

Challenges for Future Research in Exercise Physiology as Applied to the Respiratory System

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DEMPSEY, J.A. Challenges for future research in exercise physiology as applied to the respiratory system. *Exerc. Sport Sci. Rev.*, Vol. 34, No. 3, pp. 92–98, 2006. *Some of the major unresolved questions in the respiratory physiology and pathophysiology of exercise are addressed. To solve many of these difficult basic problems and to understand how systems operate alone and in combination in an integrated fashion, truly experimental integrative physiological approaches are required in both humans and animals.* **Key Words:** hyperpnea, pulmonary circulation, training effects, lung structure, integrative physiology

INTRODUCTION

Throughout the later 19th and initial two thirds of the 20th century, important fundamental principles of respiratory system physiology and methodology were established by many pioneering investigators from Zeppert and Gunst and August Krogh, to Wallace Fenn, Herman Rahn, Jere Mead, and Erling Asmussen. In the past three decades or so, many physiologists have built on this fundamental base and in addition have devoted significant amounts of their careers to deciphering how the respiratory system responds to exercise and the causes and consequences of these responses.

So what are the major questions remaining and how do we go about resolving them? To address these issues, I asked several currently active scientists in the field (see Acknowledgments) to identify their favorite unresolved problems and how they thought these problems should be investigated. I have provided a brief summary of their input, heavily spiced with my own biases. I have concentrated my efforts on problem identification with special emphasis on those requiring an integrative physiological approach for solution.

EXERCISE, ISOCAPNIC HYPERPNEA

This problem remains one of the “holy grails” of respiratory control, namely, “What is the mechanism that links alveolar

ventilation to metabolic CO₂ production, so that the downstream arterial PCO₂ and pH are so precisely regulated across a wide range of mild to moderate intensity, steady-state workloads?” This topic was recently debated in the Point-Counterpoint series in the *Journal of Applied Physiology*. Although only a relatively small group of investigators continues to investigate this problem, both the debate itself, and especially the many written commentaries, revealed that the hyperpneic mechanism remains highly controversial (14). Two classes of mechanisms have garnered the most attention and have survived the intense research and debate on this question in the 1960s through the 1980s. They include feedback from working skeletal muscle and feed-forward from supramedullary motor areas on the drive to breathe. After-effect, or short-term potentiation of ventilatory drive, has been a logical addition to either primary stimulus when viewed as a centrally mediated potentiation effect that sustains hyperpnea even after a stimulus is withdrawn.

Feed-Forward Control of Hyperpnea

There is sufficient evidence—much of it with ingenious unanesthetized animal preparations—to support the feed-forward effects as significant effectors of hyperpnea. An important advance needed here is in further refinement of the “central command” stimulus, beyond the current use of pharmacologic and/or electrical stimuli in specific brain regions, in the hope that such models will produce rhythmic locomotor responses over a wide range of intensities that mimic the physiological condition. A more thorough understanding of the neural circuitry and dendritic connections between motor areas and the medullary respiratory rhythm generator is required before the models can be developed. We need to know how central command is organized and how it affects

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Accepted for publication: March 16, 2006.

Associate Editor: Susan R. Hopkins, M.D., Ph.D.

0091-6331/3403/92–98
Exercise and Sport Sciences Reviews
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motor outputs, including subpopulations of pattern generators. My bias is that the evidence to date demonstrating a major contribution from central command to exercise hyperpnea, as established with current models (3,14), will be confirmed and its fundamental mechanisms much better understood.

An alternative feed-forward-type influence has been proposed, stimulated at least in part by the concept that the “integrative” function of the medullary respiratory neurons is likely incapable of solving the complex differential equations associated with simultaneous input from multiple peripheral reflexes. Accordingly, the higher central nervous system must rely on stored or learned information and practice “adaptive feed-forward control” to accomplish error-free ventilatory responses to exercise. Initial attempts at regional brain imaging during “imagined” exercise conditions have revealed that ventilation may be driven by neural circuitry involving both locomotion and voluntary respiratory control, such as that originating in the dorsolateral prefrontal cortex (13). Further investigation of this intriguing concept would benefit greatly from the development of methods that would permit precise regional brain imaging during actual dynamic exercise. These types of investigations should also be applied to clinical patients with lesions or postischemic damage to areas of interest. The cerebellum also deserves further intense study as a potential site for activation and storage of the respiratory motor program during exercise.

Feedback Control of the Hyperpnea

Of course, none of the locomotor-linked mechanisms are directly sensing the regulated variable, namely, alveolar or arterial PCO_2 and the key ratio of alveolar ventilation to CO_2 production. Older work, using sinusoidal exercise in varying time domains in humans, separated changes in metabolic rate from those of locomotor activity and showed that ventilation tracked the former (14). Examples obtained even in resting humans and animals from many species subjected to a wide variety of perturbations from hypoxia to extreme environmental temperatures to variations in diet show that metabolic CO_2 production is a key underlying determinant of eupneic ventilation. I refer here not to arterial or brain PCO_2 or conventional chemoreceptor stimuli—but rather to CO_2 production—as the “tonic drive” to eupnea. In addition to the many examples of a $\dot{V}_A:\dot{V}CO_2$ proportionality previously cited, simply consider the equivalent alveolar PCO_2 s achieved among individuals of drastically differing body mass and CO_2 production—obviously, alveolar ventilation tracks metabolic requirement.

Is it the metabolic CO_2 production or the gas exchange component of CO_2 acting at the lung that is the critical regulator here? Correlative data involving transient ventilatory changes with a rising metabolic rate during either exercise at a constant workload in humans (*i.e.*, so-called Phase 2 of the ventilatory response) or in response to the increasing metabolic requirements in the developing chick embryo clearly show that the *gaseous component* of tissue metabolism is the primary effector of the accompanying ventilatory adaptation. These data are analogous to older findings using extracorporeal CO_2 scrubbing in conscious resting animals, in whom ventilation fell from eupnea to apnea precisely in proportion to the removal of CO_2 venous

flow to the lung. These claims and conclusions were hotly debated throughout the 1970s and 1980s (2).

I think it doubtful that the CO_2 exchange “stimulus” is sufficiently robust to be solely responsible—or even the primary drive—for the 5- to 10-fold increase in ventilation achieved during isocapnic exercise hyperpnea (2). In addition, although there have been some receptor sites identified in the lung that directly link CO_2 flow and ventilation, the response gain of these receptors is insufficient to account for a significant portion of the hyperpneic response (2). However, somatic afferents from limb muscle receptors sensitive to venous distention have been identified that may allow medullary respiratory neurons a means of monitoring at least the blood flow component of CO_2 flow during exercise (14). Whether these afferent inputs have sufficient gain to mediate the entire exercise hyperpneic response is doubtful—but remains to be tested in intact physiological preparations.

This mechanism of $\dot{V}_A:\dot{V}CO_2$ linkage is clearly important to ventilatory control under any condition—wakefulness, sleep, exercise, hypoxic exposure, disease states, etc.—but few investigators are seriously pursuing this problem anymore at any level, from the *in vitro* brainstem spinal cord preparation to the whole animal. Is tackling the complexity of these integrative systems with multiple built-in redundant mechanisms just too burdensome anymore? Or perhaps we simply fear that grant-governing agencies will dismiss the idea out of hand? This is clearly an issue for a multitalented team of visionaries, preferably those who are willing to start with the belief that CO_2 exchange is truly the underpinning to ventilatory control and that “somewhere out there” exist the appropriate receptor sites, specific stimuli, and the neural pathways. For respiratory physiologists and neurobiologists uncovering the mechanism of the primary exercise, hyperpnea stimulus and the $\dot{V}_A:\dot{V}CO_2$ linkage should be a priority.

In summary, three primary mediators of hyperpnea have emerged, namely: central command, feedback from locomotor muscle, and the underlying CO_2 flow. The dilemma is that although each forms a significant contribution when studied in isolation, none seems to be obligatory to the response. A key to truly understanding the control of exercise hyperpnea will be to quantify the interactive effects of these combined stimuli.

THE HYPERVENTILATION OF HEAVY EXERCISE

What are the “extra” ventilatory stimuli accompanying heavy exercise that drive ventilation out of proportion to $\dot{V}CO_2$? Why is the hyperventilatory response delayed at the onset of heavy exercise? Current candidates include added input from the carotid chemoreceptors responding to arterial $[H^+]$ or $[K^+]$, or temperature and/or disproportionate increases in central command or sensory input from locomotor muscles as limb muscle fatigue progresses. None of these seem to be obligatory. Perhaps we are simply examining the wrong stimuli? What about components of the strong ion difference as the ventilatory stimulus during heavy exercise? Or changes in the peptide hormone angiotension II (8)? Given their response characteristics, the carotid chemoreceptors must contribute in part to this hyperventilatory response, but the definitive experiments to test the role of

these unique receptors have not yet been done. Denervation studies are not the answer. In all likelihood, denervation is accompanied by significant changes in key elements of the remainder of the control system—both peripheral and central. Preferably, these reflex contributions need to be studied in intact, exercising preparations in which the stimulus to the carotid chemoreceptors can be isolated and controlled. We also need to know if and exactly how the onset and progression of limb fatigue in heavy exercise recruits more motor units via central command and precisely how this central motor command is linked to medullary respiratory neurons or if it relies on cortical spinal pathways, as does a significant portion of the “voluntary” control of breathing. *In vitro* research over the last decade has brought us closer to defining exactly where the areas of rhythm generation are located in the medulla, so further work on how these are linked to higher suprapontine motor areas should be forthcoming.

REFLEXES FROM THE LUNG AND RESPIRATORY MUSCLES

Reflexes from the airways and pulmonary vasculature have been studied extensively, mostly in isolation, and shown to have important widespread influences on breathing pattern and respiratory muscle recruitment and de-recruitment. The long-held generalization is that the same reflexes are important determinants of the volume and timing of each breath so that the work of the respiratory muscles is minimized as hyperpnea develops during exercise. However, the experimental evidence is lacking during the exercising state to address such fundamental problems as the specific role of pulmonary C fibers and pulmonary stretch receptors on breath timing, the recruitment or de-recruitment of accessory respiratory muscles as diaphragm fatigue develops in heavy sustained exercise, and the regulation of end-expiratory lung volume as expiratory flow limitation is approached. Are these reflexes controlled by the many potential feedback loops from the lung, airways, and the chest wall? Or is there a significant amount of central “preprogramming” as a result of previous experience? Decades ago, a role for increases in interstitial fluid pressure in the lung during heavy exercise was postulated as a mechanism of inhibiting locomotor muscle force output and therefore exercise performance. These vagally mediated influences from the lung have been eloquently demonstrated in the exercising animal, but their role during exercise under physiological conditions remains untested.

RESPIRATORY MUSCLE FUNCTION AND RESPIRATORY/CARDIOVASCULAR INTERACTIONS DURING EXERCISE

We now have a fairly comprehensive knowledge of recruitment patterns of most of the inspiratory and expiratory muscles during exercise and a rough idea of their relative contributions to the total ventilatory response. We also have some estimates of the relative demands made on pressure generation of the inspiratory muscles relative to their dynamic capacity during maximum exercise and evidence that significant

exercise-induced peripheral fatigue of the diaphragm and expiratory abdominal muscles does occur, but only as a result of high-intensity, sustained whole body exercise. It is important to clarify that significant “fatigue” of the respiratory muscles does not mean “task failure” in terms of a compromised ventilatory response to heavy-intensity exercise; however, exercise-induced respiratory muscle fatigue may influence systemic blood flow distribution, with implications for exercise performance limitation (see succeeding sections).

Respiratory Versus Locomotor Muscle Blood Flow Distribution

A limited amount of information is available to suggest that the respiratory muscles require a significant share of the cardiac output during exercise—possibly competing with the locomotor muscles—especially in very heavy intensity exercise. What factors determine this distribution of the rising cardiac output? As sympathetic vasoconstrictor activity increases with exercise, it is likely to be nonselectively distributed throughout the systemic vasculature; accordingly, the need to compare the responsiveness of resistance vessels in these different vascular beds with adrenergic stimulation and also with local vasodilator mediators. Some *in vitro* works suggest that the diaphragm arterioles might indeed respond quite differently than those in limb locomotor muscles. However, we also need *in vivo* studies that will compare the effects of adrenergic agonists and antagonists on locomotor and respiratory muscle vasculatures at varying exercise intensities. Chronically instrumented exercising animal models with a capability for measuring multiple blood flows and for delivering drugs to specific vascular beds do exist that, along with *in vitro* systems, should be used to answer these questions (11).

Respiratory Contributions to Sympathetic Outflow

A related question is what mechanisms contribute to the increased sympathetic vasoconstrictor activity in exercise, whose purpose it is to constrain muscle blood flow and help maintain systemic blood pressure. Might there be some significant influence from respiratory system structures in addition to the documented contributions from central command and limb muscle reflexes? One possible contributor may originate in respiratory muscle metaboreceptors leading to increased phrenic nerve afferent activity and sympathetic efferent stimulation—but we do not know exactly how these reflexes might be activated during exercise. Another possible source of sympathetic activation may be via the carotid chemoreceptors—known to be sensitized during even mild and moderate exercise intensities—which, when stimulated, provide a substantial and long-lasting increase in sympathetic vasoconstrictor outflow. The carotid chemoreceptors have been implicated in many fundamental homeostatic functions. Their homeostatic role during exercise has yet to be determined in health and especially in diseases such as heart failure where chemoreceptor sensitivity is greatly augmented.

The Respiratory Muscle Pump

In addition to these reflex effects influencing sympathetic nerve activity on blood flow distribution, it has long been appreciated that changes in intrathoracic and intra-abdominal

pressures during breathing, that is, the so-called respiratory pumps, will influence venous return, ventricular preload and after-load, and stroke volume. However, although exercise produces the largest intrathoracic and intra-abdominal pressures of any physiological state, we are almost completely ignorant of how these respiratory-induced pressures influence cardiac output during exercise, primarily because almost all studies of these cardiorespiratory links to date have been carried out in anesthetized animals. The contributions of cardiorespiratory mechanical coupling to cardiac output are likely to be significant during exercise—even in health—but this needs to be quantified under physiological conditions, and the influence of both inspiratory and expiratory intrathoracic pressures induced by exercise needs to be considered. We need now to expand on these limited observations using precise measurements of cardiac output and blood flow distribution over a wide range of whole body exercise intensities in health and in such relevant diseases as chronic airway diseases and heart failure.

PULMONARY CIRCULATION AND GAS EXCHANGE

The lung parenchyma and airways are built in healthy adults to handle the challenges of increased requirements for gas exchange improved by exercise. A consistent inefficiency in the gas exchange response to exercise is the widening of the alveolar to arterial PO_2 difference, which begins with the onset of moderate intensity exercise and is usually caused by an increased alveolar PO_2 and unchanging arterial PO_2 . A minority of highly fit men and women show an additional widening of $A-aDO_2$ as PaO_2 actually falls below resting levels. The causes of this widened $A-aDO_2$ and its variability among healthy subjects remain unknown.

Ventilation to Perfusion Distribution

The application of the multiple inert gas technique to exercise has helped enormously in defining ventilation to perfusion distribution ($\dot{V}_A:\dot{Q}$) and has shown that the $\dot{V}_A:\dot{Q}$ distribution throughout the lung does increase in heterogeneity with exercise in most healthy subjects. However, our knowledge of the behavior of the pulmonary circulation during exercise is limited, and its influence on gas exchange is not completely understood. For example, during extremes of exercise in athletes, there is evidence for an increased permeability of the blood:gas barrier, allowing the transport of plasma proteins to the alveolar spaces (6); however, there is no evidence that this disruption influences alveolar-capillary diffusion or $\dot{V}_A:\dot{Q}$ distribution. Furthermore, we are not yet capable of quantifying extravascular lung water or its potential accumulation during exercise—although improved imaging techniques will hopefully soon permit such quantification.

Intrapulmonary Shunts?

Recent evidence shows that transpulmonary passage of contrast microbubbles in healthy humans is induced by exercise. One interpretation of these data was that it supported the opening of intra-pulmonary shunts, a notion that had been

suggested many years before in human autopsy specimens. However, it is far from established whether these findings actually do represent a recruitment of vessels that do not participate in gas exchange or whether this only represents extreme capillary dilation. Further detailed research is needed to determine whether biodegradable microspheres of known, fixed size do indeed bypass the lung during exercise and—if so—to reveal (perhaps using fluorescent techniques) the location and function of these so-called shunt vessels. The existence—if true—of even very small shunts of mixed venous blood could explain much of the inefficiency in gas exchange during exercise and its variability amongst normal subjects; it might also help explain individual variations in flow-mediated increases in pulmonary capillary wedge pressures during exercise.

Diffusion Disequilibrium

The assessment of alveolar-capillary diffusion equilibrium during exercise remains unquantified. We currently have only an indirect estimate, that is, using the portion of the alveolar to arterial PO_2 difference that remains after $\dot{V}_A:\dot{Q}$ distribution is quantified. Red blood cell transit time during exercise remains only an approximation, and importantly, the distribution of these transit times under conditions of increased pulmonary blood flow has not yet been quantified, although clearly it is important to gas exchange efficiency during exercise. Furthermore, what about the equally fundamental question of diffusion limitation to CO_2 during exercise? We need to follow up on older evidence that a significant equilibrium deficit for CO_2 (within the pulmonary capillary blood) may lead to sizeable arterial to alveolar PCO_2 differences during exercise.

TRAINING EFFECTS AND PLASTICITY IN THE RESPIRATORY SYSTEM—GOOD OR BAD?

Lung, airway, and vascular structures seem to be resistant to the stimulus of physical training. It is not uncommon to observe larger lung volumes, maximum flow rates, and pulmonary diffusion capacities in some highly trained endurance athletes of all ages, but these cross-sectional comparisons suffer severely from selection bias. That is, are the altered structures a result of training or does the athlete bring them to the sport? The few available longitudinal training studies of humans and animals to date are mostly negative. There are several reasons that this question needs further investigation, especially in humans throughout maturation and aging and with different types of endurance training, including aquatic training.

Structural Adaptability

Lung structures clearly adapt in response to many chronic stressors, as shown in the enhanced alveolar septation, capillary growth, and diffusion surface area in response to pneumonectomy, pulmonary artery ligation, chronic hypoxia—either from birth or during maturation. Even energy restriction and refeeding influence lung structure. Across (most) mammalian species, lung diffusion surface area relates closely to metabolic rate, implying that the animals' habitual metabolic

rate has been an important selective force in shaping pulmonary gas exchange structures.

Functional Implications

The implications to function of respiratory adaptations to training—or lack thereof—are substantial. For example, if training selectively alters only the cardiovascular and muscle metabolic determinants of O₂ transport and utilization, the once “overbuilt” lung and airways in the untrained individual may become the weak link—resulting in hypoxemia and expiratory flow limitations in the trained. This is especially true in the aging lung—even in the nonsmoker—that undergoes very large reductions in lung elastic recoil and diffusion surface at the same time as the pulmonary vasculature and chest wall lose compliance. Therefore, flow limitation, hyperinflation, and increased dead space ventilation are common during exercise in healthy older persons. It would, of course, be of great practical importance that physical training produces significant adaptations in the lung and airways in healthy older persons; but to date, the limited longitudinal findings show little or no training effect on the progressive deleterious effects of aging on lung elastic recoil and function.

Maladaptations

The lung/airways may show structural maladaptations to intense physical training, as shown via serial biopsies in the increased collagen deposition and remodeling of the airway's basement membrane in cross-country skiers. Such respiratory maladaptations are also implied by the excessively widened A-aDO₂ in many highly trained athletes, observed even during submaximal running. Does release of inflammatory mediators in the airways—especially during exercise in cold dry air—play a role in this remodeling? On the vascular side, are the acute injuries to or fractures of the alveolar-capillary interface in the athlete or profound shear stresses at high flow rates acting on the pulmonary vascular endothelium producing permanent structural alterations in the diffusion pathway?

Training and the Pulmonary Vasculature

Do the large training effects on endothelial-dependent vasodilation in conduit arteries that occur in skeletal muscle also occur in pulmonary arterioles? And if so, would this be effective in reducing pulmonary vascular resistance and therefore pulmonary artery pressures at the high cardiac outputs experienced by the athlete? If not, why should the pulmonary resistance vessels respond so differently to training than those in skeletal muscle? Alternatively, are pulmonary vascular pressures during exercise purely a function of the structural and functional characteristics of the left heart that do undergo significant potentially beneficial changes with training?

Respiratory Muscle Remodeling

Recent evidence in healthy animals and in patients with chronic obstructive pulmonary disease (using biopsy material) shows a remarkable remodeling of the diaphragm in response to chronic overload, consisting of fiber-type transformation, increased oxidative capacity and decreased glycolytic capacity, and shifts in myosin (9). Similarly, remodeling

occurs in the diaphragm in response to chronic lung hyperinflation and muscle shortening, as shown by a shift of the operational length:tension relationships that preserve force generation at a shorter muscle length. The functional significance of these remarkable morphologic adaptations, especially to the exercise response, and whether some of these morphologic adaptations might also be instigated via voluntary respiratory muscle training have yet to be defined.

Neuroplasticity

Recent evidence has accumulated showing a substantial neuroplasticity in ventilatory control in response to chronic intermittent stressors, such as hypoxia and especially intermittent hypoxia. Thus far, no attention has been paid to whether neuroplasticity might also occur in response to chronic physical training with, for example, the reflex sensitivity of the carotid or medullary chemoreceptors.

RESPIRATORY SYSTEM PATHOPHYSIOLOGY IN THE ENDURANCE-TRAINED ATHLETE

Respiratory system problems in the endurance-trained athlete often present special challenges to clinical diagnosis and treatment, principally because of the extraordinary demands their high workloads place on gas transport, both in their competitions and even in their daily training. The extraordinary lengths these athletes will pursue—ethically and otherwise—to achieve success also presents unique dilemmas. These problems have not been emphasized in the clinical literature; they need to be publicized and pursued. Some of the more interesting problems raised by colleagues in the field to me or repeatedly called to my attention by sports medicine physicians over the past several years include the following.

Beyond Exercise-Induced Asthma

Airflow limitation leading to dyspnea and curtailed performance during heavy-intensity exercise is not an uncommon complaint among the highly trained. The usual diagnosis is exercise-induced asthma, and long-term pharmacologic treatments are commonly initiated, even in the adolescent or pre-adolescent years. More and more of these cases are slowly revealing themselves to involve the *extrathoracic*, that is, upper airway at the level of the larynx, causing inspiratory stridor, severe flow limitation and dyspnea, hypoxemia, CO₂ retention and performance limitation. We know very, very little of the physiology and neurophysiology of the upper airway during exercise!

Other cases of exercise-induced airflow limitation also occur in healthy, intrathoracic airways simply because the demand for expiratory flow rate exceeds the maximum flow volume envelope. In the highly fit older person, the role of the lung and airways as a limitation to exercise and a source of exertional dyspnea is another case where appropriate use of the tidal flow:volume loop during exercise will identify normal, age-dependant loss of lung elastic recoil combined with high ventilatory requirements.

The occurrence of arterial hypoxemia in the highly trained young adult athlete seems to have many causes, including

small right to left shunts, flow limitation, even (rarely) pulmonary emboli. For example, intracardiac shunts of varying magnitude are thought to be present in more than 30% of the normal population; their effect on arterial oxygenation can be substantial, as mixed venous O₂ content falls markedly in heavy exercise. Their means of diagnosis is minimally invasive and should be used to investigate causes of exercise-induced arterial hypoxemia in the athlete.

Shear Forces in the Pulmonary Circulation

Although the pulmonary circulation is indeed the lower-resistance circuit even in heavy exercise, the extraordinary cardiac outputs in the highly trained athlete may serve to push pulmonary-capillary pressures to levels where extravascular lung water might accumulate and fracture of the blood gas barrier may occur. How prevalent are these occurrences in endurance athletes who are capable of sustaining very high intensity exercise? Furthermore, are these high pulmonary vascular pressures dangerously exacerbated when the athlete trains daily and competes at even moderately high altitudes, thereby adding the stress of hypoxic pulmonary vasoconstriction? Perhaps repeated, intermittent insults such as these result in permanent damage to the vascular endothelium?

Intermittent Hypoxia

How about the popular practice of “live high, train low?” We know that at least some elite athletes improve their performance at sea level, although appropriate, motivated placebo groups need to be incorporated into these studies. An overriding question with this practice is, at what cost are these relatively small, often-inconsistent increments in performance achieved as elite athletes seek out more and more severe levels of environmental hypoxia to gain an edge? Does sympathetic vasoconstrictor activity stay elevated even after a few hours of repeated hypoxic exposures, and if so, what are the effects on the vessel endothelium and systemic vascular resistance? Is there any remodeling of the pulmonary vascular smooth muscle with prolonged bouts of intermittent severe hypoxemia? Although not exactly analogous, the recent accumulation of evidence documenting the detrimental cardiovascular effects of intermittent hypoxia that attends obstructive sleep apnea and the carryover effects of sojourning to high altitude on sympathetic nerve activity and blood pressure upon return to sea level should provide enough impetus to look further into the potential downside of this increasingly popular practice.

It is well established that hypoxia is a stressor to which the human cardiopulmonary system in adult humans “reacts” rather than truly adapts. In many cases, the negative side effects of these responses to hypoxia, such as sympathoexcitation, pulmonary vasoconstriction, cerebral and retinal vasodilation, erythropoiesis, and hypocapnic hyperventilation, often outweigh their positive adaptive influences. We need to respect and fully explore the physiological cost of these reactions when we subject healthy humans to hypoxia!

Respiratory Limits in Subpopulations

Based on normal reference standard data derived from population studies, we know that maximal expiratory flow

rates, lung volumes, and diffusion capacity, after matching for age and body habitus, are compromised in healthy adult women (vs men) and in African Americans (vs whites). Do these apparent structural differences in the lung also mean that alveolar ventilation and/or alveolar to arterial gas exchange is compromised during exercise in these subgroups, especially in the endurance-trained athlete?

SOME SUGGESTED APPROACHES

Clearly, the problems to be solved in this field are not getting any easier and their solutions will require some truly innovative approaches. A recently published debate proclaimed the relative benefits of molecular/cellular biology versus classical physiological approaches in solving the diagnosis, prevention, and treatment of respiratory diseases (12). These types of debates (by definition) present polarized positions; however, such divisive stances are also not uncommon among scientists and policy makers in discussions held at granting agencies. Over the past decade or two, we have witnessed an explosion of cellular and molecular biological methods and the use of reductionist models. On the other end of the investigative spectrum, a population-based correlative approach has also gained great popularity. Traditional physiological approaches and physiologists themselves have been relegated to diminished roles and only recently have gradually begun to regain importance as science attempts to answer difficult biological questions in addition to carrying out sophisticated measurements.

Why is integrative physiology still relevant in the era of “new biology?” First, higher-order “expression” systems like transgenic animals can only demonstrate whether a given mechanism or pathology is *obligatory* to the function of interest. Just as with the classic denervation approach, we pretend that our perturbation only “knocked out” one specific pathway or mechanism and ignore—or at best only give lip service to—powerful secondary, redundant, compensatory changes accompanying the primary lesion. Equally frustrating, association studies linking oversimplified phenotypes with a genotype or haplotype of interest in large populations cannot distinguish correlation from cause:effect—despite efforts to statistically hold confounding variables constant. Michael Joyner argues that “...integrative physiology has the experimental tools and intellectual tradition needed to do the types of high resolution and detailed phenotyping required to actually understand how systems operate alone and in combination in an integrated way. Accordingly, it is likely to be the approach that allows us, on the one hand to put the reductionist ‘Humpty-Dumpty’ back together again and on the other hand to help the associationists determine what relationships are causal versus casual.”

To address these tough questions, truly modern “integrative physiologists” must be willing and able to apply both traditional organ system level as well as cellular and molecular level thinking and practices to experimental models that range from the intact human to an *in vitro* preparation to the single cell. It is likely that a team approach is required to fully address many of the important questions in our field,

the key point here being that *neither* the integrative, experimental systems approach *nor* the molecular methods or reductionist models be ignored in pursuit of the tough problems. Following is a mini list of potential approaches for just a few of the problems.

- The card-carrying neurobiologists need to become seriously involved in the exercise hyperpnea question—especially the question of how central command is tied to the medullary integrator, the mechanistic link of \dot{V}_A to $\dot{V}CO_2$, and the role of neuroplasticity in the maturation of the hyperpneic response. Given that there are still major disagreements over such critical details as the specific site(s) of the respiratory rhythm generator, the function of the pons, and where the central chemoreceptors and so-called central command centers for cardiorespiratory control are located, perhaps it is too much to expect at this time for the more “applied” questions to be addressed. However, some investigators are beginning to drive their reduced preparations with increasing stimuli. Hopefully, these bold new approaches will allow these powerful preparations to gradually strip away more of the “black box” that continues to mask our understanding of the neurobiology of hyperpnea.
- What genes or proteins are involved or required for the hyperpnea? The approach of chromosomal substitution is available to eventually produce a congenic rodent and allow focus on discovering the region of the chromosome where the critical genes are located (4).
- Lesioning of specific sites such as the mesencephalon or thalamic command areas in the suspected and known locomotory regions of the higher CNS needs to be tried to determine the nature of the central command stimulus; and in humans, recent exciting brain imaging work needs to be followed up (using real exercise when feasible) to uncover the neuroanatomical basis of central command.
- We need to improve our understanding of the compensatory mechanisms that minimize deterioration of exercise capacity in response to chronic stress on the respiratory system, such as environmental insults, lung resection, hypoxia, aging, or congenital defects. This approach requires whole organ combined with molecular level analysis in joining physiological, imaging, and morphometric approaches. As the genome of larger animals becomes known and as knockout animal models become more widely available, there are more possibilities than ever before to understand the integration among different levels of compensation (from gene regulation to cellular organization, tissue architecture, and organ function) in response to an imposed stress (7).
- Imaging methods aimed at the lung parenchyma and vasculature are advancing at a rapid rate and need to be applied to the exercising human to address fundamental questions concerning the microregulation of the pulmonary circulation and of extravascular lung water and turnover in exercise, as well as any short- and long-term airway adaptations that may accompany physical training (15).
- The special problems of diagnosis and treatment of special respiratory limitations uniquely experienced by the

endurance-trained athlete of all ages need to be tackled by investigative *teams* of clinicians and diagnosticians and physiologists. The potentially harmful “overdiagnosis” (and treatment) of presumed exercise-induced asthma is a special problem needing an in-depth critical examination.

Acknowledgments

The original work reported here was supported by NHLBI. The author is indebted to the following investigators who generously shared their ideas: Tony Babb, Kenneth Beck, Harold Bell, James Duffin, Marlowe Eldridge, Bert Forster, Ralph Fregosi, Norm Gledhill, Philippe Haouzi, Craig Harms, Sue Hopkins, Connie Hsia, Robert Johnson, Norman Jones, Michael Joyner, Kieran Killian, Sanford Levine, Andrew Lovering, Peter Macklem, Don McKenzie, Gordon Mitchell, Tom Robertson, Bill Sheel, Peter Wagner, Susan Ward, Karlman Wasserman, and Brian Whipp.

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