{CO_2} ratio. Another key advantage of excessive ventilation at supra-threshold intensities is the improvements in arterial oxygen tensions. As described in WHY WE BREATHE, gas exchange efficiency worsens with progressive exercise. However, excessive ventilation helps offset the gas exchange impairment by raising alveolar oxygen pressure, which in turn raises arterial oxygen tension. The increase in

ventilation in healthy individuals is often sufficient enough to offset the increasing alveolar-to-arterial oxygen difference ($AaDO_2$) and keep Pa_{O_2} near resting levels throughout all exercise intensities (Fig. 1, $AaDO_2$ and Pa_{O_2}). The driver behind the supra-threshold increase in ventilation is a combination of feedback from the active musculature along with stimulation of the peripheral chemosensors from hydrogen and/or potassium ions, temperature, and likely other stimuli.

The peripheral chemosensors (found in the carotid and aortic bodies) are ideally situated to detect changes in arterial blood given their proximity to the pulmonary capillaries and high relative blood flow. The rapid and robust ventilatory response from peripheral chemosensor stimulation can be seen in Fig. 2. In this example, a young healthy person is given two breaths of a hypercapnic gas (10% CO_2 , 21% O_2 , and balance N_2) during moderate intensity exercise (biking at 200 W) and then is quickly switched back to inspiring room air. Within seconds of the hypercapnic gas delivery, end-tidal CO_2 rises rapidly in excess of the prestimulus baseline of ~ 40 mmHg and the peripheral chemosensors are stimulated (Fig. 2). Immediately after the rise in end-tidal CO_2 , ventilation also increases at a rate of 1–2 $L \cdot min^{-1}$ per mmHg increase in CO_2 . The example also illustrates the alveolar ventilation equation in practice. After the hypercapnic breaths, when the only source of CO_2 is metabolism (\dot{V}_{CO_2}), the ventilation is relatively too high, and this relatively “high” ventilation lowers end-tidal CO_2 back down toward baseline levels. Since the hypercapnic stimulus was given at a steady-state exercise intensity, ventilation and end-tidal CO_2 eventually return back to baseline levels where ventilation is appropriate for CO_2 production. Even under normal exercise conditions (e.g., arterial blood gas values are maintained near rest), there is some amount of tonic input from the peripheral chemosensors that contributes to ventilation. Due to their location near the pulmonary capillaries, the peripheral chemosensor input is potentially the result of the within-breath oscillations of arterial PO_2 , PCO_2 , and pH. During exercise, these oscillations in blood gases increase and this also could play a role in exercise hyperpnea. The tonic input from the peripheral chemosensors can be experimentally manipulated by having an individual take several breaths of a high fraction of oxygen (typically 100%), often called the Dejour’s test. The hyperoxic breaths cause Pa_{O_2} to rise considerably, which depresses the activity of the peripheral chemosensors, and a transient depression in ventilation is observed until Pa_{O_2} returns to normal levels. Using hyperoxia to “silence” the chemoreceptors is used under laboratory experimental conditions rather than in practice, but the phenomenon highlights the contribution of the peripheral chemosensors to ventilation in the absence of other stimuli. In contrast, the depression in ventilation that is seen with hyperoxia, hypoxia stimulates ventilation. However, the ventilatory response to hypoxia is modest until the arterial blood reaches a PO_2 of ~ 50 – 60 mmHg, which corresponds to the “knee” or “shoulder” of the oxygen dissociation curve where oxygen content falls more rapidly with lowering PO_2 . An example of the hypoxic ventilatory response is shown in Fig. 3, where a young healthy female is made progressively hypoxic during mild exercise by inspiring a low fraction of O_2 . Figure 3C shows that ventilation did not increase

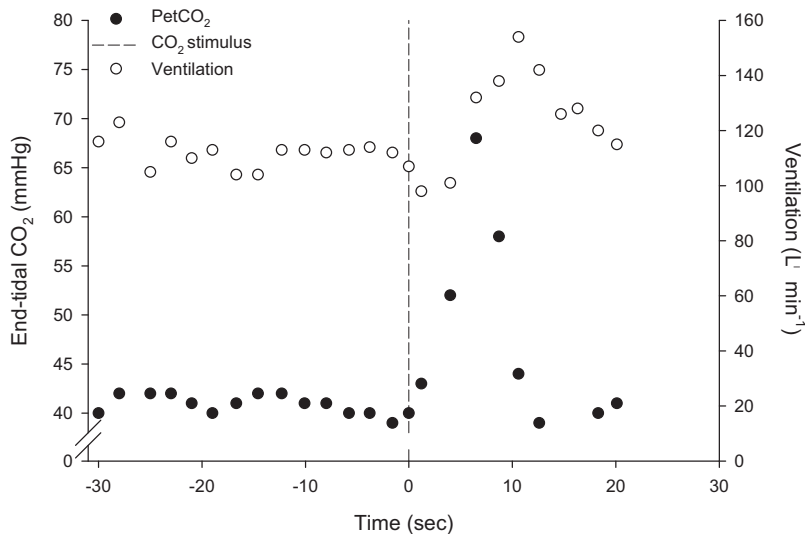


Figure 2. Representative data showing the rapid ventilatory response to transient hypercapnia. In the example, a young healthy male is exercising at a steady state of 200 W until at time “0” they are administered two breaths of a hypercapnic gas (10% CO₂-21% O₂-69% N₂). After inhalation of the hypercapnic gas, end-tidal CO₂ (PETCO₂; a reasonable surrogate for arterial CO₂) and ventilation both rapidly rise in seconds. Once back breathing room air, both end-tidal CO₂ and ventilation return to the prestimulus baseline as dictated by the alveolar ventilation equation.

(Fig. 3C, point ii) until end-tidal O₂ was ~75 mmHg, which corresponds to when oxyhemoglobin saturation starts to also fall (Fig. 3B, point i). Importantly, the values shown are end-tidal pressures, which allow for breath-by-breath measures, but especially for oxygen during exercise, and do not represent arterial blood gases. As described later in *Why We Breathe*, arterial O₂ tension is likely 10–20 mmHg lower than end tidal; thus an end-tidal O₂ pressure of ~75 mmHg corresponds to an arterial O₂ tension low enough to stimulate the peripheral chemosensors. Despite the increased ventilation, end-tidal CO₂ is held constant (or isocapnic; Fig. 3D) due to the addition of CO₂ to the hypoxic inspire, which increases the magnitude of the hypoxic ventilatory response (8). During exercise, the ventilatory responsiveness to hypoxia is increased, whereby a similar change in P_{O₂} or arterial oxyhemoglobin saturation (Sa_{O₂}) results in a greater increase in ventilation. However, a healthy person exercising at sea level maintains their Pa_{O₂} near resting levels (Fig. 1, Pa_{O₂}); thus the potential influence of “hypoxia” is unlikely relevant. However, when exercising in a low oxygen environment (e.g., high altitude), the peripheral chemosensors’ contribution to ventilation is substantial and an effective ventilatory response to compensate for the low partial pressure of oxygen. Hypercapnia is also a potent stimulator of the peripheral (and central) chemosensors but is unlikely to occur in a spontaneously breathing healthy human during exercise. However, performing exercise in some occupational settings or altered environments where carbon dioxide is inhaled via elevated ambient inspired fractions or rebreathing will result in substantially elevated ventilation in excess of metabolic production. On the other hand, hypocapnia will depress ventilation via peripheral and central chemosensor inhibition. Unlike hypercapnia, some degree of hypocapnia (Pa_{CO₂} < 40 mmHg) is normally developed during intense exercise and reflects the ventilation in excess of metabolic production at suprathreshold exercise (see Pa_{CO₂} in Fig. 1). Despite the hypocapnia-mediated depression, the net result of the cumulative inputs is an increase in ventilation. In other words, the stimuli to raise (e.g., H⁺, K⁺, temperature, etc.) ventilation is greater than the signal to lower (e.g., hypocapnia) ventilation during intense exercise.

Key Points Summary

Exercise hyperpnea is substantial and rapid and occurs via multifaceted feedforward and feedback inputs that each contribute to each phase of the ventilatory response. As of yet, no one single input is entirely responsible for the ventilatory response to exercise, and there are multiple redundancies in the control system. Overall, the goal is to match alveolar ventilation to metabolic demand to, in part, ensure blood gas homeostasis.

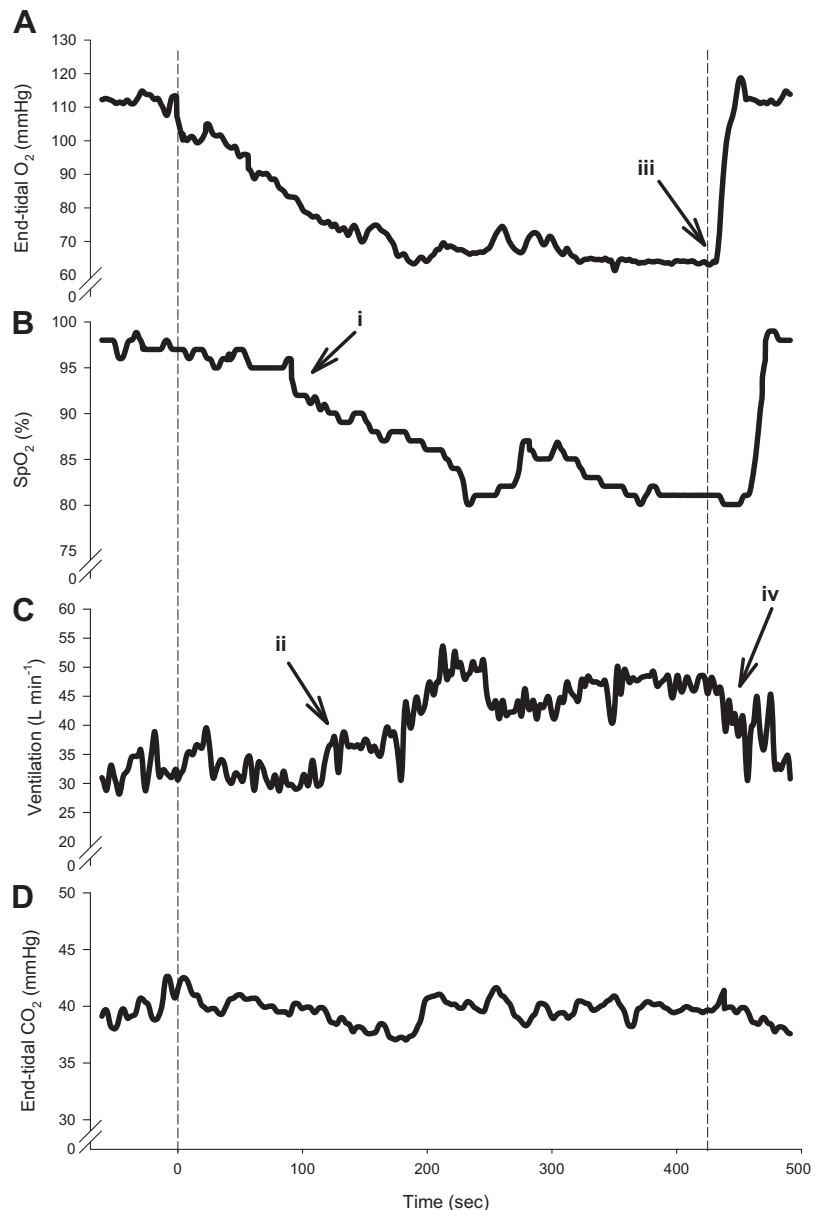
Learning through Uncertainty

Based on the alveolar gas equation, it is clear that as \dot{V}_{CO_2} increases so does alveolar ventilation. However, this raises an important question; how is \dot{V}_{CO_2} sensed? Alternatively, is the coupling of ventilation and metabolism a by-product of multiple colinearities? Evidence for the former comes from animal models demonstrating that when \dot{V}_{CO_2} is experimentally increased or decreased before reaching the lungs, ventilation changes accordingly. That is, as \dot{V}_{CO_2} is lowered, alveolar ventilation is proportionally lower. The shortcoming of this hypothesis is, as of yet, no sensor or “detector” of \dot{V}_{CO_2} has been found, as such, what is the neural and anatomic basis of this relationship?

HOW WE BREATHE

Think back again when you last performed exercise and you were breathing at a substantial rate and depth. The seemingly simple and unconscious act required fine muscle coordination, relied on physical principles of fluid mechanics, and was all done with minimal effort. In this section, we detail how one breathes from a respiratory mechanics aspect. Compared to the control of exercise hyperpnea, respiratory mechanics during exercise are better understood and rely on a variety of established physical principles. For additional review, the reader is directed elsewhere (5, 9, 11). In this section, we detail how breathing occurs starting from neural activation of the musculature. Respiratory muscle activation during breathing is highly coordinated and synchronized and most healthy humans are unaware of the act of

Figure 3. A–D: an example of a progressive hypoxic ventilatory test in a young healthy female during mild (30% of maximal intensity) exercise). At the first dashed line, the hypoxic test begins by lowering oxygen levels while keeping end-tidal CO₂ constant. SpO₂, oxygen saturation. *Point i* indicates where oxyhemoglobin begins to fall, which results in *point ii* the increase in ventilation. A similar end-tidal CO₂ (or isocapnia) is desired to ensure a robust ventilatory response and is achieved via titrating CO₂ into the inspiratory circuit. Without the added CO₂, the increased ventilation from the hypoxic gas would lower arterial CO₂ tensions, which would blunt the ventilatory response. At the second dashed line, the individual is returned to “room air,” and this is highlighted by *point iii* where end-tidal oxygen rapidly increases, which results in ventilation decreasing (*point iv*).



increased ventilation. For example, immediately before the main respiratory muscles contract, the muscles of the most “upstream” point of the airways activate. That the muscles of the upper airways (e.g., nose, throat, etc.) receive the appropriate signal to activate immediately before the typical respiratory muscles highlights this sophisticated coordination. The breathing-related role of the muscles of the upper airways is principally to ensure the airflow route is patent and has minimal resistance. Failure in the coordination of the upper airway muscles is not trivial, and the effects can be seen in individuals with exercise-induced laryngeal obstruction who often exhibit exercise intolerance owing to the high resistance from paradoxical laryngeal contractions (12).

The diaphragm is the primary muscle of inspiration and is innervated by the phrenic nerves that originate from the third to fifth cervical nerves. The other major inspiratory muscles are the external intercostals between each rib (innervated by the corresponding spinal root) and the sternocleidomastoid

(innervated by cranial nerve XI). The major expiratory muscles are the internal intercostals (same innervation as external intercostals) and the abdominal muscles (innervated by thoracoabdominal nerves). In the absence of other respiratory muscles, the diaphragm itself can maintain alveolar ventilation at rest and with mild exercise. Experimental evidence for this comes from individuals with spinal cord injuries below C5 who are able to maintain a normal resting alveolar ventilation despite the injury. With progressive exercise in health, the accessory inspiratory muscles are increasingly activated, and the expiratory muscles become active during moderate intensities to aid in regulating lung volumes. During intense and (near) maximal exercise, all the inspiratory and expiratory muscles are highly active with each breath (13).

While having appropriate alveolar ventilation is the end goal of breathing, it can be accomplished via different breathing patterns. Before explaining the architecture of

breathing patterns, we first need to define, minute, alveolar, and dead space ventilation:

$$\text{Minute ventilation : } \dot{V}_E = V_T \times F_b$$

$$\text{Dead space ventilation : } \dot{V}_D = V_D \times F_b$$

$$\text{Alveolar ventilation : } \dot{V}_A = \dot{V}_E - \dot{V}_D$$

where V_T is tidal volume (L), F_b is breathing frequency (breaths/min), and V_D is dead space volume (L). Here we emphasize the difference between V_D and \dot{V}_D . The dot above the “V” denotes a flow (which is a rate); thus \dot{V}_D is the amount of dead space ventilated per unit time (the product of volume and breathing frequency; typically $L \cdot \text{min}^{-1}$), whereas V_D is simply the volume of the dead space. For example, one can add a length of tube in front of the mouthpiece to increase the dead space volume (e.g., + 0.1 L of V_D). However, depending on the breathing frequency, the impact on dead space ventilation can be large or small. In a young healthy individual, dead space volume is relatively small (~150 mL) and represents the anatomic areas that do not participate in gas exchange (e.g., extrathoracic airways, main bronchi, etc.). With exercise, this anatomical dead space is static; that is, there are minimal changes regardless of the level of ventilation. Thus, during exercise, dead space ventilation changes exclusively due to alterations in breathing frequency. Dead space is why alveolar ventilation is always less than minute ventilation, and the difference between the two increases as a function of breathing frequency (Fig. 1, \dot{V}_E and \dot{V}_A). Recall from the earlier section that we breathe to maintain appropriate alveolar ventilation. As such, the relative change in tidal volume or breathing frequency (termed breathing pattern) can impact alveolar ventilation. Since anatomical dead space is static, the greater the tidal volume, the lower the relative amount of dead space. Consider the example in Table 1 illustrating the effect of altering tidal volume on alveolar ventilation during exercise.

Patterns A and B have the same minute ventilation (40 L·min) seen with mild levels of exercise. *Pattern A* is achieved via higher breathing frequency and because dead space is static, the dead space ventilation is greater, which results in a lower alveolar ventilation. With *pattern A*, a greater amount of the minute ventilation is “wasted” as the air does not participate in gas exchange. As such, from a maximizing alveolar ventilation perspective, *pattern B* can be considered more efficient. This is, in part, why the onset of exercise results in a rapid increase in V_T whereas the increases in breathing frequency are more modest until ~40–60% of maximal exercise where it rises more rapidly (Fig. 1, V_T and F_b). Typically, V_T increases until ~40–60% of maximal exercise where it

plateaus and the plateau volume is often ~50% of an individual’s vital capacity. However, if breathing with a greater V_T is more efficient in terms of gas exchange, why not breathe with our entire vital capacity during exercise? The answer to this relates, in part, to lung volume regulation, expiratory flow limitations and the need to consider the work of breathing (W_b).

Lung volume refers to the thoracic volume at which an individual is breathing and is delineated by residual volume and total lung capacity. That is, the lowest volume one can have at end-expiration is residual volume and the highest at end-inspiration is total lung capacity. For example, if a person has a vital capacity of 4 L (approximately what is shown in Fig. 4B) and their tidal volume is 1 L, their end-expiratory lung volume could be as low as residual volume (Fig. 4, 0 volume) or up to 3 L. Likewise, end-inspiratory lung volume could be as high as total lung capacity (Fig. 4B, point c) and as low as 1 L. With exercise, end-inspiratory lung volume (EILV) increases roughly linearly with increasing exercise intensity (Fig. 1). The increase allows for the raising of V_T and due to the shape of the maximal expiratory flow-volume curve (Fig. 4B, solid black line) access to higher expiratory flows, which allows greater breathing frequencies at maximal exercise. Given the advantage of having greater flows at higher lung volumes, why would one not always “choose” to breathe at very high lung volumes? The answer relates, in part, to the fact that lung tissue has elasticity, which is nonlinear across lung volume. This means that the lungs become less compliant or “stiff” near total lung capacity (16, 17). The reduced compliance results in greater pressures needed to achieve the same volume change (resulting in greater respiratory work) and is also associated with exertional dyspnea. As a result, EILV increases as needed to support the greater V_T , and with intense exercise, the flow is associated with higher F_b .

End-expiratory lung volume (EELV) on the other hand is reduced relative to resting values initially and then changes minimally thereafter with exercise (Fig. 1) (18). The lowering of end-expiratory lung volume allows an individual to increase their V_T by utilizing their expiratory reserve and optimizing respiratory muscle length. Specifically, for the latter, the higher the operating lung volume, the longer the muscle fibers of the main respiratory muscles (e.g., diaphragm). Like other skeletal muscles, there is an optimal length-tension relationship for the respiratory muscles and the decrease in EELV ensures an optimal length. Yet, why does not EELV continue to fall if this is mechanically advantageous for muscle fibers? As depicted by the maximal expiratory flow-volume curve, the lower the lung volume, the lower the maximal expiratory flows. There comes a point when the desired ventilation cannot be achieved at a given lung volume because the expiratory flows are too low to support the required breathing frequency. At this point, the individual increases their end-expiratory lung volume to access these higher flows, but (as outlined above) that increase is limited as end-inspiratory lung volume approaches total lung capacity and the nonlinear pressure-volume relationship. The result is the balance between required ventilation and optimizing respiratory mechanics: one way to visualize this interaction is the presence of expiratory flow limitation (19). When an individual develops expiratory flow limitation, their expiratory flow during a tidal breath meets that of their maximal expiratory flow-volume curve and cannot increase further (Fig. 4B, point d) (19). The

Table 1. Example of two breathing patterns that yield similar minute ventilations but different alveolar ventilations

	\dot{V}_E , L/min	V_T , L	V_D , L	F_b , beats/min	\dot{V}_D , L/min	\dot{V}_A , L/min
<i>Pattern A</i>	40	1.0	0.15	40	6	34
<i>Pattern B</i>	40	2.0	0.15	20	3	37

\dot{V}_E , minute ventilation; V_T , tidal volume; V_D , dead space volume; F_b , breathing frequency; \dot{V}_D , dead space ventilation; \dot{V}_A , alveolar ventilation.

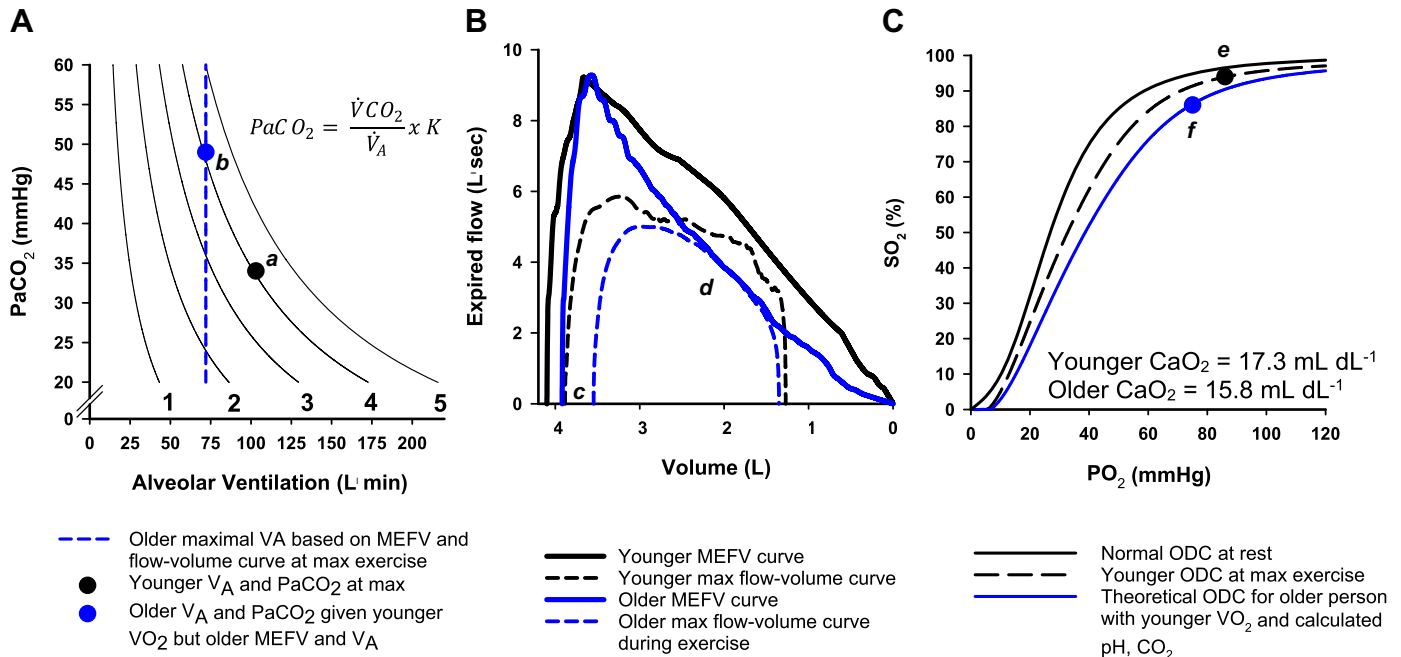


Figure 4. Representative data showing the pulmonary response at maximal exercise in a younger and older individual. Values for the young female (A–C and Table 2) were measured experimentally (14). Data from the older female were both measured experimentally (MEFV, tidal volume, and ventilation) (15), supposed to be similar to the younger female, and calculated based on other variables. A–C: illustration of the pulmonary response in an older individual if they were to work at the same output as a younger individual ($\dot{V}CO_2 = 4.1 \text{ L}\cdot\text{min}^{-1}$) but having their maximal expiratory flow-volume curve with age-related changes. Both individuals have pulmonary function that is >95% of predicted and would be classified as “normal.” Points a–f: highlighted aspects with black and blue circles and correspond to concepts in the text. The black is associated with the younger individual and the blue the older. Point a: end exercise ventilation and arterial carbon dioxide tension in the younger individual; point b: end exercise ventilation and arterial carbon dioxide tension in the older individual; point c: high end inspiratory lung volume; point d: expiratory flow limitation in the older individual; point e: end exercise saturation in the younger individual; point f: end exercise saturation in the older individual. $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production; \dot{V}_A , alveolar ventilation; $PaCO_2$, arterial carbon dioxide tension; SaO_2 , arterial oxyhemoglobin saturation; K , constant representing 0.863; CaO_2 , arterial oxygen content; MEFV, maximal expiratory flow-volume curve; ODC, oxygen dissociation curve.

changes to lung volumes that occur during exercise are also shown in Fig. 5 by examining the alterations to EELV and EILV. Note how EELV changes minimally from low-intensity exercise up to maximal, while EILV increases ~1 L. The slope of the line connecting EELV and EILV also shows total respiratory system compliance, which changes minimally despite the large increase in EILV.

Typically, in young healthy individuals, expiratory flow limitation is only observed with high-intensity exercise with the accompanying (near) maximal levels of ventilation. When an individual develops expiratory flow limitation during exercise, their ventilation can only increase by changing some aspect of their breathing pattern. Therefore, if an individual develops expiratory flow limitation and then increases their metabolic demand (e.g., $\dot{V}CO_2$), some aspect of their breathing pattern must change to accommodate the greater ventilation. For example, they could increase their lung volume and utilize higher flows, which allows greater breathing frequencies. The pitfall of this accommodation is the higher elastic W_b , potentially greater exertional dyspnea, and a less efficient breathing pattern where dead space ventilation increases. Alternatively, the V_T could increase, which would reduce the dead space ventilation. However, given the person has already developed expiratory flow limitation, they can only utilize their inspiratory reserve volume and raise their operating lung volume (lower lung volumes would result in lower expiratory flows). Similar to the first

“solution” this would result in a higher elastic W_b and exertional dyspnea.

Work of Breathing

The W_b is a measure of the energetic requirements to breathe and can broadly be split into resistive and elastic components. The resistive component relates to the work done to overcome the airflow resistance in airways, which is predominantly influenced by airway cross-section area. The elastic W_b is the work needed to overcome the elasticity of the respiratory system. Both of these components are present during inspiration and expiration but to differing degrees as described below. At rest, the total W_b is very small and largely inconsequential in terms of oxygen requirements. The metabolic requirements are low because the tissue of the healthy respiratory system is highly compliant and has very low resistance. Specifically, respiratory system compliance is ~200 mL $\text{cmH}_2\text{O}^{-1}$, meaning for a normal tidal volume at rest of ~500 mL, only a few centimeters of H_2O of pressure are required. Similarly, total airflow resistance is ~1–2 $\text{cmH}_2\text{O}\cdot\text{L}^{-1}\cdot\text{s}^{-1}$, and given flows at rest are under 1 $\text{L}\cdot\text{s}^{-1}$, the resistive component is barely 1 cmH_2O . A useful analogy to describe the elastic component of the respiratory system is an elastic band or bungee cord. In the absence of any external forces, a bungee cord sitting on a table will remain its unstretched equilibrium state. With respect to the respiratory system, it can be considered in an

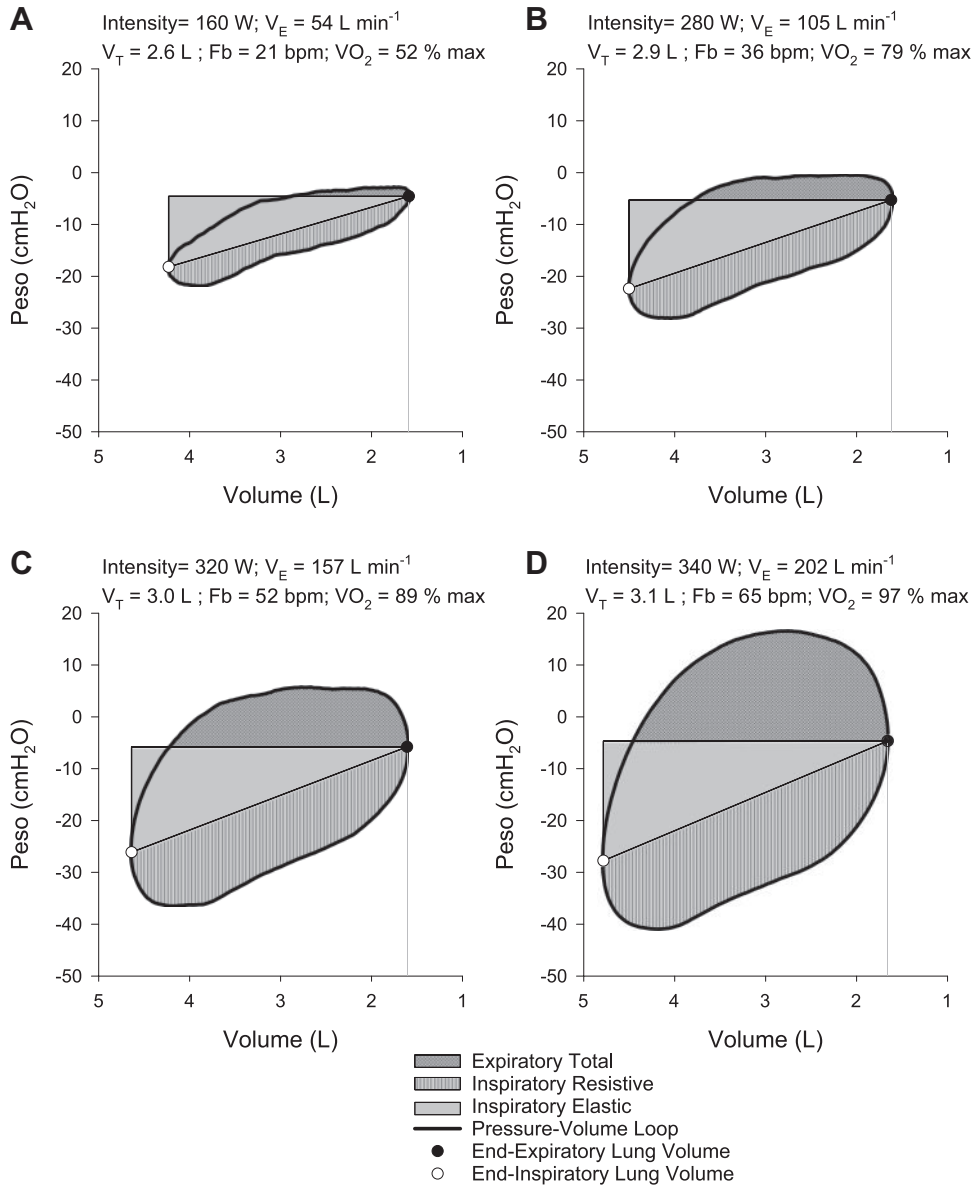


Figure 5. Representative data showing lung volumes and the work of breathing in a young male from low (A) to maximal (D) intensity exercise. A–D: composite average pressure-volume loops for the stage. The solid gray area represents the work to overcome elastic forces during inspiration, the vertical striped area is the work to overcome inspiratory resistive forces and the stippled area represents the expiratory forces. Note that much of the work that “would” have been done on expiration is accounted for and done during inspiration. The x-axis is scaled to the individual’s lung volumes and held constant in A–D to indicate the relative change throughout exercise. $\dot{V}O_2$, oxygen uptake; \dot{V}_E , minute ventilation; V_T , tidal volume; Fb, breathing frequency; \dot{V}_A , alveolar ventilation; Pesó, esophageal pressure.

equilibrium state after a normal expiration, functional residual capacity. When you breathe in and volume increases, this is analogous to stretching the bungee cord. What happens when you let go of a stretched bungee cord? It returns to an equilibrium state and, importantly, no work was needed to do this. Rather the energy put into the system during stretching (inspiration) is stored and released during contraction (expiration). Therefore, at rest, essentially no effort/work is required to expire, rather the respiratory system used the stored elastic energy from inspiration to accomplish the task of breathing out. Thus total W_b under resting conditions is predominantly from elastic components and the work is only performed during inspiration.

How does the W_b change with exercise? As detailed above, ventilation increases to meet the higher metabolic demand, and this is accomplished with increases in both tidal volume and frequency. With increasing tidal volume, the elastic work is higher largely because the volume is getting bigger. For example, if tidal volume is 2 L during exercise, that

volume requires ~ 10 cmH₂O (vs. the 1 or 2 cmH₂O at rest for a tidal volume of ~ 500 mL). Along with increasing lung volumes, compliance may worsen due to breathing at higher lung volumes, which are on the “flat” portion of the pressure-volume curve and are therefore relatively less compliant. Specifically, the relationship between lung pressure and volume is not linear, such that at high and low lung volumes, more pressure is needed to change a given volume (less compliant). The end result is that the elastic W_b increases as ventilations rises with exercise. The rise in the elastic W_b can be seen in Fig. 5, specifically the solid gray area. Figure 5A depicts the participant at $\sim 50\%$ maximal intensity, tidal volume does not increase much more (from 2.6–3.1 L in this example), and thus the area of the pressure-volume loop associated with the elastic W_b increases minimally. Likewise, the flows associated with greater breathing frequencies result in greater pressures. However, the resistive work does not show a linear relationship with ventilation. Rather, the increasing breathing frequency increases the flows thereby

requiring greater pressures, at some point, airflow in the airways becomes predominantly turbulent (rather than laminar) and this substantially increases the resistance. As such, the resistive W_b increases in a curvilinear manner with increasing ventilation. The nonlinear rise in resistive work can be seen in Fig. 5 in the vertical hashed area (inspiratory resistive) and the stippled area (expiratory total, but predominantly expiratory resistive). Note how in Fig. 5, A–D, ventilation rises by increments of ~ 50 L·min⁻¹ from ~ 50 to 200 L·min⁻¹. Despite the proportional increase in ventilation, the area associated with resistive work gets disproportionately greater. To emphasize this point, note that the rise in resistive W_b during mild exercise (Fig. 5A) comprises less than one-third of the total W_b . Whereas at maximal exercise (Fig. 5D) the elastic work is only $\sim 25\%$ of the total W_b and the rest is resistive work! Overall, as ventilation rises, the W_b does so in an exponential manner, however, one should recall that ventilation does not rise linearly with increasing metabolic demand. Rather, above threshold, the rise in ventilation becomes more rapid and the result is a profound and rapid rise in the W_b when progressing from subthreshold to suprathreshold exercise.

Despite the rapid increase in W_b , many processes occur to ensure efficiency and accomplish the task with minimal effort. For example, as detailed above, tidal volume increases initially and more rapidly with exercise, and along with making gas exchange more efficient, it lowers the W_b . Specifically, at mild exercise intensities, increases in elastic work due to higher tidal volumes are smaller than the resistive work from greater flows (and breathing frequencies). As exercise intensity increases, a larger tidal volume is no longer the best “option” from a work standpoint because any increases occur in the noncompliant or “stiff” lung volumes (near total lung capacity). The interrelationships between elastic and resistive work at different breathing patterns have been modeled, and there is indeed an “ideal” breathing pattern for a given alveolar ventilation (16). The bronchodilation that accompanies exercise also helps to minimize work by reducing airflow resistance. That the dilation of airways is intensity dependent is also beneficial given airflows (and thus airflow resistance) rise with progressive intensity.

While the W_b during mild and moderate exercise is minimal and has minimal influence on the overall bioenergetics of exercise, this is not the case with higher exercise intensities. First, respiratory muscle work, like locomotor muscle work, is linearly related to oxygen uptake of those muscles. Said another way, the higher the W_b the higher the oxygen consumption of the respiratory muscles. With mild exercise, the oxygen requirements of the respiratory muscles is barely $\sim 1\%$ of total $\dot{V}O_2$, but at maximal exercise this approaches $\sim 12\text{--}15\%$ in many individuals (20, 21). Again, the metabolic demand of the respiratory muscles is not trivial. Based on the Fick equation, in the absence of alterations in extraction, if the respiratory muscles are utilizing $12\text{--}15\%$ of $\dot{V}O_2$, they also require $12\text{--}15\%$ of cardiac output. Thus, while skeletal muscles, as a whole, receive upward of 85% of total cardiac output during exercise, a sizable amount is going to the respiratory muscles (22). The importance of respiratory muscle blood flow in terms of exercise performance can be observed by manipulating the W_b during intense exercise. When the W_b is experimentally increased, blood flow to the respiratory

muscles increases. This is not surprising given the relationship outlined in the Fick equation. What is noteworthy is the increase in respiratory muscle blood flow comes at the expense of active locomotor blood flow because cardiac output cannot increase indefinitely. The opposite blood flow relationship occurs when the W_b is lowered; blood flow to the respiratory muscles decreases and blood flow to the active locomotor muscles increases (23). The importance of this bidirectional relationship goes beyond just respiratory muscle energetics as it has been shown to impact exercise performance, sympathetic nerve activity, and locomotor fatigue (24).

Finally, the respiratory muscles, like other skeletal muscles in the face of high levels of work during exercise, will fatigue (25, 26). During intense prolonged exercise, the diaphragm can fatigue and the depression in force can persist hours after exercise. Somewhat unique to the respiratory muscles is that if the W_b of intense exercise is replicated at rest, the respiratory muscles do not fatigue (27). The lack of diaphragm fatigue under resting conditions when replicating the W_b of heavy exercise suggests that other exercise-induced changes (e.g., blood acidification, blood flow redistribution) are requisite for the development of respiratory muscle fatigue and supports the idea that the respiratory muscles are relatively fatigue resistant.

Key Points Summary

The respiratory muscles contract in a coordinated manner during dynamic exercise. Breathing patterns follow the principle of minimal effort and maximizing alveolar ventilation. During mild/moderate exercise, the work and oxygen requirements of the respiratory musculature are minimal and easily met in young, healthy individuals. During intense and (near) maximal exercise, the work performed by the respiratory muscles is substantive and can impact cardiovascular regulation and result in peripheral muscle and diaphragm fatigue.

Learning through Uncertainty

Blood flow to contracting skeletal muscles is highly regulated during exercise in humans and serves two physiological needs: 1) matching of blood flow to the demands of the contracting muscle, and 2) regulation of blood pressure is also needed to ensure appropriate perfusion pressure to all organs (28). Given the primary nature of exercise ventilation to link O_2 delivery to muscular contraction, one must also consider the substantial muscular work performed by the muscles of breathing within any regulatory scheme. Do the respiratory muscles have prioritization of blood flow distribution? This remains an open question but there is some indirect evidence to suggest this may be the case. As one example, diaphragm arterioles have less of a vasoconstrictor response to norepinephrine than those found in locomotor muscles (29). Additional indirect lines of support are summarized elsewhere (24) and we underscore that a definitive answer awaits.

WHY WE BREATHE

The previous sections summarize the control of alveolar ventilation and how it is accomplished. Here we turn our attention to the need to increase alveolar ventilation or why it

is we breathe during exercise with a specific emphasis on gas exchange and pulmonary blood flow. If we again think of the situation of a student (or the tardy faculty member!) who is late for a final examination and runs 2 miles across campus in order to make it on time. In this scenario, and to sustain locomotion, there is an increase in the amount of O_2 extracted by the working muscles that must be replaced along with a simultaneous need to eliminate the increases in CO_2 and to regulate acid-base balance (30). That the partial pressures of O_2 and CO_2 in arterial blood remain near-resting values during exercise is even more remarkable considering the further demands of heavy exercise during which mixed venous blood becomes distinctly hypercapnic and hypoxemic. Lastly, we must also consider that the lungs receive the entire cardiac output (which can be as high as $30\text{--}40\text{ L}\cdot\text{min}^{-1}$ in highly aerobically trained humans) and as such, it is critical to maintain a low pulmonary vascular resistance and minimize the turnover of plasma water into the lung's interstitium in the face of increased pulmonary blood flow. In this section, we consider the properties of the pulmonary system, both structural and physiological, that permit effective gas exchange and pulmonary blood flow. Authoritative reviews on the topic of gas exchange during exercise can be found elsewhere (31, 32).

Pulmonary Diffusion

Increasing ventilation delivers fresh inspired gas to the alveolus where it mixes with gas already in the alveoli. The process of O_2 diffusing into the blood and CO_2 diffusing out of the blood is a passive process and follows the principles of diffusion. Gas exchange across the alveolar-capillary membrane is described by Fick's law, which states that the rate of gas transfer is proportional to the surface area of the lung and the difference in gas partial pressure between the two sides (alveolus, pulmonary capillary) and inversely proportional to the thickness of the membrane. The movement of gas is also dependent on the solubility of a given gas and its molecular weight. Both O_2 and CO_2 have reasonably comparable molecular weights, but CO_2 has a much higher solubility than O_2 and as such CO_2 diffuses across the lung ~ 20 times more rapidly than O_2 . The rate of pulmonary diffusion is also highly dependent on the rate of blood flow, or perfusion, through the lung. The delivery of fresh gas must be matched to the delivery of deoxygenated blood ensuring that well-ventilated lung regions are well perfused, termed ventilation-perfusion matching (see below). A final consideration is that resistance to gas exchange also lies within the red blood cells (i.e., chemical reaction of O_2 with hemoglobin). Consider that exercise is a significant stressor with respect to O_2 equilibration because of an increase in cardiac output combined with a reduction in mixed venous O_2 . In other words, blood returning to the lung has less oxygen in it owing to uptake by the working muscles and the heart pushes blood more rapidly through the lung; thus "transit time" or the time at which gas exchange can occur is reduced. Fortunately, lung structure is well suited to meet the demands of exercise in healthy individuals. The available diffusing surface area in the lung is very large ($\sim 50\text{--}100\text{ m}^2$), the structures that comprise the alveolar-capillary barrier are thin ($\sim 0.3\text{ }\mu\text{m}$), and red blood cells remain within the pulmonary capillaries to allow for diffusion equilibrium of

alveolar gas with end-pulmonary capillary blood. The latter is enhanced by a 3-fold expansion of the volume of blood in the pulmonary capillaries from rest to minimize the reduction in red cell transit time (transit time = pulmonary capillary blood volume/blood flow). Transit time values in the resting human are $\sim 0.75\text{ s}$, whereas with maximal exercise this is reduced to 0.25 s owing to the significant increase in pulmonary blood flow (33). Despite the fall in transit time that accompanies heavy exercise in healthy people, there is sufficient time for venous blood to reach gas exchange equilibrium with the alveoli and end-capillary PO_2 remains near resting values.

Pulmonary Circulation

The lung is the only organ that must accommodate the entire cardiac output. At rest the pressures in the pulmonary circulation are low but with high-intensity exercise and the accompanying increase in cardiac output, there is potential to increase pulmonary vascular resistance, which could structurally disrupt the alveolar-capillary barrier. Given the above section describing gas exchange, a further important determinant of maintaining Pa_{O_2} during exercise is to keep the alveoli dry in the face of an increasing pulmonary blood flow. This is accomplished in two ways. First, the relatively low resistance to flow in the pulmonary vasculature means that a five to sixfold rise in pulmonary blood flow can be accommodated with minimal increase in pulmonary artery pressure. This is accomplished, in part, via recruitment of previously closed vessels and distention or increased caliber of other vessels. This serves to increase lung surface area available for diffusion of gas and helps to maintain a low resistance within the pulmonary vasculature during exercise. Second, substantial capacity of the lymphatic drainage from the lung's interstitial spaces, so that the increase in water turnover in the lung during exercise is removed by lymphatic drainage. This is an important consideration for gas exchange as it is critical to keep the alveoli dry. The outward flow of plasma from the capillaries to the interstitium increases with a rise in cardiac output and prevents fluid from entering the alveoli during exercise.

Ventilation-Perfusion Matching

A key mechanism that serves to ensure the maintenance of Pa_{O_2} is an efficient distribution of ventilation-to-perfusion throughout the lung during exercise. The precise matching of ventilation-to-perfusion (\dot{V}_A/\dot{Q}) is a primary determinant of the efficiency of pulmonary gas exchange, and under resting conditions, the healthy human lung is well ventilated with gas and perfused with blood at approximately equal flow rates. It is important to consider the regional distribution of both variables within the lung. Ventilation increases slowly from the top to bottom of the lung and blood flow increases more rapidly. This in turn means that \dot{V}_A/\dot{Q} is higher at the top of the lung and is lower at the base of the lung. These regional differences when coupled with a small amount of blood not exposed to alveolar gas (i.e., 1–2% anatomical shunt) cause a minor reduction in Pa_{O_2} relative to O_2 in the alveoli and results in a mild widening (2–6 mmHg) of the $AaDO_2$ in the resting human (see below). During exercise, \dot{V}_A/\dot{Q} distribution within any given lung region becomes

slightly more non-uniform and contributes to an expanded widening of the AaDO₂. Regional differences in gas exchange (O₂ and CO₂) and pH exist in the healthy lung from the apex to the base owing to gravitational effects (34) (among others (35)) on both blood flow and alveolar recruitment. The measurement of \dot{V}_A/\dot{Q} in humans is methodologically difficult but (36), in general, the healthy individual performing heavy exercise maintains a \dot{V}_A/\dot{Q} distribution that can be considered narrow and gas exchange is effectively accomplished and regional differences have minimal impact.

Widening AaDO₂

The alveolar-to-arterial Po₂ difference is a measure of the efficiency of pulmonary gas exchange. During exercise, the AaDO₂ widens progressively with increasing exercise intensity, and pulmonary gas exchange slightly worsens. The worsening of gas exchange is initially due to ventilation-perfusion mismatches, which, while are always present, get amplified with exercise. Ventilation-perfusion inequalities are present in all individuals and likely reflect minor anatomical variations in airways/arteries. During intense exercise, a diffusion limitation can develop, principally in highly trained athletes, whereby there is a failure to reach equilibrium between the alveoli and end capillary. The diffusion limitation predominantly seen in highly trained athletes is likely due to the very low Po₂ of the mixed venous blood. Gas exchange can also be impaired if any blood bypasses the alveolar-capillary interface. Examples include blood flow through the patent foramen ovale in the heart, noncapillary vessels in the lungs, Thebesian veins, and bronchial circulation. In these examples, deoxygenated blood ends up in the arterial circulation without passing by the alveoli. The level of gas exchange impairment this causes is related to both the volume of blood and how deoxygenated it is, both of which are exacerbated with exercise. Of note, while the AaDO₂ widens in all individuals during exercise in a roughly linear manner, the extent is highly variable between individuals. Such that some may have an end-exercise AaDO₂ under 15 mmHg, while others may be >30 mmHg (31). Despite this widening of the AaDO₂, most individuals are able to maintain arterial oxygen tension at (near) resting levels. The mechanism responsible for this maintenance is exercise hyperventilation (especially above threshold), which raises alveolar Po₂. While not controlled per se, an ideal situation would be where alveolar Po₂ raises in proportion to the worsening gas exchange to ensure Pa_{O₂} remains unchanged.

To this point, we have emphasized that Pa_{O₂} remains near resting levels during exercise in most healthy humans with some highly trained athletes being an exception to this “rule.” We now explore “why” this is so important and here we turn to the oxyhemoglobin dissociation curve (ODC) (Fig. 4C, solid black line). The ODC depicts the relationship between Po₂ and oxyhemoglobin saturation. Recall from the arterial oxygen content equation above that the majority (>95%) of oxygen in arterial blood is transported via hemoglobin. Thus, oxyhemoglobin saturation very closely reflects arterial oxygen content. Ultimately, it is the content of arterial oxygen rather than pressure of oxygen per se that is responsible for oxygen delivery. As can be seen in Fig. 4C, the ODC is not linear, rather it is sigmoidal and characterized by a “steep” part in the ~10–50 mmHg and a “flat” part in the ~80 +

mmHg range (with ~50–80 mmHg transitioning between the two). Therefore, if one can keep their Pa_{O₂} above the ~80 mmHg, they are able to stay on the flat part of the curve and keep their arterial oxygen content unchanged from rest. However, just keeping Pa_{O₂} > ~80 mmHg is not entirely sufficient during exercise because the ODC can “shift” (Fig. 4C, dashed line). Figure 4C, dashed line, is commonly referred to as a “right shift,” whereby the ODC moves to the “right” of the original curve and for a given Po₂ the saturation is lower. More correctly, the shift is actually a change in hemoglobin’s affinity for oxygen, whereby a right shift represents a lower affinity.

Key Points Summary

The demands on the lung for effective gas exchange during exercise are significant. Exercising skeletal muscle uses O₂ to accomplish movement meaning that the venous blood returning to the lung has a lower amount of O₂. When coupled with a high blood flow through the lung, this means that there is a reduced time for gas exchange equilibrium to occur. Finally, a high cardiac output has the potential to increase pulmonary vascular pressures and affect plasma water transport in the lung. Each of the above could negatively influence gas exchange; however, the structure of the lung and physiological changes that occur with exercise serve to ensure that pulmonary gas exchange is well maintained.

Learning through Uncertainty

Chronic exercise training induces numerous and well-characterized changes across organ systems (e.g., cardiovascular, skeletal muscle) to improve O₂ transport and utilization, which serve to improve exercise capacity and performance. Do similar improvements occur in the lung to facilitate gas transfer from air to blood? There is limited evidence from human studies to suggest a positive adaptation to structured physical training with respect to the lung. An exception might be highly trained swimmers who (based on cross-sectional studies) appear to have larger lungs and surface area for gas exchange. On the other hand, do these observations relate to training-induced changes to lung structure, or do they simply relate a self-selection bias within the experimental design (and sporting success)? Other factors are known to “grow” the lung (e.g., human populations residing at altitude for multiple generations and experimental animal partial lung resection). Considering the many physiological changes that accompany exercise training, why would the lung not also respond positively? For now, this is an open question but most evidence would suggest exercise fails to grow the lung (37).

NOTEWORTHY CONSIDERATIONS

Here we discuss notable examples to further understand the principles of the pulmonary response to exercise. These examples illustrate additional “stressors” and highlight the integrative response of the pulmonary system. We emphasize that the following considerations are in healthy individuals without disease. Considering the pulmonary response across a number of disease states is beyond the scope of this review.

Aerobically Trained Athletes

During exercise, some highly trained athletes do not maintain what we describe above as normal arterial blood gases (i.e., P_{aO_2} 85–100 mmHg, P_{aCO_2} 38–42 mmHg). This phenomenon is termed exercise-induced arterial hypoxemia (EIAH) and is detailed elsewhere (38). With EIAH, the arterial oxygen tension and thus arterial oxygen content is not maintained at (near) resting levels during exercise. The question becomes, what part of the pulmonary system in these apparently healthy athletes is “not keeping up?” Here we focus on several hypotheses to strengthen our understanding of integrative pulmonary physiology during exercise rather than EIAH specifically.

First, are these athletes breathing enough? Relative alveolar hypoventilation would result in P_{aO_2} being depressed, which would lower oxyhemoglobin saturation and hinder arterial oxygen content. We emphasize “relative alveolar hypoventilation” here because in many cases these individuals have high ventilation and their P_{aCO_2} is well below resting values. However, with a large $AaDO_2$, the rise in PAO_2 from greater ventilation may still not be sufficient enough to ensure P_{aO_2} is kept near rest. Moreover, as per the alveolar ventilation equation, relative hypoventilation leads to a relatively greater P_{aCO_2} , which in part contributes to a lower affinity of hemoglobin for oxygen (right shift) and exacerbates the desaturation (Fig. 4C). Therefore, if these athletes are hypoventilating, is it because they do not “want” to breathe more (control of breathing) or they “cannot” breathe more (respiratory mechanics)? The former is controversial with some showing these athletes have altered ventilatory drives and others showing a lack of differences. The role of an altered control of breathing in athletic populations with EIAH requires further study and remains an open question. For the latter, it has been demonstrated repeatedly that in some individuals who develop EIAH, ventilation is indeed limited by mechanical constraints and this contributes partly to the hypoxemia. Evidence for this comes from studies that expand the maximal expiratory flow-volume curve (via a helium-oxygen inspirate; a less dense gas), which allows for greater alveolar ventilation, which in turn improves P_{aO_2} and thus SaO_2 . We emphasize here the terminology “some” and “partly” as not all those who develop EIAH have mechanical constraints and they are never the exclusive cause.

Second, are these individuals so aerobically trained that pulmonary gas exchange is not able to meet the metabolic demands of exercise? In these individuals, a high cardiac output coupled with a very low mixed venous P_{O_2} puts considerable demand on pulmonary gas exchange.

As an example of the perplexing nature of EIAH, in Fig. 4 and Table 2, we display data from an endurance-trained female ($\dot{V}O_{2max} = 67 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) who is able to maintain their arterial oxygen tension at near resting values. That is, despite being aerobically trained, this individual does not develop substantial EIAH, so why does not this individual develop EIAH while others do? First, this participant is unlikely to exhibit substantial mechanical ventilatory constraints, as indicated by depressed P_{aCO_2} (34 mmHg) and lack of expiratory flow limitation (Fig. 4B). The ability to increase alveolar ventilation allowed the participant to raise

Table 2. Ventilatory responses of a younger and an older female at maximal exercise

Responses	26-yr-old Trained Female ($\dot{V}O_{2max}$, 67 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	60-yr-old Trained Female ($\dot{V}O_{2max}$, 37 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)
$\dot{V}O_2$, L/min	3.8	3.8
$\dot{V}CO_2$, L/min	4.1	4.1
\dot{V}_E , L/min	120	104*
\dot{V}_A , L/min	103	72
V_D/V_T	0.12	0.3†
Temperature, °C	39.7	39.7
P_{aCO_2} , Torr	115	104†
P_{aCO_2} , Torr	86	75†
$AaDO_2$, Torr	29	29
P_{aCO_2} , Torr	34	49
SaO_2 , %	94	86†
pH	7.21	7.05†

All values were measured from maximal exercise test. Values for the young female were measured experimentally (39). Data from the older female were both measured experimentally (maximal expiratory flow-volume curve, tidal volume, ventilation) (40) and calculated based on other variables. $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide production; \dot{V}_E , minute ventilation; \dot{V}_A , alveolar ventilation; V_D/V_T , deadspace-to-tidal volume ratio; PAO_2 , alveolar oxygen tension; P_{aO_2} , arterial oxygen tension; $AaDO_2$, alveolar-to-arterial oxygen deficit; P_{aCO_2} , arterial carbon dioxide tension; SaO_2 , arterial oxyhemoglobin saturation. *Measured value. †Calculated value.

their alveolar P_{O_2} (115 mmHg) to offset the gas exchange impairment (29 mmHg) and keep P_{aO_2} only minimally lowered (86 mmHg). As a consequence, SaO_2 was only minimally lowered (94%) and this was due almost exclusively to a change in oxyhemoglobin affinity due to pH (7.21), and temperature (39.7°C). Even though the level of desaturation is modest in this case, the change in SaO_2 is not trivial as every ~1% drop will result in a 1–2% drop in an individual’s $\dot{V}O_{2max}$ once SaO_2 is lowered to ~93–94% (39). Put another way, a more severe decrease in SaO_2 to 90% could result in upward of 20% reduction in $\dot{V}O_{2max}$, and this most certainly affects athletic performance. Whereas the athlete with EIAH has reductions in exercise capacity that manifests in a lower $\dot{V}O_{2max}$, depending on severity, the patient may be intolerant to simple activities of daily living. These examples serve to underscore the importance of incorporating multiple aspects of pulmonary physiology along with how exercise as a stressor in healthy humans can also help to understand pathophysiology.

Healthy Aging

As we age there are progressive changes to our pulmonary system that are unavoidable and irreversible. For an excellent review, the reader is directed elsewhere (40, 41). Some key consequences of aging include ventilation for a given metabolic demand is increased, the chest wall stiffens, elastic fibers are lost in the airways, lung volume changes, the respiratory muscles get weaker, and alveolar surface area declines. To put it differently, control of exercise hyperpnea, the mechanics of breathing along with gas exchange are all different in healthy older individuals compared to their younger counterparts. To illustrate this, we direct the reader to Fig. 4 and Table 2, where we contrast the ventilatory response to a younger and older female at maximal exercise.

First, note the young female’s pulmonary response is normal. Specifically, the ventilation for their metabolic demand

is elevated, which resulted in their arterial P_{CO_2} falling below rest. This is depicted in Fig. 4A with the black circle that falls just above the $4.0 \text{ L} \cdot \text{min}^{-1} \dot{V}_{CO_2}$ isobar and reflects their actual \dot{V}_{CO_2} of $4.1 \text{ L} \cdot \text{min}^{-1}$ (point a). In Fig. 4B, the younger individual has a maximal expiratory flow-volume curve that is not “scooped” and their tidal flow-volume loops do not intersect, indicating they are not experiencing expiratory flow limitation. With this ability to raise alveolar ventilation, the younger female’s P_{aO_2} is only minimally lower than rest, and this ensures S_{aO_2} is still on the “flat” part of the oxygen dissociation curve (Fig. 4C, point e) and their arterial oxygen content is not compromised. In fact, their Ca_{O_2} was actually maintained near resting levels (despite the mild desaturation) due to the slight hemoconcentration that occurs with exercise.

Now let us consider the older female who we reinforce is healthy, has normal pulmonary function, and would be considered similarly well trained given their age (60 yr) and $\dot{V}_{O_{2max}}$ ($37 \text{ mL kg}^{-1} \cdot \text{min}^{-1}$). To demonstrate the impact of aging, consider the following question: how would the response of the pulmonary system differ if the older and younger female performed exercise at the same workload? We first can consider the older individual’s maximal ventilation, which was experimentally determined to be $104 \text{ L} \cdot \text{min}^{-1}$, and this is depicted in Fig. 4B where significant expiratory flow limitation is noted (point d). With this upper ceiling of ventilation determined, we assume a dead space to tidal volume ratio of 0.3, which is typical of older individuals and represents worsening gas exchange as we age. The higher dead space to tidal volume ratio yields an alveolar ventilation of $72 \text{ L} \cdot \text{min}^{-1}$ and is shown by the blue vertical line in Fig. 4A. Using the alveolar ventilation equation, we can solve for P_{aCO_2} given the \dot{V}_A ($72 \text{ L} \cdot \text{min}^{-1}$) and \dot{V}_{CO_2} ($4.1 \text{ L} \cdot \text{min}^{-1}$) and this is represented by the blue circle (49 mmHg) (Fig. 4B). Having a P_{aCO_2} of 49 mmHg during near-maximal exercise would represent relative hypoventilation and has two consequences. First, alveolar oxygen tension is not elevated, and given the same gas exchange impairment ($AaDO_2$) as the younger person, arterial oxygen tension will be lower (75 mmHg). Remember though, it is likely that the gas exchange impairment is greater in the older individuals, but for consistency, we will keep it similar. Second, the higher P_{aCO_2} will result in a lower pH (7.05) in the older female if we assume a similar level of blood bicarbonate. The lower pH (along with the same degree of exercise-induced hyperthermia) results in lower oxyhemoglobin affinity (Fig. 4C, blue line) in older individuals. As a result of both the lower P_{aO_2} and lower oxyhemoglobin affinity, the S_{aO_2} would be lower in the older female (86%, Fig. 4C, point f) and this ultimately results in depressed arterial oxygen content. While the solution to the above would be to breathe more to both raise alveolar P_{O_2} and partially restore pH, inspection of the maximal expiratory flow-volume (MEFV) curve (Fig. 4B) shows how this would not be possible. Put another way, there is no way the younger individuals’ maximal flow-volume loop (\dot{V}_E : $120 \text{ L} \cdot \text{min}^{-1}$, black dashed line) would “fit” in the older individuals MEFV curve (solid blue line). While increasing lung volume would allow for greater flows, it can be appreciated that the older individual would already be operating near total lung capacity (Fig. 4B, point c) and there is still substantial (and unphysiological) overlap. In practice,

it is nearly impossible for this older individual to be able to sustain a $\dot{V}_{CO_2} > 4.0 \text{ L} \cdot \text{min}^{-1}$ from a pulmonary point of view. Cruelly, and unlike the cardiovascular and musculoskeletal systems, the pulmonary system does not appear to positively adapt to chronic exercise training. Thus, while lifelong training can result in superior cardiac function in aerobically trained older individuals (compared to untrained older individuals) the same is not the case for the pulmonary system.

Probing Question

Consider our earlier example of the young (20 yr) and healthy student who is running to class in order to not be late. Contrast this with the healthy older (60 yr) professor who is equally late and also needs to run to try and remain punctual. What key features of the ventilatory response might differ between the two individuals and why? Consider some of the structural and functional changes that accompany aging and how this may impact how ventilation is achieved and what that might mean with respect to the cost of breathing and pulmonary gas exchange.

Perspectives

The gas exchange demands of the lung are tremendously increased with exercise and the act of breathing during exercise typically occurs without thought or awareness in healthy humans. Given the primacy of breathing it remains remarkable that we are generally unaware of the process of ventilation when we perform exercise. The large reserves, both anatomical and functional, of the normal lung enable the lung to effectively transfer O_2 in and CO_2 out. The contraction of the respiratory muscles to achieve appropriate ventilation represents a major energy cost and must be accomplished in a highly regulated manner. Therefore, the neural control of ventilation must, by necessity, be highly precise and have as little energetic cost as possible. Fortunately, lung structure suits function in healthy humans performing exercise.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

P.B.D. prepared figures; P.B.D. and A.S. drafted manuscript; P.B.D. edited and revised manuscript; P.B.D. and A.S. approved final version of manuscript.

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