HOW WE TEACH | Classroom and Laboratory Research Projects

The control of ventilation during exercise: a lesson in critical thinking

© Richard. M. Bruce
Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

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Bruce RM. The control of ventilation during exercise: a lesson in critical thinking. Adv Physiol Educ 41: 539–547, 2017; doi:10.1152/advan.00086.2017.—Learning the basic competencies of critical thinking are very important in the education of any young scientist, and teachers must be prepared to help students develop a valuable set of analytic tools. In my experience, this is best achieved by encouraging students to study areas with little scientific consensus, such as the control mechanisms of the exercise ventilatory response, as it can allow greater objectivity when evaluating evidence, while also giving students the freedom to think independently and problem solve. In this article, I discuss teaching strategies by which physiology, biomedical science, and sport science students can simultaneously develop their understanding of respiratory control mechanisms and learn to critically analyze evidence thoroughly. This can be best achieved by utilizing both teacher-led and student-led learning environments, the latter of which encourages the development of learner autonomy and independent problem solving. In this article, I also aim to demonstrate a systematic approach of critical assessment that students can be taught, adapt, and apply independently. Among other things, this strategy involves: 1) defining the precise phenomenon in question; 2) understanding what investigations must demonstrate to explain the phenomenon and its underlying mechanisms; 3) evaluating the explanations/mechanisms of the phenomenon and the evidence for them; and 4) forming strategies to produce strong evidence, if none exists.

exercise; ventilation; critical thinking

CRITICAL-THINKING SKILLS encompass the abilities to assess, interpret, and evaluate ideas, concepts, or arguments. John Dewey, often considered the father of modern critical thinking, defined the process as: “active, persistent and careful consideration of a belief or supposed form of knowledge in the light of the grounds which support it” (25). Although today we might replace “grounds” with “evidence,” the definition is still pertinent, and, putting it in less formal language, it essentially proposes that critical thinking is the process of examining the reasons for believing something.

Learning the basic competencies of critical thinking are a vital part of the education of any young scientist, and, of course, these skills are easily transferable to other academic areas and everyday life. Indeed, equipping students with a set of analytic tools and an appropriate degree of scepticism for newly encountered material is becoming ever more important in modern times, in which the internet provides ever increasing amount of information, much noncorroborated and some deliberately misleading. The importance now placed on these skills is highlighted by the increasing number of critical-thinking courses available in schools and universities. Here, skills are often taught directly, whereas the aim of this article is to explore methods of teaching them more indirectly in a scientific context: in this example, the control of ventilation in exercise.

The Control of Ventilation During Exercise

During submaximal steady-state exercise, increases in ventilation are proportional to the increase in carbon dioxide production (\(\dot{V}CO_2\)) and oxygen consumption (\(\dot{V}O_2\)). As such, this tight regulation of ventilation to metabolic rate ensures the homeostasis of the arterial partial pressure of oxygen (\(PaO_2\)), carbon dioxide (\(PaCO_2\)), and pH. However, despite the long-lasting curiosity of physiologists (e.g., Refs. 3, 5, 22, 27, 30, 37, 41, 60), the mechanism(s) by which ventilation matches changes in metabolic rate, such as that during muscular exercise, has largely remained a mystery throughout the previous century and up to the present day.

Despite this, it is important for teachers to offer physiology students a full discussion of the proposed mechanisms, and their evidence, for two principal reasons. First, ventilatory control mechanisms are obviously a fundamental aspect of physiology and important areas for students to develop an understanding, particularly as exertional dyspnea and exercise intolerance are significant aspects of several chronic disease states. Furthermore, its teaching will emphasize our present poor understanding of respiratory regulation and so may spark a resurgence of interest and research in the area.

Second, and most importantly for this article, I have found that it offers an excellent opportunity for students to advance their reasoning and problem-solving skills and develop the healthy degree of skepticism required to assess evidence thoroughly. Critical-thinking skills could of course be taught using pretty much any area as reference, and so the overarching aim of this article is to provide a framework for how this might be done. However, I believe that examining the control of the exercise hyperpnea is particularly ideal for these purposes for several reasons described below.

In my experience, when university students study a subject area, they will only examine (or be asked to examine) the best available evidence that supports the current consensus. This is important of course, as it allows an understanding of why something is believed to be true. However, it is difficult for students to critically evaluate this evidence in an objective manner, as their views will likely be prejudiced by the scientific consensus about which they have learned. Conversely, assessing weak and/or contradictory evidence allows students the broad freedom to postulate for themselves how the phenomenon in question might occur, and how it might be dem-
onstrated through scientific investigation. As such, studying an area with no scientific consensus can allow for the better development of critical evaluation skills and an understanding of what is considered weak evidence and also encourages students to think independently and problem solve.

In addition, several further reasons exist as to why examining the control of the exercise hyperpnea is particularly ideal for developing critical-thinking skills. 1) As stated above, it is an area of great interest and relevance to physiology/medical students. 2) It does not require a great deal of in-depth or wider physiology knowledge, as the area in question is rather fundamental. 3) In general, when students first learn about the possible mechanisms involved in the exercise ventilatory response, the newly learned information almost always contradicts any preexisting ideas and assumptions and so reminds students that scientists should only be concerned with evidence rather than conjecture. 4) Several excellent review articles exist (e.g., Refs. 28, 38, 43, 56), which will allow students to compare and contrast their assessment of evidence with senior figures within the field, a form of quasi-feedback.

The aims of this article are as follows: 1) to describe teaching strategies that will simultaneously develop students’ understanding of respiratory control mechanisms and their critical reasoning skills; and 2) to demonstrate a systematic approach of critical assessment that students can be taught, adapt, and apply independently, taught, in this instance, within the context of exercise ventilatory control mechanisms. This systematic approach is divided into four parts (below) and describes a process that students could take when encountering new information to help form reasoned, informed conclusions. These four parts provide a useful framework for a set of teaching sessions on exercise respiratory control, and they also form separate sections within the remaining article. They are:

1. What is the precise phenomenon or problem in question?
   i.e., The exercise hyperpnea.

2. What must investigations demonstrate to explain the phenomenon or solve the problem?
   i.e., What would investigations need to demonstrate to provide evidence for a proposed mechanism for the exercise hyperpnea?

3. What are the plausible explanations, and what is the evidence? Does the evidence fulfill the criteria laid out in Investigating the Phenomenon or Problem: the Control of the Exercise Hyperpnea below?
   i.e., What physiologically plausible mechanisms might explain the exercise hyperpnea? What is the mechanism’s rationale? How strong is the evidence? What is the overall conclusion?

4. If no strong evidence exists, why might this be? How can it be resolved?
   i.e., What new studies might uncover stronger evidence?

In the author’s opinion, acquiring these types of problem-solving skills is far more important for a student’s academic development than simply learning (or memorizing) facts and figures for an exam. After all, strong critical-thinking skills are greatly sought after in any postgraduate work, and universities must prepare students accordingly. This is best achieved by using a broad range of teaching strategies, such as the one I present here. Within each of these next four sections I will describe why each aspect of the approach is important to consider when critically assessing information, what the content of the teaching sessions could be, and how one might go about teaching it.

Overview of teaching sessions, target student population, and learning objectives. Clearly, there are several important considerations when deciding on the overall organization of teaching sessions: the students’ degree course, their year of study, class size, and the time available for both in-class and out-of-class learning exercises. I consider the most suitable target audience are those studying a third-year or masters module in respiratory/cardiorespiratory physiology as part of a wider human physiology/biology, biomedical science, or sport and exercise sciences degree program, students with whom I have the most personal teaching experience. Of course, any student of the basic or clinical sciences must be given opportunities to develop similar critical appraisal and problem-solving skills as that described here, but the subject matter should be relevant to their choice of study.

The amount of time that should (or can) be devoted to these teaching and learning sessions depends on many factors, such as the overall organization of the degree program (e.g., will they learn these skills elsewhere?). The teaching sessions described in this article are based on lessons I have delivered, and enjoyed receiving, and altogether they would require a significant proportion of a single module, the equivalent of ~10 lectures. However, the structure is an example of what could be accomplished with minimal time constraints, and so interested readers would be encouraged to adapt and incorporate whatever aspects they believe most important into their own teaching sessions; many of the learning objectives can still be achieved. Nevertheless, it is worth reemphasizing the importance for students to learn and practice using these transferrable skills, not just for future scientists, but for any graduate career. As such, degree organizers must ensure that students are given sufficient opportunity to develop these vital skills, preferably during each year of study. Furthermore, the time is not exclusively devoted to teaching critical thinking, as students simultaneously learn about the control of the respiratory system.

The number of students is a critical factor as, generally, it is inversely proportional to the realistic ambitions of the module/course. It is still possible to achieve many of the learning objectives described in this article with larger class sizes (e.g., 100+), but, with finite time and teacher numbers, it becomes impractical to hold several small-group seminars. Therefore, the optimal class size is probably between 20 and 40 and, consequently, is most suitable at the third-year or masters level, where there are usually fewer students.

A summary of the teaching methods, lesson organization, and learning objectives are shown in Table 1. It is vital that, before their commencement, the learning objectives and the overall structure of the planned teaching sessions are explicitly stated to students. This is best achieved at the beginning of lecture 1 (Table 1). In addition, students can also be introduced to the systematic approach to critical analysis they will use when assessing evidence, preferably be provided with handouts explaining its details, and informed that this approach forms the basic structure for the series of teaching sessions.
and $V\dot{O}_2$) during submaximal exercise follow a similar pattern above anaerobic threshold; Fig. 2), this steady-state ventilation is never reached and will continue to rise until volitional exercise cessation or exhaustion. Gas exchange kinetics ($V\dot{O}_2$ and $V\dot{CO}_2$) during submaximal exercise follow a similar pattern as ventilation, but often with slightly faster phase II time constants (11, 63). In addition, like ventilation, $V_{O_2}$ and $V_{CO_2}$ fail to reach steady state during heavy exercise.

The key characteristic of the steady-state ventilatory response during submaximal exercise is that it is proportional to $V_{O_2}$ and $V_{CO_2}$. This can perhaps be best observed during an

**Table 1. A summary of learning objectives from the planned teaching sessions and the methods used to achieve them**

<table>
<thead>
<tr>
<th>Learning Objective</th>
<th>Teaching Method</th>
<th>Lesson Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understand the cardiorespiratory responses to exercise</td>
<td>Lecture 1</td>
<td>Teacher-led lecture to all students. Includes a summary of learning objectives and an introduction to a systematic approach at evaluating evidence.</td>
</tr>
<tr>
<td>Understand how to critically analyze evidence</td>
<td>Seminar 1</td>
<td>Student-centered seminar. Class size, 8–12. Students prepare by reading 2 research articles. Aim is to discuss research design and how to critically analyze evidence (see Investigating the Phenomenon or Problem: the Control of the Exercise Hyperpnea of main text).</td>
</tr>
<tr>
<td>Apply critical analysis skills independently</td>
<td>Preparing for a group oral presentation</td>
<td>Students are divided into groups (4–5 people); workload is organized among themselves. Students are required to perform a literature search and then review and evaluate evidence for a hypothesized control mechanism.</td>
</tr>
<tr>
<td>Develop communication and teamwork skills</td>
<td>Developing and performing group oral presentations</td>
<td>Groups (as above) develop and perform an oral presentation based on the evidence they have systematically analyzed (30 min, with 5 min of questions).</td>
</tr>
<tr>
<td>Develop problem-solving skills by creating novel research questions</td>
<td>Seminar 2</td>
<td>Group size, 8–12. Students identify the problem that the control of the exercise hyperpnea is unknown and discuss hypothetical mechanisms. Each mechanism provided the basis for each group oral presentation. A moderator guides the session. See Describing the Phenomenon: the Breathing Response to Exercise of main text for details.</td>
</tr>
<tr>
<td>Consolidation of information</td>
<td>Written course work</td>
<td>Raw data from a study examining exercise ventilatory control is given to students to individually organize and interpret. Appropriate tables/graphs should be produced, followed by a discussion of the study’s results in the context of the wider literature.</td>
</tr>
<tr>
<td>Practice data handling, presentation, and interpretation</td>
<td>Written course work</td>
<td>Raw data from a study examining exercise ventilatory control is given to students to individually organize and interpret. Appropriate tables/graphs should be produced, followed by a discussion of the study’s results in the context of the wider literature.</td>
</tr>
<tr>
<td>Develop problem-solving skills by creating novel research questions</td>
<td>Seminar 2</td>
<td>Student-centered seminar. Class size, 8–12. Students discuss possible reasons why no strong evidence currently exists in the field and propose research questions that might uncover solutions.</td>
</tr>
<tr>
<td>Consolidation of information</td>
<td>Lecture 2</td>
<td>Teacher-led lecture to all students. Aim is to put all student presentations into overall context.</td>
</tr>
</tbody>
</table>

**Describing the Phenomenon: the Breathing Response to Exercise**

To critically assess a body of evidence, clearly one must first have a firm understanding of the area in question. So, in this instance, to uncover the underlying mechanisms driving the exercise hyperpnea, we must first establish what the cardiorespiratory responses to exercise actually are; in other words, for what the control mechanisms must be accountable. This is best achieved through a lecture (or a teacher-led, small-group teaching session), as it ensures that all students have a similar baseline understanding.

The content should contain information about the breathing responses to constant-load and incremental exercise tasks (and the blood-gas changes that occur; see further below). Traditionally, the increase in ventilation and gas exchange during a bout of constant-load submaximal exercise is divided into three phases (Fig. 1; Refs. 11, 19, 24, 63). Phase I is characterized by an immediate increase in ventilation at exercise onset with a time constant of ~1 min. By the third minute of exercise, ventilation reaches a steady state (phase III); however, during “heavy” exercise (i.e., above anaerobic threshold; Fig. 2), this steady-state ventilation is never reached and will continue to rise until volitional exercise cessation or exhaustion. Gas exchange kinetics ($V_{O_2}$ and $V_{CO_2}$) during submaximal exercise follow a similar pattern as ventilation, but often with slightly faster phase II time constants (11, 63). In addition, like ventilation, $V_{O_2}$ and $V_{CO_2}$ fail to reach steady state during heavy exercise.

The key characteristic of the steady-state ventilatory response during submaximal exercise is that it is proportional to $V_{O_2}$ and $V_{CO_2}$. This can perhaps be best observed during an

![Fig. 1. The ventilatory response to submaximal constant-load exercise (shaded area), beginning at 0 min. The response is characterized by three phases: phase I, an immediate increase in ventilation at exercise onset (fast component), phase II, an exponential increase in ventilation (slow component) until phase III, steady state.](Image)
incorporate PaCO₂ decreases.

whereas PaCO₂ remains relatively constant, indicating that ventilation matches more than V˙CO₂ (Fig. 2), and so PaCO₂ consequently declines.

anaerobic threshold), ventilation increases somewhat more than V˙CO₂, and the increasing metabolic rate. Beyond 2.5 l/min (i.e., “heavy” exercise above aerobic threshold), ventilation increases somewhat more than V˙CO₂ and consequently PaCO₂ decreases.

incremental exercise task (Fig. 2). In the steady state, ventilation increases linearly with metabolic rate during submaximal exercise intensities. Importantly, PaCO₂ remains similar to resting levels with only small (1–3 mmHg) changes observed (29), and so highlights that increases in ventilation closely match that of VCO₂.

During heavy exercise, ventilation increases proportionately more than VCO₂ (Fig. 2), and so PaCO₂ consequently declines. The traditional explanation for the hyperventilation of heavy exercise is that the simultaneous metabolic acidosis (a result of increased arterial plasma lactic acid/H⁺, released by contracting skeletal muscle) results in the stimulation of peripheral chemoreceptors and so provides the extra drive to breathe. The hyperventilation is important as it partially compensates for the reduction in arterial pH. However, while this mechanism probably does significantly contribute to the observed hyperventilation, debate still exists as to whether other mechanisms (such as muscle fatigue) also significantly contribute to the phenomenon (for review, see Ref. 28). At maximal exercise intensities, ventilation can increase above 150 l/min in healthy adults and even beyond 200 l/min in elite athletes (44), a potential for more than a 30-fold increase over resting ventilation. However, this exercise intensity can only be maintained for 1–2 min at most (44).

What must any control mechanism(s) be accountable for? Students should be encouraged to think about what features of the normal breathing response to exercise are most significant or remarkable, because, of course, any control mechanism(s) must be responsible for producing all of them. Perhaps the three most important features are as follows:

1. The immediate increase of ventilation at exercise onset
2. The great magnitude of ventilations possible during exercise
3. The tight matching of ventilation with metabolic rate.

The mechanism(s) responsible for the exercise hyperpnea must be capable of generating these three features. As such, it might be useful to think of them like a set of criteria that should be fulfilled when assessing any evidence relating to control mechanisms.

Blood gases during exercise and chemoreceptor involvement.

From my experiences as a teacher (and memories as a student), it is usually presumed by students that the breathing response to exercise is a simple reflex initiated by central and peripheral chemoreceptors. This chemoreflex is generally imagined, logically, as a response to the increased metabolic rate (VO₂ and VCO₂) and consequential changes in mean arterial PO₂ and/or PaCO₂/H⁺. In other words, it is thought that chemoreceptors act as simple “metabolic rate sensors.” This, of course, is incorrect, as mean PaO₂ and PaCO₂/H⁺ fluctuate very little in submaximal exercise (29, 59), and a stimulating approach to highlight this notion is to organize a problem-based learning (PBL) teaching session. This student-centered approach allows them to learn about a subject area through discussion and trying to solve an open-ended problem.

In this session, groups of students first produce a simple schematic diagram of the cardiorespiratory and circulatory system, complete with standard arterial and mixed venous blood-gas values during rest and submaximal and maximal exercise, and also illustrate the locations of chemoreceptors and what they would consider to be an ideal location of a “metabolic rate sensor.” This can be completed with the aid of textbooks or other sources, and hopefully something similar to Fig. 3 will be produced, perhaps also with a “hypothesized”
mixed venous chemoreceptor (as a metabolic rate sensor) sensitive to fluctuations in mixed venous $P_{CO_2}$ as a consequence of changes in $V_{CO_2}$ during exercise.

However, students should be made aware that no receptors capable of monitoring mixed venous blood in the heart or pulmonary circulation, have been identified in humans (59). Furthermore, by producing this diagram, it should be abundantly clear that central and peripheral chemoreceptors are in the wrong location to monitor increase in metabolic rate during exercise, because mean $P_{aCO_2}/H^+$ remain similar to resting levels. This is because of the characteristics of the exercise hyperpnea itself: ventilation increases immediately and in proportion to metabolic rate, maintaining arterial blood-gas homeostasis. Indeed, preventing hypercapnia, despite an increasing $V_{CO_2}$, is an impressive accomplishment of the respiratory system, given that its most tightly controlled variable, $P_{aCO_2}/H^+$, provides no error signal for a reflex ventilatory response.

So, in this way, students will actually produce their own “problem” for the PBL teaching session, i.e., what physiological mechanism(s) drives the increase in ventilation during exercise? Based on their current level of knowledge, students can then discuss this problem and create a list of potential candidate mechanisms. This list should be refined, and can be added to, by the teacher/moderator of the session and provides the basis for control mechanisms that students should research and critically assess (discussed in Physiologically Plausible Mechanisms Controlling the Exercise Hyperpnea and Their Evidence below).

Investigating the Phenomenon or Problem: the Control of the Exercise Hyperpnea

Before students are asked to critically examine primary sources of evidence, teachers must ensure that they are equipped with the analytic tools to do so and understand what investigations must demonstrate, if they are to provide strong evidence to support a hypothesis. As a first step, students should read two or three relevant research articles and be told to place particular scrutiny on the methodology sections, before attending a seminar that aims to provoke discussion on how scientific investigations are designed. I enjoy creating a flexible learning environment that can be either student led or teacher led, depending on the requirements of the group. Ideally, students will be leading most discussions, comparing the strengths/limitations in design of the research studies they have read and what appropriate conclusions can be drawn from them. However, teachers must ensure that students discuss, or are explicitly taught, important aspects of research design; some of the aspects I believe are important are summarized in the remainder of the section.

The great French physiologist Claude Bernard, the first to develop the concept of homeostasis (of the “milieu intérieur”), described what he regarded as differences between scientific “observation” and “experimentation” (12). Observation consists of recording phenomena as they “naturally” occur, whereas experimentation consists of recording phenomena “created” or “defined” by an experimenter, in other words, where variation or disturbance to the natural state has been applied. The specifics of the nomenclature are unimportant, and their definitions are certainly not fixed, but what might be useful for students to keep in mind is that for scientific investigations to demonstrate the mechanisms underpinning a phenomenon, both of these concepts (i.e., what Bernard described as “observation” and “experiment”) must be fulfilled. This idea will be expanded upon in the context of exercise respiratory control mechanisms:

**Observation.** Investigations must establish the normal physiological response of exercise. Not just the characteristic response of the respiratory system, but systemic changes that might act as a “signal” to increase ventilation. This will provide insight into the physiological credibility of potential control mechanisms under question (e.g., does the mechanism’s “signal” arise during and throughout exercise, and is it in proportion to metabolic rate?). This “observational” evidence is clearly important but, alone, it cannot definitively establish causation, only correlation. For that, so-called “experimentation” is required (below). However, if experimentation is impractical, impossible, or unethical, how can investigators provide evidence toward a causal relationship?

The English epidemiologist Sir Austin Bradford Hill conceived a set criteria (Bradford-Hill criteria; Ref. 34) useful for providing evidence of causal associations. These criteria have since been further developed (e.g., Ref. 31), and, although they are more specific to public health research, many are helpful to keep in mind when determining the strength of evidence of respiratory control mechanisms (Table 2).

**Experimentation.** Based on observations (a posteriori), or theoretical ideas (a priori), experiments aim to manipulate phenomenon to uncover their properties. This requires a comparator (control), generally the unmanipulated or “natural” phenomenon, for the effects to be revealed. Similar to many other physiological fields, when uncovering mechanisms of exercise respiratory control, experiments often fall into two categories, stimulation and inhibition, and both are required, if strong evidence is to be provided.

Stimulation occurs when a single mechanism is experimentally stimulated at rest (e.g., the application of an agonist for a receptor), and any ventilatory responses are recorded. Inhibition occurs when the mechanism in question is abolished or impeded (e.g., the application of an antagonist for a receptor), and any reductions in the exercise hyperpnea are recorded. Unlike “observational” investigations, well-controlled “experimentation” should establish causation, only correlation. For that, so-called “experimentation” is required (below). However, if experimentation is impractical, impossible, or unethical, how can investigators provide evidence toward a causal relationship?

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporality</td>
<td>Does the “signal” occur before/at the onset of the breathing response?</td>
</tr>
<tr>
<td>Consistency</td>
<td>Are the findings consistently observed within/ between investigations?</td>
</tr>
<tr>
<td>Dose-response relationship (biological gradient)</td>
<td>Does a bigger metabolic rate lead to a bigger “signal”? Does bigger “signals” exist with bigger responses? Are they proportionate?</td>
</tr>
<tr>
<td>Cessation of exposure</td>
<td>Does the “signal” stop at the end of exercise?</td>
</tr>
<tr>
<td>Strength</td>
<td>What is the effect size of the association?</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Is there plausible physiological mechanism between signal and response?</td>
</tr>
<tr>
<td>Coherence</td>
<td>If an experiment is possible, is its findings concordant?</td>
</tr>
</tbody>
</table>

Activities provided here should also inform students that some criterion is impeded (e.g., the application of an antagonist for a receptor), and any ventilatory responses are recorded.
items” can firmly establish cause-effect relationships. However, for investigations to provide strong evidence for a particular control mechanism, or group of mechanisms, they need to demonstrate that it can account for the specific characteristics of the normal exercise response, as described above (e.g., stimulation of the control mechanism should result in a large increase in ventilation; indeed, if it is the only mechanism involved, then it should cause the +150 l/min observed in heavy exercise).

**Experimental design.** When evaluating any research study, it should be made clear to students that the design of the investigation should first receive thorough critical attention. After all, inadequately controlled methodology produce meaningless results and conclusions. All investigations are different, and so there is no set strategy to achieve this, but both reliability and validity should be questioned. Reliability refers to the findings’ repeatability when the same (or similar) methodology is used, either within the same research group, or preferably when employed by independent investigators. Unfortunately, what students will likely find is that several important exercise respiratory control experiments have only been attempted once.

Validity can be divided into both internal and external components and refers to the credibility of the research. Internal validity describes whether the study has measured what it aimed to measure, or how well it has been controlled. For example, during a “stimulation” study, it is vital that the applied stimulus must be similar to that observed during normal exercise, if the physiological relevance and plausibility of the control mechanism are to be established. External validity refers to how well the results can be applied to populations beyond the immediate study. Although many studies are only possible in animals, largely due to their invasive nature, human studies will always have a greater degree of external validity. However, as a counterbalance, animal studies might provide greater internal validity, as they have the potential to be better controlled (e.g., anesthetization, spinal cord transection, etc.).

Another important factor to consider is sample size. In the area of exercise ventilatory control, published investigations comprise a wide range. There is no consensus on “how many is enough”; one could argue that generating statistically significant data indicates a sufficient sample size. So even studies with two or three subjects are suitably powered if their effect sizes are large and variability low enough (i.e., a high signal-to-noise ratio). However, too few participants clearly risks reducing external validity and might provide a poorer estimation of variability. Furthermore, if statistically nonsignificant findings are generated, it becomes difficult to establish whether this is indeed at true negative or a false negative (type II error) due to insufficient sample size.

Conversely, findings from larger samples enhance their external validity by increasing confidence that they are representative of the true population. However, it is not practical, or ethical, if invasive experimental techniques are used, to conduct studies with unnecessarily large numbers of subjects. In addition, very large sample sizes will help small effects find statistical significance and could generate false positives (type I error). As such, students should be aware that finding statistical significance does not necessarily infer meaningfulness: physiological/clinical significance always remains at the reader’s discretion.

**Other considerations.** Should the design of the investigation meet the required standards, there are a few final questions students might consider when evaluating the conclusions drawn from the study. Are the conclusions supported by the evidence? If so, is the degree of certainty supported by the strength of evidence? How well do the conclusions fit with other evidence? Are any assumptions made? Are the claims made by a credible source (e.g., good reputation, any vested interests, appropriate expertise, peer reviewed?). And finally, what is your overall judgment?

**Physiologically Plausible Mechanisms Controlling the Exercise Hyperpnea and Their Evidence**

Due to the immediacy of the ventilatory response to exercise and its tight coupling to metabolic rate during submaximal exercise, it has long been postulated that multiple mechanisms, both neural and humoral in nature, control the hyperpnea, a neurohumoral theory (24). This is because it is assumed that only neural feedback or feedforward mechanisms can account for its speed, and only a humoral mechanism would work as an effective metabolic rate sensor, and so could explain the characteristic phases I and II/III (Fig. 1) of the hyperpnea, respectively. However, it must be noted that the control of the response is likely far less discrete in nature, with complex interactions occurring between different mechanisms that integrate onto common pools of neurons involved in cardiorespiratory regulation (10, 16, 17, 38, 48, 50, 55, 56).

The aim of the present article is not to critically review the numerous postulated mechanisms and their evidence (see Table 3 and reviews listed above), but to demonstrate how students can learn critical-thinking skills by evaluating them. As a first step, students should be provided with an objective and systematic process of analyzing evidence, which they can learn, develop, and apply themselves. Broadly, for each mechanism, this process consists of:

1. Examining the mechanism’s rationale
2. Assessing its “observational” evidence
3. Evaluating the strength/limitations of its “experimental” evidence
4. Finally forming an overall conclusion.

Of course, evaluating observational and experimental evidence will use those concepts laid out in Investigating the Phenomenon or Problem: the Control of the Exercise Hyperpnea.

Table 3. A selection of some the most widely hypothesized exercise ventilatory control mechanisms, and examples of their key research studies

<table>
<thead>
<tr>
<th>Hypothesized Control Mechanism</th>
<th>Ref. Nos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oscillations in arterial CO2/H+</td>
<td>2, 6, 7, 13, 35, 46, 53, 65</td>
</tr>
<tr>
<td>Increased chemosensitivity</td>
<td>2, 5, 13, 20, 21, 23, 26, 35, 53, 61</td>
</tr>
<tr>
<td>Skeletal muscle afferent feedback</td>
<td>1, 3, 4, 37, 39, 45, 52, 62</td>
</tr>
<tr>
<td>Central command</td>
<td>14, 27, 30, 32, 53</td>
</tr>
<tr>
<td>Arterial potassium and/or catecholamines</td>
<td>8, 15, 18, 22, 33, 47, 49, 51, 57</td>
</tr>
<tr>
<td>Cardiac afferent feedback</td>
<td>9, 14, 36, 40, 60</td>
</tr>
<tr>
<td>Learned response</td>
<td>42, 54, 64</td>
</tr>
</tbody>
</table>
Depend on previous knowledge, I have found that an effective method of ensuring that students practice examining bodies of evidence is to ask small groups to prepare and perform a presentation to their peers. The aim of each presentation is to describe and evaluate one proposed mechanism (Table 3), each of which has been drawn from their previous PBL session (above). Students must follow a systematic approach in their analysis and presentation of evidence, perhaps similar to the process provided to them, although they should be encouraged to adapt it if they feel necessary. Presentations are then followed by questions from their peer audience members and the provision of written feedback. Peer-to-peer presentations have several advantages: they give students the opportunity to independently apply critical assessment skills; they often encourage wider reading beyond the suggested reading material; they help to develop collaboration and oral communication skills; and they are very helpful at highlighting those areas of understanding that are lacking. I have found it useful if teachers provide an example presentation first, and, after the completion of all presentations, they should give a lecture (or small-group teaching session) to cover any points missed, answer questions, discuss the wider implications of the research, and to bring each individual presentation into an overall context.

To introduce additional learning opportunities, alongside the peer-to-peer presentations, written course work can be set that involves data handling and interpretation. I provide students with a set of respiratory data in an excel spreadsheet and the written methodology of a study from which it has been gathered. The study and its data are invented (but based on previous works in the literature), and they offer insight into one of the potential mechanisms. I then ask students to plot the data into the most appropriate graph(s) and write a results and discussion section similar to those found in a research article. In this way, students can better understand the most suitable formats to present different types of data, but also critically assess the methodology of the study and discuss the results in the context of the wider literature.

The variety of teaching methods described above (presentations, PBL, course work, lectures/seminars) offers students the opportunity to learn a mixture of important and transferable skills. The feedback that I have received also shows that they help keep students engaged and interested in the topics under question, far more than a set of one-dimensional lectures. Furthermore, because creating and performing presentations, or participating in PBL sessions, are much more student-centered approaches, it encourages the development of learner autonomy and independent problem solving. Indeed, I am always impressed to see how quickly students can develop the confidence to discuss scientific evidence and offer their own insights.

If No Strong Evidence Exists, Why Might This Be? How Can It Be Resolved?

In general, this could be due to a variety of reasons. Perhaps few scientists have studied the area, and so there is still a limited body of evidence available. Maybe technology is not advanced enough to reveal the evidence needed. Perhaps the focus of scientists has been to naively test unimportant hypotheses (shooting in the dark), or test incorrect hypotheses inappropriately. Maybe the true answer is so complex that it will always remain beyond our understanding, or at least beyond our capacity to uncover it.

In the case of exercise ventilatory control, the lack of strong evidence is certainly not due to a lack of trying (e.g., Refs. 3, 5, 22, 27, 30, 37, 41, 60), and I refuse to believe (perhaps naively) that our understanding will always remain so limited. So, with this in mind, I enjoy challenging students in seminars and small-group teaching sessions to think for themselves as to why this distinct lack of evidence exists, “because I certainly don’t have the answer.” Have scientists been testing ideas in the wrong way? How could we improve on previous experiments? This is a great opportunity for students to integrate all of the knowledge and understanding they have picked up while studying the area and apply it onto something new, and, because the area is so broad, a real freedom is given to them.

Students raise two concepts repeatedly: redundancy and synergy. Perhaps multiple mechanisms are responsible for the breathing response to exercise, but, when one is experimentally manipulated, the effects are masked. So, if we inhibit a mechanism during exercise, no/small changes are observed because other mechanisms are still capable of generating the entire response: redundancy. Conversely, if we stimulate one mechanism at rest, no/small changes are observed as synergistic interactions may exist between mechanisms, where the overall response is greater than the sum of its parts: synergy. These concepts in exercise ventilatory control have not been well examined (16, 17), but that is certainly not because studies would be impossible or impractical. Therefore, I like to ask students to propose research studies designed to uncover these concepts, as in doing so it can help them understand the processes of forming a research question and developing an appropriate protocol to help them answer it.

Concluding Remarks

Offering physiology students a thorough education of the control mechanisms underlying the ventilatory response to exercise provides them with an excellent opportunity to further develop critical-thinking skills. Studying an area with little or no scientific consensus allows for the better development of skills required to objectively evaluate evidence, while also giving students the freedom to think for themselves and problem solve. These transferable skills are vital tools for students to learn, adapt, and then apply themselves, and a mixture of teaching strategies is discussed within this article that aim to develop them.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

R.M.B. conceived and designed research; prepared figures; drafted manuscript; edited and revised manuscript; approved final version of manuscript.

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