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AIR HUNGER: A PRIMAL SENSATION AND A PRIMARY ELEMENT OF DYSPNEA

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Abstract

The sensation that develops as a long breath hold continues is what this article is about. We term this sensation of an urge to breathe ‘air hunger’. Air hunger, a primal sensation, alerts us to a failure to meet an urgent homeostatic need –maintaining gas exchange. Anxiety, frustration, and fear evoked by air hunger motivate behavioral actions to address the failure. The unpleasantness and emotional consequences of air hunger make it the most debilitating component of clinical dyspnea, a symptom associated with respiratory, cardiovascular and metabolic diseases. In most clinical populations studied, air hunger is the predominant form of dyspnea (colloquially, shortness of breath). Most experimental subjects can reliably quantify air hunger using rating scales, i.e., there is a consistent relationship between stimulus and rating. Stimuli that increase air hunger include hypercapnia, hypoxia, exercise, and acidosis; tidal expansion of the lungs reduces air hunger. Thus, the defining experimental paradigm to evoke air hunger is to elevate the drive to breath while mechanically restricting ventilation. Functional brain imaging studies have shown that air hunger activates the insular cortex (an integration center for perceptions related to homeostasis, including pain, food hunger and thirst), as well as limbic structures involved with anxiety and fear. Although much has been learned about air hunger in the past few decades, much remains to be discovered, such as an accepted method to quantify air hunger in non-human animals, fundamental questions about neural mechanisms, and adequate and safe methods to mitigate air hunger in clinical situations.

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FURTHER READING

For information on dyspnea in general and how air hunger fits in:

Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau SC, Mahler DA, Meek PM, and O'Donnell DE. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 185: 435–452, 2012.

Keywords

Dyspnea; Breathlessness; Shortness of Breath; Suffocation alarm; Breathing Discomfort; Unsatisfied Inspiration; Silent hypoxia

Introduction

Most of us have held our breath. The sensation that develops as the breath hold continues, and eventually overwhelms our will and causes us to breathe again, is what this article is about. We use the term ‘air hunger’ to describe this sensation. Air hunger is a primal sensation that alerts us to a failure to achieve what is arguably our most urgent homeostatic need – to maintain gas exchange. As with other homeostatic warning signals such as thirst, hunger for food, and pain, ignoring them can be perilous so “they may dominate the stream of consciousness, and can have plenipotentiary power over behaviour.” (72). Denton has proposed that homeostatic warning sensations are the root of primal consciousness (71, 72). Maintenance of sufficient oxygen delivery to support cellular metabolism and maintain carbon dioxide levels to sustain pH are so critical and immediate that air hunger has evolved to be a powerful, emotionally potent signal that can divert attention from other homeostatic warnings, even pain. Air hunger is difficult to ignore because it can be very immediate and unpleasant, and because it generates fear and anxiety.

Finely tuned reflex responses control cardiopulmonary function – chemoreceptors adjust ventilation to regulate blood gasses, mechanoreceptors in lungs and respiratory muscles adjust respiratory muscle activation to adjust for changes of mechanical impedance and respiratory muscle function, blood flow is regulated to meet local tissue demands, cardiac output is controlled to meet blood flow demand, etc. Why is it necessary to devote cortical territory to conscious awareness of air hunger? There are many instances in which adjusting drive to respiratory muscles is insufficient to solve the homeostatic problem – complex and varied behaviors are needed. Consider the diving animal, who must be aware of the need to return to the surface. Consider the fleeing prey who must adjust running speed – fast enough to escape a predator, but not so fast that he collapses before reaching safety. In fact, the awareness of air hunger modulates common activities such as aerobic exercise, breath-hold diving, speech and food intake.

In addition, ***dyspnea*** (breathing discomfort) is one of the leading symptoms that cause people to seek medical care (a complex behavioral act), and it has a very significant impact on the lives of people with respiratory, cardiovascular and metabolic diseases. When describing their dyspnea, patients choose descriptors related to air hunger more frequently than other forms of respiratory discomfort. As described vividly by one patient: *“like a suffocation, frightened the life out of me…breath is more important than water”* (181). Sadly, inescapable air hunger has also been used as a means of torture (23).

Air hunger can safely be evoked in the laboratory by manipulating blood gasses and breathing pattern, and we can measure its intensity using well-established psychometric methods. This article will discuss what we know about the physiological mechanisms underlying perception of air hunger and related topics such as the language and

measurement of air hunger, afferent and central neural pathways underlying air hunger, and the relationship of air hunger to other sensations that comprise the larger category of dyspnea.

Definitions of 'Air Hunger' and 'Dyspnea'.

We define '***air hunger***' as the uncomfortable or unpleasant urge to breathe. Subjects most frequently liken air hunger to the feeling at the end of breath hold. As will become evident below, this sensation can be provoked either by a rise in respiratory drive or by a reduction in achieved ventilation; it reflects imbalance between respiratory drive and achieved ventilation. The 'Official American Thoracic Society Statement on Dyspnea' (ATS Statement) defines '***dyspnea***' as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity [and] vary in their unpleasantness and in their emotional and behavioral significance" (187). Air hunger is, we argue, the most important of those distinct dyspnea sensations.

The first published use of the term "air hunger" that we have discovered dates to an 1892 paper by Haldane and Smith (101): The experiment was conducted to test the proposition "that there are poisonous, volatile, and probably inodorous, impurities given off in respiration and perspiration along with carbonic acid". After remaining for 6 hours in a small sealed chamber in which CO_2 concentration rose to 5.8% and O_2 concentration fell to 14%, a subject reported *"very great **air hunger**",* expanding upon this he noted *"feeling as if one were not breathing at all".* The authors thus adopted the term "**hunger for air**" to describe the sensation that "must necessarily result from breathing such an atmosphere". Wright and Branscomb, in a paper that provided the fundamental definition used the term "air hunger" to refer to "breathlessness induced by the restriction of breathing" (245).

Laboratories vary somewhat in the language used, and another term in frequent use, '***unsatisfied inspiration***', has been agreed to be effectively synonymous with air hunger (180, 187). A number of other terms are related to air hunger, and it would be difficult to provide a complete list, but some examples may be found in a principle components analysis of a list of 45 common terms related to dyspnea (217); 8 terms were statistically related closely to air hunger: 'Cannot breathe deeply enough' (component loading = 0.86), 'Need to take a deeper breath' (0.83), 'Breathing too shallow' (0.77), 'Not satisfied by my breathing' (0.67), 'Can't get enough air into my chest' (0.67), 'Cannot breathe enough' (0.67), 'Hunger for more air' (0.52), 'Need to breathe' (0.47).

More general descriptors are commonly used by healthy subjects during exertion and by patients; these include 'short of breath' and 'out of breath' (USA), 'breathless' and 'puffed' (UK). These probably imply substantial air hunger as well as the sensation of breathing work and effort, but language studies to better define what specific sensations are covered by these terms have not been done.

Other prominent dyspnea sensations mentioned in the ATS Statement are *chest tightness* and sense of *respiratory work & effort*. The ATS Statement links specific sensory mechanisms to particular sensory descriptors. The sensation of excessive breathing work or effort is thought to arise from sensory mechanisms similar to those in other somatic muscles (muscle

afferents, and awareness of cortical motor command). The sensation of tightness associated with bronchoconstriction is likely to arise from pulmonary receptors. The sense of air hunger/unsatisfied inspiration is thought to arise from an awareness of medullary respiratory motor drive not matched by appropriate pulmonary mechanoreceptor feedback indicating appropriate lung expansion (discussed in greater detail below) (134, 187, 214, 215). Air hunger is arguably the most unpleasant of these sensations (20)

The importance of air hunger in clinical dyspnea

"By air hunger is meant the subjective experience of air want. Dyspnea, tachypnea, hyperpnea and cyanosis are attendant phenomena and can be evaluated by objective observation, but the feeling of air hunger is what alarms the patient and leads him to seek medical aid. The physician is called for a single reason and that is to relieve air hunger, a subjective symptom that always is alarming to the patient." (112). The eminent physician Charles Franklin Hoover (noted today for Hoover's Sign) was writing in 1926 from his clinical experience, and presented no data in substantiation; however, as described later in this article, data are now available to support his assertion.

Air hunger is common and powerfully unpleasant. A number of recent studies have shown that clinical dyspnea is nearly always a mix of sensation, and that air hunger (or a synonym) is chosen as the most apt descriptor of dyspnea in most patient populations, especially when dyspnea is more severe (see section below on 'Prevalence of air hunger in patient reports'). Air hunger, especially severe air hunger is far more unpleasant than other dyspnea sensation, and evokes greater frustration, anxiety, and fear (see section below on 'Emotional impact of air hunger').

The ATS statement makes note of the prevalence of dyspnea and associated mortality risk. It is often difficult to judge dyspnea from external signs, so it is usually underestimated by clinicians (25, 106). Recent studies in which subjects are quantitatively queried about dyspnea show that some dyspnea is present during exertion in 22% of the nominally healthy population, and is significantly associated with risk of mortality (208). Dyspnea at rest is reported by about 11% of patients admitted to non-ICU medical/surgical units, and is associated with substantially higher risk of dying during that hospitalization (223, 224).

Psychophysics in the study of respiratory sensation

Much of the data presented in this article was obtained using 'psychophysics'. Psychophysical methods systematically quantify relationships between sensory experiences and the physical stimuli that elicit them. Since the late 19th century these methods have been applied to sensory modalities, most notably vision and hearing. The stimuli evoking these sensations can be presented and the perceptual response can be measured with great precision (226). The basic procedures of classical psychophysics involve obtaining a person's responses to systematically repeated application of a range of stimuli varying in magnitude or quality; these responses are usually measured either in the form of a verbal or numerical scale or by the frequency of stimulus detection. Psychophysical methodology underlies our understanding of the physiology of human sensation and perception; it allows us to quantify perception. These methods have been shown to yield precise and

reliable measures of perceptual responses to stimuli in all modalities (e.g., sight, hearing, pain, touch). They have been a basic tool for establishing the physiological processes which mediate sensation. For example psychophysical thresholds and response functions for mechanoreceptive afferents have been used to determine the degree to which their perception is determined by the properties of peripheral neurons vs central mechanisms (166).

The application of formal psychophysical methods to breathing sensations began in 1961 when Campbell and associates studied the threshold for detection of resistive and elastic loads (39, 41). Direct scaling of the magnitude of respiratory sensation began with the studies of Bakers and Tenney (9), who instructed subjects to give numerical estimates of expiratory pressure and of inspired volume under different conditions. They produced reliable psychophysical stimulus-response measures for volume, ventilation and respiratory pressures. The extensive use of psychophysical methods in the study of respiratory sensation that followed has been reviewed extensively (118, 132, 248). Air hunger is now measured routinely by ratings of its intensity or its frequency of selection and identification – reliable relationships between several stimuli and air hunger ratings have been demonstrated in many experiments discussed in the section on the quantitative relationship between stimulus and air hunger.

There are particular challenges in studying interoceptive sensations such as air hunger: First, the lack of external reference has inhibited the development of common language. Second, the stimuli and sensory responses may be slow, requiring minutes to reach a new steady state after sudden stimulus change; this precludes experimental designs that require many rapid presentations of stimulus. Third, there are a few subjects (perhaps 10–15% of the population) who find it difficult to translate their perceptions into ratings. In laboratory studies and population studies this is a minor problem – one can test this ability before proceeding, or accept the resultant noise that will have only a small effect on population averages. However, one must be aware of this problem before interpreting results for a single patient. These challenges notwithstanding, application of psychophysical methods to the study of air hunger has led to the quantification of its relationship to the physiological conditions which evoke it, and has enabled experiments defining adequate stimuli, afferent pathways, and cerebral activations. These methods have also provided a means to test the effect of pharmacological interventions, both experimental and therapeutic.

Emotional impact of air hunger

Air hunger provokes a very strong emotional response. Laboratory studies using stimuli designed to evoke air hunger in healthy subjects (see below section on stimulus response relationships for descriptions of stimuli) show that air hunger is immediately unpleasant, and gives rise to emotions of anxiety, fear, and frustration. In one of the earliest publications on breath hold more than a century ago, subjects who held their breath for an extended period "described their feelings as those of '*being about to die.*'" (110). Similar phrases recur in subjects' descriptions in subsequent studies. Wright and Branscomb noted that if strong air hunger sensations were to occur under circumstances beyond one's control, "they would be

terrifying in the extreme sense" (245). Subjects in another study described the experience as "*frightening*," "*panicky*," or "*scary*" (12).

These emotions can be quantitatively reported by subjects. When subjects used rating scales to quantify the experience of a maximal respiratory work stimulus vs the experience of a maximal air hunger stimulus, they reported far more unpleasantness, anxiety, frustration, and fear during air hunger (see Figure 1). These ratings are situational – subjects know they can stop the experiment, and that it is conducted safely – in the words of one subject "If I didn't trust the experimenters, I would have rated a 10 for fear"(20). Even in this safe situation, air hunger has the ability to generate substantial primal emotion.

Emotions motivate behavior. The strong negative emotional response that accompanies air hunger has evolutionary adaptive value in motivating avoidance or escape behaviors in situations in which respiratory needs cannot be met. It also motivates people to seek medical attention. However, in disease states where air hunger cannot be eliminated, it degrades quality of life. (See section on air hunger in clinical dyspnea.)

Quantitative Stimulus-Response Relationships

"When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge of it is of a very meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts, advanced to the stage of science." Lord Kelvin (William Thomson) (117)

The defining experimental paradigm to evoke air hunger is to elevate the drive to breath while restricting the ability to increase ventilation, as proposed by Wright and Branscomb 75 years ago, but these authors provided no quantitation of stimulus or response (245). Happily, we have progressed to the point where we can measure air hunger intensity and can measure the stimuli that evoke air hunger, thus satisfying Lord Kelvin's criterion – we "know something about it". To measure air hunger in humans we employ psychophysical methods such as detection and magnitude estimation (see above section on psychophysics in the study of respiratory sensation). Providing quantifiable (and safe) stimuli requires the methodology of respiratory physiology. Because air hunger reflects the balance between respiratory drive arising from chemoreceptors and other inputs versus respiratory tidal excursions reported by mechanoreceptors, stimulus design is more complex than, say, auditory, visual or cutaneous pain stimuli. Respiratory drive is easy to increase in a quantifiable, graded fashion using inspired gas mixes and/or exercise. It is more technically difficult to limit ventilation, and several methods have been used: voluntary targeting of tidal volume and rate, external wraps around the chest and abdomen, external impedance to breathing via mouthpiece or mask using mechanical ventilation, external resistance, and collapsing gas bags. The experimental outcome can depend on the experimental model used – some laboratory dyspnea models are very effective in generating air hunger, while others generate a mix of uncomfortable sensations harder to interpret. We will focus on those experiments in which it is highly likely that air hunger is the dominant sensation – either because subjects have directly reported air hunger, or because the method used has

been shown in other experiments to generate air hunger. An example of the latter is breath hold – many earlier studies simply report the tolerance level for breath hold ('breakpoint') without reporting what subjects felt (perhaps because it seemed obvious) –later studies have confirmed that the limit of breath hold in normal circumstances is determined by intolerable air hunger, and that air hunger can be quantified by the average healthy subject. The various experimental model components used are discussed here, and inferences from these methods are presented below.

Stimulus Part A: Methods to Increase Respiratory Drive (stimulates air hunger)

Exercise—Physical exertion is certainly the most common method of elevating drive in daily life, and can be used to study air hunger in the laboratory setting (177, 245). Although it is the most 'natural' stimulus, it also has drawbacks. The sensory input is complex, arising not only from respiratory structures, but also from the limbs, so afferent inputs are harder to define. Exercise levels are difficult to standardize across subjects of varying body size and fitness. Instrumentation can be challenging, even when exercise is performed on a stationary bike or treadmill. Exercise in free-breathing healthy subjects is frequently limited by leg or arm work capacity, thus many subjects do not experience much air hunger during exercise. Limiting ventilation during exercise is an effective air hunger stimulus, but adds technical challenge (103, 104, 245).

Hypoxia.—Low inspired PO_2 is encountered at altitude, and occasionally in enclosed spaces. Hypoxemia is also a common feature of moderate to severe respiratory disease due to limited ventilatory capacity, ventilation-perfusion inhomogeneity, etc. Hypoxia has been used to increase respiratory drive in some studies that report air hunger, or in which air hunger may be inferred (e.g., references 101, 154, 159). Hypoxia during free breathing is a notoriously poor stimulus for air hunger; the relief of air hunger produced by increased mechanoreceptor input and by the accompanying hypocapnia blunts air hunger to the point that subjects usually have severe decline in cognitive function or lose consciousness before reporting air hunger. This was colorfully described by J.S. Haldane when he was exposed acutely to a barometric pressure equivalent to 7,500 meters altitude: *"This increased temporarily the hyperpnea in J.S.H., whose lips were now of a rather dull colour, with pulse 112 and respirations 27. He also had great difficulty in making observations or even counting his pulse, and especially in calculating the pulse from a 20 seconds observation, or remembering at what point on the seconds hand the observation had begun. … [He] took up a mirror to look at his lips, though some little time elapsed before he realized that he was looking at the back, and not the front, of the mirror"* (102). Lack of awareness of hypoxic impairment presents a hazard for aircraft pilots (168). Even when tidal volume and $PETCO_2$ (end-tidal PCO_2, an approximation of arterial PCO_2) are controlled to near resting levels, severe hypoxia ($PETO_2$ in the range of 40–50 torr) is need to generate mild to moderate air hunger (159), requiring close medical monitoring.

Hypercapnia.—High inspired PCO_2 is seldom encountered in ordinary activities, apart from enclosed spaces; however, hypercapnemia is a feature of severe respiratory disease. Because of its relative potency and safety, hypercapnia has been used to increase respiratory drive in a number of studies that report air hunger. Intense air hunger can be generated with

an acute $PETCO_2$ rise of only 10 torr if breathing is limited (see below); thus, avoiding the side effects of severe hypercapnia such as headache, visual disturbances, impairment of consciousness, etc. Hypercapnia is thus both safe and potent as an experimental stimulus.

Metabolic Acidosis.—Transient metabolic acidosis is encountered in intense exercise, and metabolic acidosis is a feature of metabolic, renal, and cardiovascular disease. Because it is difficult and slow to induce acidosis in healthy subjects, it has seldom been used to evoke air hunger. In a study using NH_4Cl to produce metabolic acidosis, Lane et al concluded that the sensation of breathlessness was related to the reflex ventilatory drive, whether that drive was produced by acidosis, exercise, or CO_2 (130).

Stimulus Part B: Methods to Limit Breathing – (breathing inhibits air hunger)

Because air hunger is a balance between ventilatory drive and achieved ventilation (see below), any stimulus-response study must consider ventilation. Steady-state restriction of ongoing respiration opens the possibility to examine stimulus-response relationships in more detail. Wright and Branscomb (245) reported using a ‘smothering machine’ to restrict ventilation during exercise and hypoxia, but they provided no detail on how their invention functioned. Restriction of breathing during elevated drive can be used to generate the full range of steady-state air hunger intensity from mild to intolerable without significant side effects. Following is a summary of the various experimental paradigms used.

No Restriction - Free breathing—It is possible to generate mild to moderate air hunger during unencumbered breathing in healthy subjects using the natural limits of breathing. However tidal expansion of the lungs relieves air hunger so effectively that extreme levels of hypercapnia or hypoxia are necessary to produce moderate to severe air hunger and these stimuli have side effects that complicate the interpretation of sensory reports – headache, warmth & flushing, impairment of consciousness (110, 153). The level of exercise needed to generate substantial air hunger during free breathing is not achievable in many subjects because exercise is limited by other factors such as leg or arm fatigue.

Complete restriction -- Breath Holding—Breath hold provides a simple means of both limiting ventilation (to zero) and increasing drive (via metabolic O_2 consumption and CO_2 production). Breath hold is within the common experience of most people, and in ordinary circumstances breath-hold time is limited by intolerable air hunger. There have been many studies of breath hold, but most of them have not explicitly assessed the sensation experienced by the subjects; they have instead expressed outcome as breath-hold duration and/or $PETCO_2$ and $PETO_2$ at ‘breakpoint’, without requiring subjects to report their sensation either quantitatively or qualitatively. To be fair, most of these studies pre-date the adoption of psychophysical methods to study respiratory sensation (9, 41). Many of these studies are reviewed by Mithoefer in the first edition of the APS handbook (152). The inherent non-steady-state nature of breath hold makes it difficult to quantify stimulus response relationships; PCO_2 and PO_2 change constantly during breath hold and normal breath hold durations fall in the first or second time constant of the dynamic response of air hunger (14, 157). Nonetheless, it can be inferred that most maximal breath holds are terminated by air hunger (Described in an early breath-hold study as the “imperative desire

to breathe" 110). (In elite breath-hold divers who hyperventilate to extremely low $PETCO_2$ before breath hold, impending loss of consciousness terminates breath hold (8, 27, 141). Breath-hold studies have brought to our attention the primary factors that contribute to generation of air hunger: respiratory drive and lung volume change (e.g., references 94, 110, 124).

More recently, psychophysical methods have been employed to examine the course of sensation during breath hold, and subjects have been questioned about the quality of the experience. In one study subjects rated "respiratory distress" beginning with no distress early in breath hold and ranging to 'intolerable' at breakpoint; subjects described the sensation using terms such as 'hungry for air', 'suffocating', 'out of breath', and 'short of breath' (91); the first three terms are synonymous with air hunger, while 'short of breath' is more general, but not inconsistent. In another study, subjects used a visual analog scale to rate 'unpleasant urge to breathe' (synonymous with air hunger) throughout breath hold, again showing a progression from no perceptible air hunger early in breath hold to 'intolerable' sensation at breakpoint (172, 173).

Voluntary Targeting of Tidal Volume and Rate—Another way to constrain breathing is to require subjects to voluntarily follow a visual target with a visual signal that reflects the subject's respiratory excursions. Motivated subjects have been able to voluntarily restrain inspiration during heightened drive (48, 49, 70, 135, 203, 211), but it is difficult for most subjects to achieve substantially reduced ventilation; this imposes a limitation on the range of air hunger that can be explored in a more general population. Even with well-motivated subjects, suppressing breathing is a difficult task, thus it is important to focus subjective reports and ratings on air hunger rather than 'difficulty'.

External Chest Wall Binding—An instance of air hunger during external chest wall binding was mentioned by Wright & Branscomb (245). Several studies have used chest wall strapping to limit tidal volume and evoke respiratory discomfort (96, 104, 127, 150, 174, 179); reports of the quality of respiratory sensation, however, are inconsistent or absent. Some studies suggest air hunger is the primary sensation (174, 179), while others found that other sensations such as tightness and effort overshadowed air hunger (96, 104). These discrepancies may be explained both by differences in protocol and differences in measurement method. The complexity of the sensory input and inability to tightly control respiratory parameters make chest strapping sub-optimal for the study of air hunger *per se*, although it has value in simulating some aspects of pulmonary disease.

Inspiratory Resistive, Elastic, And Threshold Loads Administered Via Mouthpiece—Inspiratory resistive, elastic, and threshold loads administered via mouthpiece have been widely employed to study respiratory sensation, mainly centered on describing detection thresholds and magnitude estimation of loads applied for one or two breaths (248). However, the loads employed in this kind of study have usually not been sufficiently large to reduce ventilation and have not usually been applied for sufficient time to allow development of air hunger – in such circumstances they elicit sensations of work and effort, but not air hunger (e.g., reference 238). However, a more prolonged application of sufficient resistance (240–280 $cmH_2O \bullet liters^{-1} \bullet sec^{-1}$) together with

hypercapnia or hypoxia to increase respiratory drive can effectively generate air hunger, generally accompanied by a sense of work and effort (173, 215). Very large elastic loads (>50 $cmH_2O•liter^{-1}$) or threshold loads (>70 cmH_2O) can also generate air hunger (129, 215). Subjects given unsustainable loads report that air hunger, not work and effort, is the reason for quitting (129). Again, the complexity of the sensory input and the inability to tightly control respiratory parameters make external loading sub-optimal for the study of air hunger *per se*, although it has value in simulating some aspects of pulmonary disease and is relatively simple to implement.

Limited air supply ('bag limit')—Maximum tidal volume can be limited by providing a defined allotment of air in a collapsible vessel, most commonly a rubber anesthesia bag attached to a mouthpiece or mask. If combined with a metronome signal to set respiratory frequency, tidal volume, and minute ventilation will be controlled. Initial application of this method used a closed system, thus both gas concentrations and bag volume changed during the test as oxygen was absorbed from the bag while most of the metabolic CO_2 remained in the blood and tissues (153). More recently, steady-state conditions were enabled by an open system with high-impedance gas input refreshing the bag (15, 20, 158, 159, 162, 176). Although bag-limit restriction also requires cooperation from the subject, the task is not as difficult as voluntarily restricting tidal volume. Because this method allows good control of tidal volume, frequency, and end-tidal gasses it is useful for studying stimulus-response relationships, drug interventions, and neural imaging.

Mechanical Ventilation—A standard clinical ventilator set to 'volume control' mode without the possibility of patient-triggered breaths has been used to maintain constant tidal volume respiratory frequency and inspiratory flow rate. Respiratory drive can then be altered by changing inspired PO_2 or PCO_2. The first published instances of this method were used in patients who were dependent on mechanical ventilation because of polio. Chronically ventilated, awake patients ordinarily receive sufficient ventilation to eliminate air hunger. In the first of these studies $PETCO_2$ was raised slowly until the patient "demanded immediate relief" at an average of 20 torr above baseline. The authors used the term "shortness of breath" to describe what patients experienced, although the subjects' own descriptions were not reported (183); on the basis of later studies, we presume the quality of the sensation was air hunger. A following study of a similar patient (189) did not quantify the relationship of stimulus to response, but did provide us with the patient's own description of the sensation: *"felt like air not going deep enough…felt like if I could only take a couple of deep breaths, it would go away…smothering… needed to breathe real deep real bad"*; these descriptors align with air hunger. More than 2 decades later, this same approach was used in healthy subjects, who were hyperventilated at the outset (44); as $PETCO_2$ was slowly raised, subjects were "instructed to indicate when they first sensed that their ventilatory needs were no longer being fully satisfied" (i.e., the sensation of air hunger). Our laboratory later combined this method with psychophysical methods to assess the magnitude of air hunger at various levels of $PETCO_2$, $PETO_2$, and tidal volume as well as with pharmaceutical interventions (12, 16, 18, 21, 27, 85, 105, 159, 213). Compared with bag-limit, mechanical ventilation provides slightly better control of tidal volume, frequency, and end-tidal gasses; this method is useful

for studying stimulus-response characteristics, the effect of pharmacologic interventions, and functional brain imaging.

Note—For subsequent sections dealing with normative responses to stimuli, neural pathway studies, and brain imaging we draw inferences from reports in which it is explicitly stated that air hunger was measured, or from reports in which we can infer with high confidence that air hunger was being studied.

The quantitative relationship between stimulus and air hunger. Part A – changing ventilatory drive while holding ventilation constant.

Hypercapnia as a stimulus for air hunger—When ventilation is held constant at just above resting level using bag limit or mechanical ventilation, respiratory drive can easily and safely be altered by manipulating inspired PCO_2 to control $PETCO_2$. See Figure 2, upper panel. $PETCO_2$ changes can be effected more rapidly by overshooting or undershooting the final value of inspired PCO_2 and a quasi-steady-state measurement of air hunger can be obtained 2–3 min following the $PETCO_2$ change (see dynamics of air hunger section below). The air hunger response to $PETCO_2$ under these conditions can be characterized as a linear rise above a threshold (Figure 2 lower panel). At this ventilation, the threshold for air hunger is slightly above resting $PETCO_2$, and rises at an average linear slope of about 8.6% of Full Scale per torr $PETCO_2$. Intolerable air hunger is reached, on average, about 13 torr above resting $PETCO_2$ under these conditions. (See Table 1 for the data from which these average numbers are derived).

Variation among subjects and relation to ventilatory response.: The air hunger response varies among healthy subjects as shown in Figure 3 – the average standard deviation of air hunger vs $PETCO_2$ slope among subjects was ±3.0%FS/torr, a coefficient of variation of 0.35. The reflex ventilatory response to CO_2 also varies among individuals, and the variation in ventilatory response is similar to the variation in perceptual response (average coefficient of variation =0.34 as calculated from Table 3 in reference 111). There is, however, only a weak relationship between air hunger response and ventilatory response among normal individuals (12), even though these responses are presumed to arise from the same afferent inputs. The most obvious explanation is that the output pathways differ substantially: To produce a ventilatory response, medullary respiratory motor activity travels via descending spinal motor pathways and synapses, and is translated to ventilation via the mechanical characteristics of respiratory muscles, lungs and airways. To produce the air hunger perceptual response, medullary respiratory motor activity travels via ascending corollary discharge involving thalamic and cortical synapses and conscious decision processes before being translated to a rating of air hunger.

Other studies—The observant reader will have noticed that the core stimulus response data in the foregoing section comes entirely from one laboratory, because no other groups have published comparable observations over the range of air hunger intensities. However, there are some confirmatory single-point observations: two published reports of the $PETCO_2$ tolerance limit for air hunger during ventilation restricted to near resting levels (154, 203),

and one published report of the threshold for air hunger under similar conditions (44). These are discussed immediately below, and a comparison of results will be found in Figure 4.

Assessing Air Hunger Perception by Tolerance—Mithoefer (154) caused several subjects, including himself, to breathe various gas mixtures from a closed anesthesia bag at 18 breaths/min; this set a maximum tidal volume defined by the volume of gas in the bag, which changed somewhat as O_2 was consumed. The dependent variable was the limit of toleration (breakpoint); bag gas composition and volume at breakpoint were independent variables. The trial with parameters closest to Table 1 data was the initial bag volume of 1 liter with hyperoxic mixture, declining to about 0.7 liters at breakpoint. We analyzed the data on the first author presented in the publication, combined with 3 other subjects whose data we obtained from the Library of Congress data repository. The average $PETCO_2$ at tolerance limit was 55 Torr, ranging from 50 to 58 among subjects. Although Mithoefer et al also examined tolerance of hypoxia, we are disinclined to trust the data, as the levels of hypoxia at breakpoint were low enough to interfere with sensory processes – indeed Mithoefer reports "*marked cyanosis, loss of consciousness and convulsions*" prior to breakpoint in some hypoxic runs.

Remmers et al studied 4 healthy men (3 were authors), who volitionally controlled respiratory frequency, tidal volume, and duty cycle using visual feedback (203). CO_2 added to the inspiratory gas caused $PETCO_2$ to rise at about 3 torr per minute. They described a "slowly increasing urge to breathe", but did not rate the intensity of sensation. The reported outcome variable was the $PETCO_2$ at which the subject could no longer tolerate this sensation. At a tidal volume of 1 liter and frequency of 10 breaths•min^{-1}, the average $PETCO_2$ at the tolerance limit was 54 torr – similar to the observations in Table 1.

Assessing Air Hunger Perception by Threshold—Castele et al (44) ventilated 11 healthy subjects at constant tidal volume and frequency comparable to the studies in Table 1, and slowly raised $PETCO_2$ until the subject indicated when they first "sensed that their ventilatory needs were no longer being fully satisfied"; the average $PETCO_2$ at this threshold was 42.3 Torr (±3.2 SD).

Despite different methods of restricting breathing and controlling blood gasses, utilization of different outcome measures, and personal and situational factors that may affect threshold and tolerance, the various studies agree remarkably well (See Figure 4).

Hypoxia as a stimulus for air hunger—There are fewer data relating air hunger ratings to levels of hypoxia. Hypoxia is a relatively weak stimulus, as might be expected from ventilatory response data. One study showed that with tidal volume and $PETCO_2$ controlled at near resting levels, the $PETO_2$ threshold for air hunger averaged 53 torr (±8SD) (159). The hypoxia stimulus vs air hunger response data could be adequately fitted with a hyperbola, similar to that traditionally used for hypoxic stimulus ventilatory response data. Few subjects rated air hunger more than 50%FS within the study's ethical limit of hypoxia; two additional subjects had changes in ECG that terminated the experiment. Another study found that at $PETO_2$ of 40 torr during free breathing, subjects rated 'difficulty of breathing' 20% of full scale, but this fell to 11% after 20 min of hypoxia (50). Air hunger may not

even occur in response to hypoxia if the subject is allowed to breathe freely, a well-known hazard to pilots, described in the first APS Handbook: "*Fatal accidents at altitude due to in adequate protection against hypoxia are well documented since the reports of early pioneers in aeronautics. A characteristic feature of such accidents is the complete unawareness of danger on the part of the victim. Unfortunately man is not endowed with any conscious sensory perception of hypoxia that might alert him to the impending danger, such as the marked dyspnea caused by an excess of carbon dioxide in his environment.*" (144). We now understand that humans can consciously sense hypoxia if $PETCO_2$ and ventilation are near normal, but that hypoxic hyperpnea increases mechanoreceptor feedback and lowers $PETCO_2$, thus suppressing the air hunger signal prior to loss of consciousness. The relative insensitivity of air hunger to hypoxia has clinical implications, an example of which is described in the section on Air Hunger in Clinical Dyspnea.

Hypoxia and hypercapnia appear to produce additive effects on air hunger, without changing the slope of the relationship (12, 148), but data on this interaction are sparse, so this observation should be further tested.

The quantitative relationship between stimulus and air hunger Part B – changing ventilation while holding ventilatory drive constant.

Mechanoreceptor Relief of Breath Hold—The inhibitory effect of breathing on air hunger during essentially constant chemoreceptor drive has been known since at least 1908 when breath hold was extended greatly by having subjects rebreathe alveolar gas from a bag (thus not improving blood gasses); the authors reported that "*Breathing freely in and out of a small closed space extends the power to withstand excess of CO_2 and want of oxygen*" (110). This experiment was repeated more formally by Fowler half a century later (94), confirming the earlier results. It was nearly a century after the first study that subjects were asked to quantitatively report the developing sensation of air hunger throughout the breath hold and the subsequent rebreathing period using a rating scale, an example of which is shown in Figure 5 (91).

Steady state controlled ventilation—The previously mentioned studies by Mithoefer et al and Remmers et al included systematic variation in tidal volume. Mithoefer et al (154) began to quantify the relationship between tidal volume and air hunger by varying the amount of gas available for subjects to rebreathe from a bag while paced by a metronome at 18 breaths per minute. Again, the authors measured only tolerance, subjects did not rate discomfort. They report that tolerance of $PETCO_2$ increased as allowable tidal volume was increased. The data plotted for a single subject in the publication show that during hyperoxia altering permissible tidal volume in steps from less than 0.5 liter to 3.5 liters progressively increased $PETCO_2$ tolerance from less than 40 torr to nearly 80 torr. Thus, the tolerable level of PCO_2 increased overall by about 0.74 $Torr \bullet liter^{-1} \bullet min^{-1}$ ventilation. Results from 3 other subjects in the unpublished archive showed similar effect of permissible tidal volume, but were not as dramatic or orderly as those from the first author (perhaps because the first author understood how to best utilize the breathing circuit).

The subjects in Remmers et al (203) voluntarily targeted minute ventilation at 5, 10, 15 and 20 L•min-1 at different frequencies and tidal volumes changes at each level. Subjects did not rate air hunger, but the $PETCO_2$ at maximum tolerable air hunger was recorded. Subjects tolerated substantially higher $PETCO_2$ at higher ventilation; the relationship between ventilation and maximum tolerable $PETCO_2$ was nearly linear, we calculated a slope of 0.76 Torr•liter^{-1}•min^{-1} at a frequency of 10 breaths•minute^{-1}, with an extrapolated y-intercept at 46 Torr at zero ventilation (the y-intercept can be thought of as virtual breath hold). For the most part the tolerable level of $PETCO_2$ was not sensitive to the particular combination of tidal volume and frequency used to achieve the minute ventilation.

Several studies have reported 2-point determinations of the effect of an increase in ventilation on subjects' ratings of air hunger when $PETCO_2$ is held constant. Although these studies used different ventilation strategies and different groups of subjects, they all showed that if initial air hunger ratings of 50 to 60%FS are established by hypercapnia at a ventilation restricted to about 10 L•min^{-1}, doubling minute ventilation reduces air hunger by about 50%FS – i.e., nearly complete relief. See Figure 6.

The full relationship between air hunger and the physiological variables that comprise the stimulus has not been described – we attempt to assemble what we know and can reasonably speculate about the interaction of ventilation and $PETCO_2$ in Figure 7. The 3-D representation in Figure 7B simplifies the relationship between mechanoreceptor afferent feedback, but forms a starting point to think about the issues.

Short term dynamics: air hunger response to abrupt change in stimuli

Response to Step Changes in Chemoreceptor input ($PETCO_2$ and $PETO_2$)

Hypercapnia.: When a sudden increase in $PETCO_2$ is effected, the onset of air hunger occurs following a delay and subsequent slow rise, as can be discerned in Fig 2. This has been modelled as a delay of 15 sec and a linear rise with half-time = 52 sec (14). This model had a strong correlation with the data, and is sufficient to design experiments and analyze data to obtain reasonably steady-state measures. It is not, however, sufficiently precise to predict the exact time course of air hunger ratings following rapid stimulus transients. The authors did point out that it is not the only model that fits the data well ("In most subjects, selection of a time constant half or double the best-fit value would not significantly degrade the correlation between air hunger and model output…"). The model's precision was limited by the relatively coarse resolution of the data in both the time and air hunger dimensions.

Hypoxia.: When a sudden decrease in $PETO_2$ is effected, the time course of air hunger is more complex, showing an initial delay, sharp rise, and subsequent rolloff after the first few minutes (Figure 8) – this mirrors the ventilatory response to hypoxia (75, 157, 186).

Response to Step Changes in Mechanoreceptor input

Tidal Volume.: One might think that the inhibition (relief) of air hunger by mechanoreceptors would be essentially instantaneous – we know that the Breuer-Herring reflex occurs within a breath, that people can sense tidal volume change within a single breath, and that at the end of a long breath hold, we feel better as soon as we take the

first breath. It is true that some relief occurs on the first breath, but as can be seen in Fig 5, first-breath relief is partial, and progressive reductions in air hunger occur with several subsequent breaths. Several studies (26, 85) have shown that the air hunger change following a step change in tidal volume requires half a minute to reach its final value, as shown in Figure 9.

End-Expiratory Lung Volume.: Information above clearly shows that increase in tidal inflation relieves air hunger, but does a steady state change, such as a prolonged change in end expiratory volume (EEV), have the same effect? Again, breath hold experiments provide the initial insight. It is common knowledge that breath hold is longer if the starting lung volume is higher – most of us intuitively take a deep breath before diving under water. (We intuitively ascribe the longer resulting breath hold to greater oxygen stores, but the modest increases in total oxygen stores and CO_2 capacity at maximal lung volume vs those at end expiration are not sufficient to explain the increase in breath hold time.) Subjects can hold their breath to a lower $PETO_2$ and higher $PETCO_2$ at higher lung volumes (153), clearly obviating the intuitive explanation, and leading to the conclusion that quasi-static increase in lung volume does diminish air hunger via mechanoreceptor input. Will a sustained increase in EEV provide air hunger relief? Slowly adapting pulmonary stretch receptors (SAPSRs) that respond to an increase in EEV sustain this response for at least an hour (167), suggesting that relief of air hunger ought to be sustained if central synapses do not adapt. The response to sustained changes in lung volume may be important clinically in ventilator management, and in understanding interventions for dyspnea such as pursed-lip breathing. To our knowledge there is only one study of the effect of EEV on air hunger (240), and that study maintained EEV changes for only 1 min; air hunger relief was sustained for the full minute, but clearly study of longer EEV shifts is needed.

Inferences from short term dynamic responses—Understanding the time course of responses is important for experimental design, but beyond this we can draw some inferences about mechanism. Because we hypothesize that air hunger arises from ascending information from medullary respiratory centers, it is useful to compare the dynamic response of air hunger to the dynamic response of ventilation following a sudden stimulus change. Tidal volume and respiratory frequency require 2 or 3 minutes to arrive at the new quasi-steady state ventilation after a sudden increase or decrease of arterial blood gasses (reviewed by reference 186). Because a similar time course of ventilatory change is seen after a sudden change of electrical stimulation of chemoreceptor afferent nerves, it is believed this slow response is mainly due to neural synaptic phenomena, rather than equilibration of the chemoreceptor environment with new gas levels. The synaptic phenomenon that slows rise time (a sort of low-pass filter) was initially called ‘respiratory after discharge’ but with greater understanding of synaptic mechanisms is now termed ‘short term potentiation’ (79, 80, 107). In the case of hypoxia, a second and slower phenomenon, short term depression, causes ventilation to fall in the following minutes. Proposed synaptic mechanisms for these phenomena are described in reference (186). The time course of air hunger response to sudden increases or decreases in $PETCO_2$ and $PETO_2$ is similar to the dynamic response of ventilation following changes in these gasses. This similarity is consistent with the notion that air hunger arises from the same neurons that drive the ventilatory response to CO_2.

This does not preclude, however, an additional neural mechanism that slows the dynamic response of air hunger, *per se*, in the information pathway from respiratory centers to cortex.

The dynamic responses to sudden changes in mechanoreceptor input present a different picture. The ventilatory response to lung inflation (Hering-Breuer response) occurs in full on the first breath following a change in lung volume, tidal volume, or stimulation of vagal pulmonary afferents. In contrast, the air hunger dynamic response is much slower, requiring nearly a minute to reach the new level. This implies a neural mechanism akin to short term potentiation operating in perceptual pathways downstream of the brainstem, e.g., in thalamus or cortex.

The long-term dynamics of air hunger will be discussed below, as it requires some understanding of the information on neural pathways. See heading ‘Long term dynamics: air hunger response to maintained stimuli (Adaptation)’.

Neural Inputs Underlying Air Hunger Stimulation and Relief

Overview of current understanding

As discussed more fully below, our current understanding is that the signal for air hunger arises in the medullary respiratory motor centers and projects to cortical areas involved in conscious perception. The medullary centers integrate the various stimuli that reflexly stimulate ventilation, and produce both descending motor signals to respiratory muscles and ascending projections to the forebrain. The ascending projection, termed ‘corollary discharge’, stimulates air hunger. Mechanoreceptors sense tidal inflation (most likely slowly adapting pulmonary stretch receptors, SAPSRs), and report whether ventilation is appropriate for the current motor activity – if ventilation is inadequate, air hunger results, if tidal volume is adequate, air hunger is relieved. The intensity of air hunger is thus a function of the degree of mismatch. This schema is shown in Figure 10.

Separating Air Hunger from Work & Effort

Before discussing afferent pathways for air hunger, we need to be clear that air hunger is a distinct sensation from the sense of increased respiratory work and effort. Both respiratory muscle afferents and cortical (volitional) motor command play a role in the sense of work and effort, as reviewed by Zechman and Wiley in the 1986 Handbook (248). At that time, little attention had been paid to the differences in sensory quality with different interventions, but advances in the field have brought a clear understanding that there are several different uncomfortable respiratory sensations. This understanding is recognized in the most widely cited definition of dyspnea: “*a subjective experience of breathing discomfort that consists of* ***qualitatively distinct sensations*** *that vary in intensity*” [emphasis ours] (187). Several studies have shown that the sensory quality of respiratory discomfort can be altered by altering the physiological stimulus. The foregoing section details the response to stimuli that evoke the sensation of air hunger but evoke little or no sensation of increased work/effort of breathing; this is part of the evidence needed to determine the distinction between air hunger and work/effort. In this subsection we will briefly describe studies in which both air hunger and work/effort sensations were

measured while physiological stimuli were applied that caused the two sensations to vary independently.

Simon et al (215) showed that different stimuli resulted in different descriptions of the sensations felt, but subjects were not asked to quantify sensations, nor were physiological parameters quantified – however this study did form a foundation of respiratory sensation language that was later refined and used to define sensations in quantitative experiments. Demediuk et al instructed 8 healthy subjects to rate breathlessness, defined as an "unpleasant urge to breathe" [i.e., air hunger] and "effort", described as a respiratory sensation analogous to the one that accompanies the volitional act of lifting a weight (70). Subjects breathed to a target ventilation of about 56 L•min^{-1} while $PETCO_2$ was raised from 40 Torr to 50 Torr. At the higher $PETCO_2$, ratings of air hunger increased modestly but significantly from 9%FS to 19%FS ($p = .008$), while effort ratings fell slightly from 19%FS to 15%FS ($p=.064$; paired T tests done by us using data from Figures 1B and 2B in reference (70)). The finding that the sensations changed in opposite directions showed that the two sensations could be manipulated separately depending on the physical stimulus (thus the sensory afferent input). A similar experiment in which both the level of targeted ventilation and $PETCO_2$ were varied among several levels showed that air hunger and work/effort sensations could be manipulated independently, but again the effects were modest (135). Perhaps most convincing is the evidence from partial neuromuscular block (160). Healthy subjects breathed to a target of 30 liters•min^{-1} while $PETCO_2$ was maintained at eucapnic levels with inspired CO_2. Subjects rated 3 sensory qualities: air hunger ('the discomfort caused by your urge to breathe'), effort of breathing ('how hard you are having to try to breathe') and work of breathing ('what you accomplish with your efforts to breathe'). After control measurements were obtained, neuromuscular block was administered sufficient to reduce vital capacity to 60% of control values. Voluntary hyperpnea (presumably driven by primary motor cortex) during the control condition evoked mild 'work' and 'effort' sensations, but no air hunger. Partial paralysis tripled ratings of work and effort, but had no effect on air hunger (Figure 11). In contrast, hyperpnea driven by mild hypercapnia (presumably driven by medullary motor centers) elicits little air hunger, effort or work sensation in the control condition, but all three sensations were increased markedly by partial neuromuscular block.

Another line of evidence that air hunger and work/effort are distinct sensations with separate neural pathways comes from the differential effects of opioids on dyspnea evoked in healthy subjects by different laboratory models. Opioids are a front-line treatment for dyspnea. As shown in Figure 12, experiments using contrasting laboratory models of dyspnea have shown that opioids have no effect on work/effort sensation evoked by inspiratory threshold loads (232), but have a powerful effect on air hunger generated by hypercapnia during tidal volume restriction (15). Aerosol furosemide is a potential treatment for dyspnea (156, 169, 173). Recent work shows that aerosol furosemide acts to reduce air hunger generated by hypercapnia during tidal volume restriction, but does not act to reduce work/effort sensation generated by voluntary hyperpnea against a resistive inspiratory load (98).

Afferent Pathway for the Air Hunger Signal

As described above (Section on Quantitative Stimulus-Response Relationships), we know that elevating respiratory drive stimulates air hunger. There are several hypothesized pathways through which this message could get to the sensory cortex where perception is sited. In **Hypothesis 1**, respiratory muscle contraction produced by descending brainstem signals is detected by mechanoreceptors in the respiratory muscles, and sends an ascending signal to the sensory cortex. In **Hypothesis 2**, afferent information that projects to the brainstem and stimulates ventilation projects in parallel to the cortex – this would include separate projections of arterial and central chemoreceptors and exercise related stimuli such as limb muscle afferents sensing somatic work and projections from locomotor centers in the brain (77, 93). In **Hypothesis 3**, brainstem motor centers that integrate all of the individual afferent pathways stimulating breathing produce a descending motor output to respiratory muscles and also send an ascending copy of that output to the cortex (termed ‘corollary discharge’).

Hypothesis 1 held sway during the latter part of the 20th century and persists in some quarters today despite strong evidence to the contrary. In 1963 Campbell and Howell proposed a novel “Length Tension Inappropriateness” theory of breathlessness based on the idea that muscle spindle receptors in the respiratory muscles sense the balance between motor command to the extrafusal fibers and consequent muscle length change, and if the balance is inappropriate, the spindles would signal a problem, resulting in breathlessness (43). This theory was given credence by a courageous experiment – two subjects (including Campbell) were completely paralyzed with tubocurarine to determine whether paralyzing respiratory muscles would abolish breathlessness (40). Ventilation during paralysis was maintained by an anesthesiologist using manual bag inflation. To allow signaling, one hand was excluded from neuromuscular block by tourniquet. Subjects signaled the anesthesiologist to begin a ‘breath hold’ (stop compressing the bag), and to resume ‘breathing’. These breath holds exceeded breath holds in the control state by more than 3 min. The authors reported that the “unpleasant sensation of breath hold” was absent (we equate “unpleasant sensation of breath hold” to air hunger). The reported absence of air hunger during breath hold supported the “Length Tension Inappropriateness” theory previously posited earlier by Campbell and Howell. Unfortunately, the initial paralysis experiment, though clever in concept, was subject to some methodological flaws, chief among them was that the anesthesiologist hyperventilated the subjects prior to breath hold, lowering $PaCO_2$, and providing an attractive alternative explanation for the result. The experiment was repeated with better control of $PaCO_2$ on a single subject (Campbell), who again denied experiencing air hunger, however he did report “impending loss of consciousness” (42). Perhaps owing to the dramatic nature of the experiments, the Length-Tension Inappropriateness hypothesis was anchored in the minds of many as the explanation for all dyspnea, and dominated thought in the field for many years.

There were some pieces of prior evidence that were swept aside in order to accept the idea that respiratory muscle contraction was necessary for perception of breathlessness. In 1947 a single subject was paralyzed with tubocurarine to determine whether the drug had effects on pain or other sensations (218). The subject (Smith himself) provided detailed commentary

on the experience, including a description of air hunger during an inadvertent breath hold while he was completely paralyzed. "*I felt that I would give anything to be able to take one deep breath. The period of a few seconds taken for the tracheal intubation seemed unusually long, and I was awfully glad when artificial respiration was resumed.*" In a later study, 6 patients severely paralyzed by polio and supported by mechanical ventilation were exposed to hypercapnia by increasing PCO_2 in the inspired gas (183). The patients were asked to report "any unusual sensations" during the period of increasing $PETCO_2$ (shortness of breath was not mentioned by the experimenters). When $PETCO_2$ was increased by 18 torr (mean) above the starting point of 20 torr (mean), subjects reported intense shortness of breath and demanded immediate relief. None of the above studies were conducted with formal psychophysical methods, and the field remained in some conflict, largely ignoring earlier observations in favor of Campbell and Howell's respiratory muscle Length-Tension Inappropriateness hypothesis (a version of Hypothesis 1).

Several subsequent studies suggested that respiratory muscle contraction was unlikely to be the cause of air hunger. Adams et al exposed freely breathing healthy subjects to bouts of hypercapnia, mean $PETCO_2$ 55 Torr (Table 2, in reference 1). The subjects used a visual analog scale to rate their "feeling of an 'uncomfortable' need to breathe", equivalent to air hunger. The mean sensation rating during hypercapnia was 31%FS. (Ventilation at this point was 43 liters/min, thus mechanoreceptor relief mitigated air hunger). The subjects then voluntarily breathed to a target matching the ventilatory pattern recorded during hypercapnia; the mean air hunger rating was 5%FS, despite equivalent levels of ventilation achieved. The authors concluded that the feeling of an uncomfortable need to breathe cannot be explained solely by perception of afferent information arising from either chemoreceptors or respiratory mechanoreceptors, but was related to stimulation of medullary respiratory centers (Hypothesis 3).

In another study, subjects rated "difficulty in breathing" rather than air hunger during targeted breathing, and reported increase in sensation both above and below spontaneous ventilation during moderate hypercapnia (48, 49); The subjects commented that the sensation experienced was different when the target was below vs above the spontaneous ventilation at that $PETCO_2$. The authors conjectured that sensory quality above spontaneous ventilation consisted of increased effort, whereas the sensory quality experienced when ventilation was suppressed below spontaneous level was "different and more uncomfortable" and reflected different neural mechanisms. (They did not mention terms related to air hunger). Logically, it would seem that the failure of voluntary hyperpnea to produce air hunger suggests that respiratory muscle contraction is not responsible for air hunger. These experiments did not, however, produce a shift of thinking in the field.

Banzett and colleagues undertook to repeat earlier total paralysis studies and improve them by 1) utilizing psychophysical methods, 2) using an intervention that could be blinded, and 3) using steady-state stimuli (16, 17). In the first such study, four subjects paralyzed by spinal injury (ventilator-dependent high quadriplegics with clinically complete C1-C2 injury) were exposed to 3 torr increments of $PETCO_2$ every 3 minutes by increasing inspired PCO_2 during volume control ventilation (17). Subjects were asked a non-specific question about how they felt. All subjects detected the rise in $PETCO_2$ (mean reported

detection at 10 torr increase) and selected ‘air hunger’, ‘shortness of breath’, and ‘urge to breathe’ to describe the sensation. Three of the subjects were then tested in a forced-choice experiment to account for the possibility of guessing; all detected the change in $PETCO_2$ ($P<.05$). Because these subjects, unlike polio patients, had lost both motor and sensory innervation of the rib cage and diaphragm, it is unlikely that chest wall afferents played any role in detection of the CO_2 stimulus, providing strong evidence against the length-tension inappropriateness hypothesis. Nonetheless, proponents of the length-tension inappropriateness hypothesis pointed out that clinical determination of injury could not rule out some undetected spared chest wall afferents.

To address this criticism, Banzett and colleagues performed complete neuromuscular block in four healthy physiologists using a modern curare analog (16), depicted in Figure 13 right panel. In this experiment subjects rated air hunger on a scale ranging from none to ‘intolerable’. Constant ventilation was maintained by a volume control ventilator, while $PETCO_2$ was altered in random fashion in steps lasting 4 min (approximate steady state). This design had the advantage of being double blind, in contrast to the breath hold studies of Smith et al, and Campbell et al. Despite paralysis, subjects experienced strong air hunger at higher $PETCO_2$, and no air hunger at lower $PETCO_2$; total paralysis had no detectable effect on the quantitative relationship between $PETCO_2$ and air hunger. This provided strong disproof of Hypothesis 1.

A similar paralysis experiment was repeated by Gandevia and colleagues with similar result (95), depicted in Figure 13 left panel. In addition to testing the effect of paralysis on the relationship between air hunger and $PETCO_2$ during constant volume ventilation as Banzett et al. had done, this group also repeated the breath hold experiment of Campbell et al. Their results were contradictory to those of the Campbell et al studies - paralysis had no effect on the break point of breath hold or the intensity of dyspnea during breath hold, again providing strong disproof of Hypothesis 1.

To summarize, the available evidence clearly shows that afferent information from contraction of respiratory muscles is not required to produce the sensation of air hunger, disproving the first hypothesis. The remaining viable hypotheses are Hypothesis 2, direct projection to the cortex of the various inputs (such as chemoreceptors) that stimulate ventilation, and Hypothesis 3, the projection of corollary discharge from brainstem respiratory motor centers to the cortex. We favor Hypothesis 3, but this conclusion is based on a number of pieces of indirect evidence, rather than a definitive disproof of Hypothesis 2.

One line of evidence favoring Hypothesis 3 is that several forms of respiratory information produce air hunger in proportion to their ability to produce respiratory motor output. In one set of studies in freely breathing healthy subjects, breathing was stimulated by exercise alone, or to a similar ventilation with combinations of exercise with hypoxia or hypercapnia or metabolic acidosis (130, 131). The authors conclude that their findings were “*consistent with the hypothesis that the degree of reflex ventilatory activation is an important determinant of the intensity of the sensation of breathlessness in healthy humans, irrespective of the exact nature of ventilatory stimulus*.” In another study, hypoxic and hypercapnic stimuli were matched for their ability to stimulate ventilation during free

breathing in healthy subjects (159); the matched stimuli were then applied during restrained ventilation. Hypoxia and hypercapnia showed equal potency for air hunger when matched by ventilatory drive. These observations could be explained by proposing separate but matching effects on ventilation and air hunger for each of the stimuli – this is not impossible, but seems less likely than the corollary discharge hypothesis.

An entirely different line of evidence favoring Hypothesis 3 comes from patients who congenitally lack the normal respiratory response to hypoxia or hypercapnia (Congenital Central Hypoventilation Syndrome, CCHS); this genetic syndrome in its complete form obliterates chemoreflexes of the medullary respiratory centers (reviewed by reference 99). These patients fail to breathe during sleep, but do breathe while awake, presumably due to descending 'wakefulness drive' to respiratory centers (45, 184). They require external ventilatory support when sleeping from the time of birth. These patients do not experience air hunger during hypercapnia or during maximal breath holds, and can hold their breath far longer than age-matched controls (212). One might propose that the neural deficit affected several separate pathways – one projecting directly to the cortex, the other affecting the respiratory motor centers, but again this seems less likely than the idea that air hunger arises from corollary discharge from the medulla to cortex.

Although these observations are consistent with both hypotheses 2 and 3, the most economical explanation is that corollary discharge arising from brainstem respiratory motor centers projects to sensory cortex, giving rise to air hunger.

What can we infer about the air hunger pathway from animal experiments?— There are animal data to support the existence of the corollary discharge pathway – rhythmic activity approximating phrenic motor output has been detected in neurons in the midbrain and thalamus of decorticate cats (46, 47). During constant volume ventilation, stimulation of carotid chemoreceptor afferents evoked activity in a substantial population of single neurons recorded in the mesencephalon and thalamus; this ascending activity had a threshold around the resting $PETCO_2$ of cats, and became stronger and stronger as carotid afferent stimulation was increased (see Figure 14). The response characteristic of these neurons follows the characteristic of air hunger perceptual ratings in human subjects. The authors concluded that that these midbrain and thalamic neurons are part of an ascending pathway that conveys information about the magnitude of respiratory drive from the brainstem to thalamus and cortex (corollary discharge) and suggested that "*the sensation ultimately generated may be that of 'air hunger*'.

Afferent Pathway for Mechanoreceptor Relief of Air Hunger – Lung or Chest Wall receptors?

As discussed above (section Relief of Breath Hold), it has long been known that breathing relieves air hunger even when blood gasses are not improved (94, 110). The authors of these studies attributed this relief to a mechanical effect on the circulation (110) or to "considerable voluntary effort … required to prevent flow of gas" in the face of involuntary contractions of respiratory pump muscles (94); we now know these inferences to be wrong. Wright and Branscomb also reported relief produced by a deep re-inspiration of expired air following a maximal breath hold and further found that a deep inspiration of 7.4%

CO_2 in nitrogen completely relieved air hunger. Unlike the foregoing authors, Wright and Branscomb correctly posited that the best explanation for the rapid relief of air hunger with a deep inspiration was that "showers of impulses were transmitted from the lung via the vagus nerve to the brain", an hypothesis later borne out by experimental evidence.

Evidence from Neural Lesions—Opie et al altered $PETCO_2$ in mechanically ventilated polio patients using 2 methods – by increasing inspired PCO_2, and in a separate trial, by lowering tidal volume and allowing $PETCO_2$ to rise due to metabolic production (183). When inspired PCO_2 was increased at high ventilation, subjects reported intense shortness of breath 18 torr above starting $PETCO_2$; when ventilator tidal volume was decreased by a third, intense shortness of breath appeared when $PETCO_2$ had risen by only 6 torr. Because time course of the experiments was quite different, and because the intensity of air hunger was not quantified using psychophysical methods, it is difficult to quantitatively compare these findings with other studies, but the results clearly show that tidal volume relief does not require active breathing. There remains the caveat that some motor activity was undetected (airway pressure data were not provided), and that this clinically undetectable activity explained the result. This seems unlikely, and the authors accordingly concluded that "…the effect of chemical stimuli on the conscious appreciation of the adequacy of ventilation is modified by stretch receptors in the lungs and chest wall."

Chest wall afferents could have explained mechanoreceptor relief in polio patients, as polio primarily affects motor, not sensory, neurons. To test this proposition, Manning et al conducted a similar experiment in 5 patients with clinically complete lesions at the C1-C2 cord level; such lesions denervate both motor and sensory nerves to rib cage, abdomen, and diaphragm. Subjects provided periodic ratings of air hunger throughout repeated, blinded changes in tidal volume at constant mildly elevated $PETCO_2$ (and during repeated, blinded changes in $PETCO_2$ at constant tidal volume). There was significant relief of air hunger at higher tidal volumes. Interestingly subjects gave very similar descriptions of the sensations associated with increased $PETCO_2$ at constant ventilation and sensations associated with reduced ventilation at constant $PETCO_2$; they reported that breaths seemed smaller when air hunger increased regardless of whether $PETCO_2$ was increased or tidal volume was reduced. This study was repeated with 2 of the same patients and 2 additional C1-C2 quadriplegics with the additional aim of examining the locus of control (29). These experiments showed that chest wall mechanoreceptors are not necessary for relief, and in fact, the relationship between mechanoreceptor relief and ventilation seemed unaltered in quadriplegia compared with healthy controls (Figure 15). Because these quadriplegic subjects had no somatic innervation below the neck (insofar as can be determined with clinical testing) and the vagus nerve is spared in spinal cord injury, it is presumed that vagal pulmonary afferents were responsible for air hunger relief in this study. The most likely candidates are slowly adapting pulmonary stretch receptors (SAPSRs).

To test the effect of pulmonary mechanoreceptors on relief, the same experiment was performed in heart-lung-transplant patients to test chest-wall mechanoreceptor relief in the absence of pulmonary afferent information (92, 105). Both of these studies showed diminished, but not abolished, mechanoreceptor relief after lung transplant (see Figure 15). At the time of study, the authors presumed that the lungs were denervated; later work,

however, showed signs of lung reinnervation surprisingly soon following transplant (38). Thus, it is possible that the partially re-innervated lung explains the diminished relief seen in transplant patients, and chest wall receptors play no role in relief.

Evidence from pharmacological intervention.—One might imagine that aerosolized local anesthesia could be used to temporarily denervate the lung, but it is difficult to anesthetize pulmonary stretch receptors using safe doses of aerosol local anesthetics (62, 133, 146). A positive result (diminution or elimination of mechanoreceptor relief) would support the SAPSR theory, but a negative result could be ascribed to failure of anesthesia.

Aerosolized furosemide has been shown to sensitize SAPSRs in animals (231) and is safe to use in humans, thus it could be used as a probe to determine the role of stretch receptors in air hunger relief. An important caveat is that the effect of furosemide on air hunger is quite variable among subjects, providing substantial relief in about a quarter of subjects tested (21, 158, 162); one study re-tested the same individuals and found consistent response within individuals (98). A recent study (98) tested the effect of furosemide on discomfort produced by two different stimuli in the same healthy subjects: hypercapnia during tidal volume restriction (air hunger), and voluntary hyperpnea with resistive loading (work/effort sensation). A quarter of the subjects experienced relief of air hunger during the first stimulus, but none experienced work/effort relief during the second stimulus. Since aerosol furosemide acts on SAPSRs, this supports the hypothesis that SAPSR activity relieves air hunger.

What can we infer about the pathway for mechanoreceptor relief from animal experiments?—The putative respiratory corollary discharge that has been observed in cats (described above) is inhibited by lung inflation. A series of experiments by Eldridge and colleagues (78) showed several important features of this inhibition: 1) The inhibition is graded – larger inflations caused more inhibition, similar to the graded air hunger relief seen in human subjects. 2) Vagal sectioning and cooling studies pointed to slowly adapting pulmonary stretch receptors as the primary afferent pathway of the inhibition (see Figure 16); this is consistent with results described above on air hunger mechanoreceptor relief in patients with neural lesions. 3) Lung inflation can inhibit corollary discharge independent from its effect on respiratory drive, as well as through Hering-Breuer suppression of respiratory drive. This latter is notable because in awake humans Hering-Breuer suppression of respiratory drive is weak, but lung inflation suppression of air hunger is strong.

Long term dynamics: air hunger response to maintained stimuli (Adaptation)

Acute air hunger response adapts to chronic level of $PETCO_2$.—Does the acute response to air hunger persist during prolonged hypercapnia, or does it adapt to the chronic condition? If it does adapt, does the sensitivity decrease, does the threshold (x intercept) shift, or both? This question is of more than academic interest – patients with severely impaired lungs exist with chronic hypercapnia, and ‘permissive hypercapnia’ is a routinely practiced mechanical ventilation strategy.

We are aware of only one study of the adaptation of air hunger to prolonged hypercapnia (28). In this study, four chronically ventilator-dependent neuromuscular patients without

lung disease were exposed to 2 to 3% inspired CO_2 (normal FIO_2) for 5 to 8 days. Because these patients could not alter ventilation (it was set by their volume control ventilators), $PETCO_2$ rose an equal amount (group average 15 torr), and $PETO_2$ did not change – thus any adaptation would be to the altered PCO_2 or consequent respiratory acidosis. After 2 to 3 days the acute air hunger response adapted completely to the prevailing level of resting $PETCO_2$ over the course of several days (28). There was no detectable change in slope of the acute air hunger response to CO_2, but the X-intercept of the response shifted 15 torr, i.e., the threshold for air hunger shifted equally to the shift in chronic $PETCO_2$, indicating complete adaptation. An elevation of $PETCO_2$ that evoked intolerable air hunger in the control state produced no air hunger after adaptation. Figure 17. The mechanism of this complete adaptation of air hunger to prevailing resting $PETCO_2$ is not well understood.

Possible mechanisms of adaptation to chronic PCO_2—Since the primary excitatory input to air hunger is corollary discharge from medullary motor centers, an obvious question is whether the ventilatory response adapts completely to prolonged hypercapnia. In the air hunger study cited above, a true ventilatory response could not be obtained because the subjects were unable to breathe, however, slight changes in pressure and flow due to accessory muscle contractions provided a qualitative estimate of ventilatory drive. Some adaptation of ventilation was observed, but could not be adequately quantified.

In 1982, Dempsey and Forster summarized half a dozen studies of humans exposed to chronic hypercapnia as follows: “most evidence indicates ventilation remains above normal during chronic CO_2 exposure. The hyperpnea during chronic exposure equals or exceeds the hyperpnea during acute CO_2 exposure.” This implies that ventilation does not adapt to chronic PCO_2 change. An additional study since then has largely supported this view, although there was evidence of slight adaptation, about a 20% drop in ventilation over the first day (170).

However, in a more recent study of spontaneously breathing subjects, there was evidence of ventilatory adaptation similar to the above evidence of air hunger adaptation (61). The acute ventilatory response to CO_2 was tested daily – there was a rightward shift of 2 Torr, but no significant change in the slope of the response – This rightward shift in ventilatory response was similar in form to the rightward shift of the air hunger response.

One might also consider renal/metabolic acid-base compensation during respiratory acidosis. Due to the difficulty in obtaining arterial samples, there was only partial information on arterial acid base status in the Bloch-Salisbury et al air hunger adaptation study. Those data available suggested that the respiratory pH change was only partially compensated by renal/metabolic mechanisms, consistent with other studies showing that respiratory acidosis is only partially compensated in healthy humans and other mammals exposed to prolonged inspired CO_2 (36, 52, 61, 115, 170, 209). Compensation of cerebrospinal fluid pH seems to be even less effective (52, 115), and adaptation of cerebral blood flow is in the wrong direction to explain adaptation (170).

Thus, results are divided on whether ventilation adapts to chronically elevated PCO_2. It does seem clear that partial pH compensation to chronic hypercapnia cannot account for the

observed complete adaptation of air hunger to a chronic change in $PETCO_2$. We surmise, therefore, that adaptation of ventilatory and air hunger responses probably occurs at the synaptic level. This synaptic adaptation could occur at the level of the medulla, or at some level between the medullary motor neurons and the cortical perceptual areas. A study has shown plasticity at the level of the brainstem in response to chronic $PETCO_2$ changes (73), but further research is needed on perceptual pathways.

Practical consequences of adaptation to chronic PCO_2—When managing ventilator patients, attention should be paid to the rate of increase in $PaCO_2$. Although it may not be possible to gradually increase PCO_2 to allow adaptation, the period of incomplete adaptation after a rapid rise in PCO_2 (approximately 2 days) is likely to evoke air hunger, requiring close attention to pharmacological and non-pharmacological symptom management techniques.

In research applications, resting $PETCO_2$ should be measured and considered when comparing air hunger responses among different subjects – in the normal population this is a minor consideration amongst the numerous factors that cause variation in both ventilatory response and perceptual response; as a consequence, there is only slight reduction in variance when measurements are referenced to resting $PETCO_2$ in these studies ($\Delta PETCO_2$). (Table 1 depicts the air hunger response variance both in relationship to absolute $PETCO_2$ and relative to resting $PETCO_2$.) In cases where resting $PETCO_2$ is far from normal (for example severe COPD), however, it is essential to reference the air hunger response to prevailing 'resting' $PETCO_2$.

Lack of adaptation of air hunger to repeated exposure to air hunger—The question remains, is there adaptation to the air hunger sensation itself? Without training or practice, most individuals cannot tolerate holding their breath for more than a minute because of the air hunger that arises. This tolerance is increased dramatically in elite breath-hold divers. This achievement requires many months of breath hold training during which the divers experience many extended breath holds. Have these divers adapted to air hunger through repeated exposure? Binks et al studied four elite breath hold divers who could maintain breath-holds for 6 to 9 minutes (27). Three of these divers showed air hunger responses ranging from normal to low normal when referenced to resting $PETCO_2$; the 4^{th} diver denied any air hunger-like discomfort, but had a history consistent with congenital hypoventilation syndrome. This pilot experiment suggests that three divers did not adapt sensation of air hunger per se, but rather found methods to avoid it. Indeed, it would likely be an evolutionary disadvantage to adapt to air hunger. More study is necessary to test this hypothesis.

Cerebral Mechanisms in Air Hunger Perception

In 1954, Dell used electroencephalography (EEG) to measure the response of the reticular system to hypercapnia and hypoxia and postulated that the purpose of the observed reticular activity was to generate an arousal to disturbed blood gases and promote a homeostatic response (30, 69). This was the first data-based consideration of the central mechanisms of air hunger. Other EEG studies that specifically focused on respiratory sensations followed,

the first of which showed evoked potentials in the somatosensory cortex associated with brief inspiratory airway occlusions (66). However, the airway occlusions used in this and later studies were too brief to induce air hunger; they were chosen in order elicit rapid neural responses better suited to evoked-response EEG methodology. The slow dynamics of air hunger generation are unsuited to evoked-potential methods. This, along with EEG's limited capability to distinguish anatomical locations of regional activity has impeded the use of EEG methods on air hunger *per se*.

Just prior to the turn of the 21st century technical advances in positron emission tomography (PET) allowed the first 3-dimensional functional brain imaging studies. A pioneering study of brain activity related to breathing employed hypercapnia as a stimulus to examine cortical respiratory control (56). In an observation unrelated to the original hypothesis, the authors detected limbic activations unlikely to be motor activity, and retrospectively postulated that these limbic activations were related to the sensation of air hunger. The first study specifically designed to map brain activations related to dyspnea perception (in this instance air hunger) was published a few years later (18). Soon after, functional magnetic resonance imaging (fMRI) became more widely available, and the first fMRI study of air hunger was published (85). Functional brain imaging studies in all fields have since primarily used fMRI because of its higher temporal and spatial resolution and absence of exposure to ionizing radiation. Both PET and fMRI indirectly measure regional cerebral blood flow as proxy measures of local synaptic activity.

Although there have been a number of functional brain imaging studies of dyspnea, very few have focused on air hunger – most have instead used mild to moderate resistive loads that produced little or no change in ventilation or blood gasses, thus are unlikely to have evoked the sensation of air hunger (86, 89, 108, 228, 229, 237, 238). Although it is possible that subjects experienced some air hunger during these studies, they were not required to rate air hunger, and there is no debriefing data to suggest that the subjects felt air hunger. We will therefore concentrate on the few studies in which air hunger was clearly the dominant sensation. Figure 18 graphically summarizes the regional activations that have been observed in these diverse studies. There are several reviews of functional brain imaging that cover the broader territory of dyspnea as a whole, as well as cortical control of breathing (83, 84, 87). Some common findings have arisen with all studies that have studied respiratory discomfort in general, if not air hunger *per se*. The relationship of activated regions to the interoceptive pathway and salience network are discussed below.

Three studies, all from our group, used stimulus methods described in forgoing sections to provide a condition with substantial air hunger (moderate hypercapnia with restricted tidal volume), and a 'control' condition with no air hunger (moderate hypercapnia with ample tidal volume) (18, 26, 85). A fourth study used facemask breathing during moderate hypercapnia to provide a condition with substantial air hunger, and mouthpiece breathing during moderate hypercapnia to provide a 'control' condition with moderate air hunger; this stimulus has not been otherwise characterized, but presumably depends on facial afferents (142). In all of these studies an effort was made to use comparison conditions at constant $PETCO_2$ and $PETO_2$ to avoid false positives due to the direct action of blood gasses on brain blood flow. Both hypercapnia and hypoxia have potent dilatory effects on the

cerebral vasculature; protocols that involve changing blood gasses to generate air hunger are therefore problematic for brain imaging methods because the effect of PO_2 and PCO_2 on blood flow is not necessarily uniform across the brain (24, 90, 116); direct action of gas concentrations on vasculature may be misinterpreted as neural activations or deactivations.

Insular Cortex and Homeostatic monitoring

The first functional imaging study of air hunger identified anterior insula as the cortical region whose activity was most strongly correlated with the air hunger stimulus (18); this finding was affirmed by further studies of air hunger (26, 85, 142). Examples of anterior insular activation during air hunger are shown in Figure 19. The first functional imaging study of inspiratory resistance also identified activity in the anterior insula (191). Using the greater resolution of fMRI, Evans et al showed that air hunger activated two distinct regions of the insula, granular and agranular (85). The distinct activations were later shown to exhibit different time courses of activation: several insular activations were related to the onset of air hunger while a different activation was related to sustained air hunger (26).

The insula is a primordial region of the cortex, involved in interoceptive & visceral input – it can be thought of as the ‘primary visceral sensory cortex’. The insula provides a link between cognitive, homeostatic and emotion systems (58, 60, 151). The role of the insula in visceral sensations has been appreciated since Wilder Penfield’s mid 20^{th} century studies of epileptic patients; for instance, stimulation of insular cortex in awake patients gave rise to sensations localized to abdominal viscera (192). Functional imaging studies have shown that anterior insula is involved with perception of other homeostatic warning signals such as pain, hunger, thirst and temperature (58). A number of studies of inspiratory resistive loading have also shown activation of anterior insula (86, 89, 108, 228, 229, 237, 238). Although several sensations activate the insula, it is worth noting that even a 3mm square voxel (typical resolution for fMRI) probably contains a million neurons and is capable of processing numerous and diverse interoceptive sensations. So, it is likely that we are not able to identify specific sensations with the spatial resolution of the imaging techniques that have been used.

Anterior Cingulate: Integrating emotion and behavior

Activity in the anterior cingulate cortex has been observed in studies that have specifically induced air hunger (26, 85) or have conditioned subjects to anticipate air hunger (82, 108, 109). Similar to the observed sub-regional activations in the insula cortex, multiple areas within the anterior cingulate are activated by air hunger (85). Likewise, some of these distinct anterior cingulate regions are associated with the onset of air hunger, others with sustained air hunger (26). The anterior cingulate is highly connected with the brainstem, with areas associated with emotion (e.g. amygdala) and with higher cognitive centers such as the orbitofrontal cortex. Although the role of the anterior cingulate is not fully understood, it has representations from cognitive and emotional networks (37) and is likely an important region for integration of emotion and behavior. The anterior cingulate has been associated with the emotional response to pain (195). It is proposed that this is where nociceptive inputs are integrated with contextual information and memory from which develops a cognitive

response to pain. It is possible that the anterior cingulate serves a similar role in the processing of air hunger, which is in some sense analogous to pain (13).

Amygdala & limbic processing of emotional responses

As described above in the section on Emotional Impact, air hunger gives rise to anxiety and fear, so it is not surprising that *limbic regions* associated with anxiety and fear are active when air hunger is induced. Air hunger generated by tidal volume limitation during hypercapnia (85) or facemask breathing during hypercapnia (142) causes activation of the amygdala, an important component of the limbic 'fear network' (138). See Figure 20 for examples of amygdala activity during air hunger. The amygdala plays an important role in fear generation in response to a wide variety of stimuli (193), including pain and in particular visceral pain (236) that has a stronger affective component than somatic pain (230). As the amygdala is activated by fearful anticipation of dyspnea (i.e. while no dyspnea is present, 227, 228) it is likely that the amygdala is part of the emotional response, rather than sensory perception of air hunger itself. Similarly, the amygdala's response to loaded breathing can be manipulated by modifying the subject's affective state, but the same is not true for the insula or anterior cingulate cortex (229); again suggesting that the insula and anterior cingulate cortex are involved with air hunger perception, while the amygdala mediates the fear component of the emotional response.

A related region associated with processing homeostatic threat signals is the 'extended amygdala' or bed nucleus of the stria terminalis (137). Binks et al showed activation of this region when tidal volume was reduced to induce air hunger (26). The bed nucleus of the stria terminalis integrates descending cortical information with ascending interoceptive information to perform its role in mediating defensive responses consistent with a role in air hunger perception. Both the insula and the stria terminalis are associated with anticipated threat responses (221) and aversive stimuli (68).

Neural connections between the amygdala and insula (7) provide the potential for air hunger activation in the insula to drive the amygdala's response. The anatomical connections between the stria terminalis and amygdala are more substantial and there is a strikingly similar cytoarchitecture (149) to the point that the stria terminalis is sometimes referred to as the 'extended amygdala'. However, the roles of the amygdala and stria terminalis in the emotional responses maybe distinct (reviewed in 123). The stria terminalis mediates threat anticipation, i.e. anxiety; whereas the amygdala emotionally confronts the threat, i.e. fear (121). Von Leupoldt et al saw an increased activation of the stria terminalis (described as the extended amygdala) when uncomfortable breathing was induced while subjects were in a negative emotional state, induced by viewing unpleasant photographs (238). While this is consistent with involvement of the stria terminalis in the unpleasantness of dyspnea, an alternative explanation could be that the stria terminalis activation was a response to overall state of arousal and feelings unpleasantness that the subjects were experiencing.

Cerebellum and learned responses?

Although the cerebellum has long been thought to learn and control motor actions (35, 147, 204), it has recently been suggested that it also integrates sensory and cognitive inputs

(reviewed in reference 35). For example, cerebellar regions are involved in the modulation and perception of pain (165, 205), particularly visceral pain (51). The cerebellum's integrative function may modulate the response to pain (54, 165), and as such the cerebellum may also play an integrative role in the response to air hunger. Three specific cerebellar regions have been identified as having a role in air hunger. The two air hunger studies that included the cerebellum in the field of view both showed activity associated with air hunger in the Crus II and lobule VI of the cerebellum (26, 85). Cerebellar activity is not consistently observed in studies using resistive loads.

All three cerebellar regions (Crus 1, Crus II and lobule VI) are connected to the anterior cingulate cortex (219), suggesting a role in affective integration. The role of lobule VI and Crus I in encoding the response to generalized aversion (164) has led to the postulation they are involved in associative learning and conditioning to aversive stimuli (97). Evidence consistent with a cerebellar role in associative conditioning to air hunger exists, as Crus I and lobule VI are activated when respiratory patients imagine 'breathlessness' (109) or anticipate it (228), but no air hunger is actually present. Similar cerebellar activations are seen during empathy for pain (216), and the anticipation of pain (194), two situations when again the actual sensation (pain) is not present. A cerebellar role in associative conditioning is also supported by anatomical data showing projections between association networks in prefrontal regions and both Crus I and II (31, 100, 182) The idea that the cerebellum is part of an adaptive, conditioned response is intriguing. If true, it would suggest that some part of the air hunger response maybe learned. This conditioning/learning could happen early in life when air hunger is experienced during exercise, e.g. during childhood play.

Few brain-imaging studies have specifically investigated conditioned dyspnea responses. Acute conditioning to an impending respiratory threat (imposed resistive load) has been performed in humans (88) but no activations of Crus I, Crus II or lobule VI were observed (only lobule IX was seen to deactivate when a load was either anticipated or delivered). Instead, the prominent activation was in the periaqueductal gray; a cluster of neurons at the top of the brainstem previously associated with the motor response to airway occlusion (188, 249). The lack of involvement of Crus I, Crus II and lobule VI may be a result of the acute nature of the conditioning and/or the use of resistive load as a stimulus. Unlike air hunger, exposure to resistive loads in day-to-day life is rare, so the opportunity for conditioning/learning is limited in healthy individuals. Asthmatic patients who more frequently experience increased airway resistance show an exaggerated periaqueductal gray response to resistive load, not the cerebellum (239), suggesting the cerebellar response to air hunger is distinct.

While the precise role of the cerebellum in air hunger is still unclear, the regions associated with air hunger (26, 85) appear to be different from those associated with resistive load (82, 88). It is possible that the cerebellum is engaged in conditioned augmentation of respiratory motor drive in response to air hunger.

Frontal lobe and behavioral responses

In studies where air hunger was specifically generated by physiological stimuli or was recalled by subjects, activity in the frontal lobe was commonly found; but frontal lobe

activity was not seen in studies that use resistive loads. The superior frontal gyrus is involved in the response to air hunger generated by tidal volume limitation (85). This region is involved with higher cognitive function and working memory, so it likely plays a role in developing a behavioral response to air hunger through connections to the ACC (126) allowing integration of emotional components into the behavioral response.

Activity in the middle frontal gyrus is also seen during air hunger generated by tidal volume limitation (85) and face-mask breathing during hypercapnia (142) and is likely associated with fear-related memory processing (10, 11) via connections from the amygdala (119). Herigstad *et al* showed that middle frontal gyrus activity is more prominent in patients with lung disease than in healthy controls when they are prompted to recall 'breathlessness', presumably because the patients have more experience of fear-generating breathlessness (109). Activity observed in the inferior frontal lobe is observed only in tidal volume limitation protocols using mechanical ventilation (18, 85) and is likely associated with the subjects suppressing the urge to breathe in order to cooperate with the ventilator (6, 125).

Activation of the primary motor cortex is rarely seen in studies of air hunger, but is common in studies using resistive loading (82, 86, 108, 190, 191, 228, 237, 238, 247). Full ventilatory compensation for applied resistive loads depends on consciousness, thus is likely to involve primary motor cortex (113, 202, 207). Transcranial magnetic stimulation (143) and EEG studies (65, 122) also suggest the ventilatory response to external loads involves the motor cortex. Tidal volume limitation (air hunger) protocols show activity in the pre-supplementary motor area (18) and pre-motor area (85), but akin to the activity seen in the inferior frontal lobes, this activity is likely due to subjects attempting to inhibit reflex respiratory muscle contraction when they become uncomfortable.

Augmentation of the reflex motor drive to breathe during exposure to respiratory discomfort may also come from the cerebellum. Two of the three tidal volume limitation studies (26, 85) showed cerebellar activity associated with air hunger (the other study (18) did not include the cerebellum in its field-of-view) and similar activity has been seen with imagined 'breathlessness' (109). Cerebellar activity is less commonly observed in studies using resistive loads unless there was a concurrent rise in CO_2 when the load was introduced (190, 191).

Somatosensory Cortex

Notably, there is no evidence of air hunger-related activation in the somatosensory cortex – the sensory cortical representation of air hunger seems to be limited to the visceral sensory cortex (insula). This is consistent with the afferent pathways described above, which either originate in visceral receptors (pulmonary stretch receptors, chemoreceptors) or other areas of the brain itself (medulla). In contrast, inspiratory resistive loading studies (mainly work/effort sensation), do activate somatosensory cortex (e.g., references 82, 86, 108), consistent with involvement of somatic afferent pathways (oropharyngeal receptors sensing mouth pressure, chest wall muscle receptors sensing force and displacement).

Air hunger activates interoceptive pathway and salience network

Both the insular and cingulate cortices receive visceral homeostatic information via an 'interoceptive' *spinothalamocortical pathway* that is highly developed in humans and carries information for a number of bodily sensations such as temperature, pain, and touch (53, 57, 59). Originating in the lateral spinothalamic tract, the 'interoceptive' pathway passes through the homeostatic control regions of the brainstem and intersects with areas involved with the control of breathing, including the nucleus of the solitary tract that receives input from arterial chemoreceptors and pulmonary stretch receptors. The interoceptive pathway then rises toward higher centers, passing through the *medial thalamic nuclei*. The thalamus may act as a gate that blocks some ascending signals related to respiration giving priority to other inputs (67), but there is no functional evidence that air hunger can be gated out-in fact, there is some evidence that air hunger can close the gate for pain sensation (63, 64, 246). Air hunger related activity in the human medial thalamus has been observed in two studies (18, 142). In addition, respiratory-related projections from the medulla have been observed in the thalamus of cats (47). The interceptive pathway then leads onto the insula and anterior cingulate as well as the regions of the frontal lobes. A number of regions activated by air hunger are components of the interoceptive pathway, while additional regions outside of the pathway have also been associated with air hunger. We have proposed in Figure 21 a role of the interoceptive pathway as a possible tract for ascending air-hunger related information.

Recently attention has been focused on a "Salience Network" thought to be activated by a wide variety of inputs having importance to the organism – these include interoceptive signals such as air hunger, thirst, etc., as well as exteroceptive inputs such as stressful visual images (234). There is extensive overlap between the cortical areas of the interoceptive pathway, the salience network, and activations seen with air hunger as well as other respiratory discomforts. The anterior insula is a key part of the salience network (151). Other elements of the salience network include the anterior cingulate cortex and amygdala (234).

The interoceptive pathway and salience network are engaged by a wide variety of internal and external stimuli. Clearly, these diverse stimuli result in distinctly different sensory experiences that have some common basic features – they grab attention and demand action to preserve homeostasis. These different experiences undoubtedly engage different populations of neurons, but the current resolution of functional imaging methods makes it impossible to distinguish one from another. For instance, these methods are unable to distinguish activations of insula, dorsal anterior cingulate cortex, amygdala and medial thalamus caused by respiratory discomfort from activations in the same regions caused by the very different experience of skin heat pain (237). Likewise, it is difficult to determine which of the activations observed in anterior insula and anterior cingulate are specific to air hunger and which are part of a common response to air hunger, pain, and other salient stimuli. The anatomically distinct activations within the insular and cingulate associated with the onset of air hunger and steady state air hunger (26) may be associated with an initial general salience response of the insular and cingulate at the onset of air hunger, followed by a distinct and specific air hunger response when air hunger is in steady-state. Although we

understand much more than we did how sensations are processed in the brain, we are not yet at the point where we can infer what someone feels from brain images.

Future study of cerebral mechanisms

Prior to the functional imaging studies published at the outset of this century, nothing was known about the brain regions serving the sensation of air hunger. At this time, our understanding of central mechanisms underlying air hunger is still meager, but the future is promising. For example, improvements in the spatial resolution of fMRI may help us further distinguish between neural networks associated with general arousal, air hunger and the emotional and behavioral responses. Fundamental questions remain about the role of the thalamus; for example, does it serve as a threshold gate for respiratory-related afferent information, or does it filter out non-critical information when air hunger arises? Can we identify direct pathways from chemo- and mechanoreceptive afferents to higher centers with focused, high resolution connectivity studies? Can we interfere selectively with pathways to alleviate air hunger in patients without compromising respiration?

Animal Models

Although many of the stimuli that evoke air hunger in humans could be applied to animals, there is no current paradigm that allows us to infer the perception of air hunger in animals. The lack of an animal model has thus far restricted research to humans and has understandably limited the interventions that have been made, for instance creation of precise neural lesions to identify pathways, testing of drugs not approved for human use, etc. Development of an animal model would allow numerous studies to confirm and advance findings from human studies. The first issue is whether non-human species perceive air hunger. It is reasonable to infer that animals can perceive air hunger, as it is a critical homeostatic warning of inadequate gas exchange. Air hunger has been termed a primordial sensation, one that animals must perceive in order to ensure survival (72). The necessary limbic and paralimbic brain structures for air hunger perception are present in vertebrates from reptiles to primates (34, 196). Behavior indicative of anxiety and fear has been demonstrated in animals exposed to hypoxia and hypercarbia. But to generate an animal model, we need accepted methods to assess air hunger using cortically-driven behavioral responses in animals; developing such a paradigm presents some obvious and some not so obvious problems.

The most obvious problem is finding a suitable method to measure air hunger without verbal communication or a scaled response. This has proved problematic with non-verbal humans (e.g. intubated patients) and assessments based on observation of their behavior is poorly correlated with levels of air hunger (25, 106). Despite the lack of an acceptable paradigm, there are numerous studies that purport to show that animals are experiencing ‘shortness of breath’ or dyspnea. These claims are based on observation of ‘labored’ abdominal breathing, increased airway flow (155, 220) or ‘gasping’ (140, 242). These visible respiratory efforts can be entirely generated by reflex pathways, thus do not necessarily indicate the presence of air hunger or dyspnea (which are perceptions). The tail flick model used to estimate pain in rats is analogous to observations of respiratory efforts (3); a rat’s noci-defensive

withdrawal of the tail from a heat source has been used as an indication of pain, but the tail-flick is a reflex response limited to the circuitry of the spinal column (just as the ventilatory response hypercapnia is a reflex that can be accomplished by the brainstem). Yet perception of pain or air hunger requires cortical processing. If animal behavior is to be used as an estimate of air hunger, the measured behavioral response must be complex enough to allow one to confidently infer cortical perception and processing.

Animal responses to hypercapnia and hypoxia

Some clues on how to proceed can be gained from research on humane methods of animal sacrifice in research. Common methods use hypoxic and hypercapnic gas mixes used to kill laboratory and food animals, and several laboratories have reported aversive behavioral responses to these gasses. Because they are conducted in the context of animal welfare, these studies usually use lethal gas concentrations used in euthanasia, i.e. very high CO_2 (e.g. 70–90%, see Table 2) or very low levels of O_2 (e.g. 0–2%) to assess animal stress. While these studies were not intended to form a model of air hunger, they do provide some encouragement that air hunger models can be developed. Rats placed in a chamber with a gradually rising PCO_2 show increased activity, rearing and escape behaviors when CO_2 concentration becomes greater than 5% (171). Mice show panic-like escape attempts at 20% CO_2 (222). However, measuring behavioral responses that are specific to the stimulus (and not just a generic escape or reflex responses) would improve the reliability of the measurement (241). More complex behavioral responses are seen when animals are not confined to a single chamber and can make free decisions about competing drives (e.g. approach a reward that is placed in an aversive environment). Although not designed to study air hunger, the experiment depicted in Figure 22 shows a possible paradigm – rats show an aversion to CO_2 strong enough to prevent them from remaining in a chamber with tasty food rewards (171). When more complex behavior is permitted, significant species differences in the behavioral response to raised CO_2 are observed (see Table 2). For example, rats (171) and hens (199) appear to be relatively sensitive to CO_2 whereas turkeys appear behaviorally insensitive (198). Even within a species the behavioral responses appear to vary across strains (33) and even individual animals (2, 171); these differences must be considered in the construct of any future air hunger model. The observed behaviors in hypercapnia studies may also be confounded by other unpleasant sensations induced by high CO_2. Rats experience pain in the nasal mucosa when breathing CO_2 above 37% (5) due to the formation of carbonic acid as CO_2 dissolves into the water in the nasal cavity. A similar response and CO_2 pain threshold is observed humans (4). At lower CO_2 (7.6%-10.4%) humans also report headache, dizziness, sweating, restlessness and faintness (74), as well as air hunger. If these extraneous sensations are also perceived by non-human species (which seems particularly likely in the studies that used very high CO_2), they would likely contribute to the observed aversive behavior. Separating behaviors that are due to air hunger from those that are due to other effects of CO_2 presents methodological challenges for an air hunger model.

Development of a robust animal model

Evidence of avoidance allows a measure of aversion (206). However, a more robust measurement of unpleasantness can be obtained using conditioning paradigms that require

perceptual discrimination. Conditioning paradigms reduce the confounds of extraneous side-effects and provide opportunity for experimental protocols to investigate air hunger. Such paradigms have been used in pain and pain treatment research for decades and allow the aversion (to pain) or the preference (for treatment) to be assessed without the stimulus being present, i.e. in the absence of immediate physiological or reflex responses. In brief, animals are restricted to a chamber and exposed to a stimulus until they are conditioned to associate the chamber with the stimulus (233). Then, without the stimulus present and with the animal given the ability to pass in and out of the chamber, it is determined whether the animal wishes to leave (condition placed aversion) or stay (conditioned placed preference) in the conditioning chamber. To our knowledge, no published studies of air hunger using conditioning paradigms exist, but such paradigms might be developed to avoid the confounding side-effects of hypercapnia and hypoxia and progress from assessing reflex responses to assessment of the complex cerebral processing that air hunger involves.

Air hunger in clinical dyspnea

"Not being able to get air is the worst thing that could ever happen to you. Air is everything" (Hospitalized patient commenting on the experience of dyspnea. 22).

Prevalence of air hunger in patient reports

Dyspnea (breathing discomfort) is a leading symptom of many clinical conditions – lung disease, cardiovascular disease, metabolic disease, obesity, and anxiety disorder. There are several kinds of uncomfortable breathing sensations; the most commonly cited definition of dyspnea states that dyspnea comprises "qualitatively distinct sensations that vary in intensity… unpleasantness and… emotional and behavioral significance" (187). Air hunger is one of these distinct sensations. Data now available show that air hunger is usually the principle sensation in clinical dyspnea, although it is also clear that clinical dyspnea is nearly always a mix of sensations, almost always includes a sense of elevated work and effort, and often includes a sense of chest tightness.

An early content analysis of interviews with 68 pulmonary patients found that "not getting enough air" was expressed by nearly 2/3 of the patients (114). Other studies, although not designed to quantify the relative contribution of sensory qualities, also suggested that air hunger is a prominent sensation in dyspneic patients; air hunger-related descriptors dominated patient reports (81, 217).

A recently developed questionnaire (the Multidimensional Dyspnea Profile, MDP) requires patients to choose the most applicable sensory quality among 5 sensations (respiratory muscle work, air hunger, chest tightness, mental concentration on breathing, and awareness of hyperpnea) (19). This approach eliminates the problem of having unequal numbers of synonymous terms for various sensations. Six studies have provided information on the most applicable sensory quality descriptors in patients with various diagnoses: Morelot-Panzini et al, studying COPD outpatients, found that air hunger was most often chosen as the most apt descriptor (chosen by 27%), second most often picked was awareness of hyperpnea (19%) (161). The same group, studying ALS outpatients, found 56% chose air hunger, the second most often picked was the need to concentrate on breathing (19%) (163). Williams

et al studied COPD outpatients and found that air hunger was the second most often chosen sensory quality (26%), while tightness was most often chosen (37%) (243). Ekstrom et al allowed COPD outpatients to choose the two most applicable sensory qualities and found that air hunger was the most commonly chosen descriptor followed by awareness of hyperpnea (76). Stevens et al studied hospital inpatients with mixed diagnoses and found that 36% chose air hunger, the second most often chosen was chest tightness (22%). Stevens et al examined patients' responses in greater detail, and found that when overall breathing discomfort was low, air hunger did not stand out clearly as the most apt descriptor, while at higher levels of breathing discomfort air hunger became much more prominent (see Fig 23). After the most apt descriptor is chosen, the MDP instructs patients to rate the intensity of each of these sensations. Ratings data were consistent with the descriptor choices (i.e., there was high correlation between most apt descriptor and highest rated descriptor) (225, 243), but ratings also revealed that clinical dyspnea in inpatients is nearly always a mix of sensations.

Pathophysiological mechanisms

As described in detail above, air hunger arises when achieved ventilation does not match the demand for ventilation. Several pathophysiological mechanisms can lead to this mismatch.

The simplest case may be motor neuron disease – demand is normal, but the respiratory muscles simply won't answer the demand of the medullary respiratory centers because the motor signal is interrupted, hence tidal volumes are lower than demanded and pulmonary stretch receptor feedback is low. Amyotrophic Lateral Sclerosis is an example – of the patient groups surveyed thus far with the MDP, ALS patients chose air hunger as most apt descriptor more often than others (163).

A more complicated example is the patient with lung disease, who may be comfortable at rest, but encounters dyspnea during exertion. During exercise, the increase in ventilation produces dynamic hyperinflation raising end-expiratory lung volume and thus reducing inspiratory capacity. As inspiratory capacity falls, the increasing desired tidal volume approaches inspiratory capacity, and further increase minute ventilation can only be achieved by increasing breathing frequency. This, in turn, comes at the cost of increased deadspace ventilation, decreased respiratory compliance, and disadvantaged inspiratory muscle sarcomere length. The patient cannot match ventilation to the prevailing respiratory demand, pulmonary stretch receptors report the failure, and air hunger (unsatisfied inspiration) ensues (178, 187). An example of the emergence of air hunger as the most prominent sensation when exercise level increases is shown in Figure 24.

Opiates are the only widely recognized pharmacological intervention to provide symptomatic relief of dyspnea (187). Opiates specifically relieve air hunger, as discussed above (15). Thus, opiates operate on the dominant sensory quality in clinical dyspnea.

An example of insufficient air hunger has been reported in connection with the 2020 COVID-19 pandemic. Case reports indicate that some patients are severely hypoxemic, have compliant lungs, and report little or no dyspnea (139, 185). An explanation for this apparent conundrum rests on well understood physiology, and the fact that hypoxia is a weak stimulus

for air hunger (see section above ‘Hypoxia as a stimulus for air hunger’). We know that very poorly ventilated lung units or shunts will cause hypoxia even if there is other lung that is healthy, due to the non-linear shape of the O_2-hemoglobin dissociation curve. We also know that shunts will not cause hypercapnia if there is other lung that is healthy, due to the linear shape of the CO_2 - blood dissociation curve. As the reader of this article knows, it requires severe hypoxia to produce air hunger. Thus, in cases of regional pneumonia and shunt we may see dangerous hypoxia with little air hunger.

Impact on patients

As C.F. Hoover noted, air hunger is alarming to the patient (See quotation in Introduction. 112). Air hunger has a strong impact on emotions, activating limbic and paralimbic cortex engendering anxiety, frustration and fear (see above sections on Emotional Impact of Air Hunger and Cerebral Mechanisms in Air Hunger Perception). Although in clinical situations it is difficult to untangle the emotional import of the different sensory qualities, laboratory studies show that air hunger stimuli are more potent in provoking anxiety, frustration and fear compared to stimuli requiring maximal work of breathing (20). Thus, air hunger is likely a more urgent motivator to seek medical care as well as a cause of substantial suffering when unrelieved by treatment.

Mechanical ventilation of patients with acute lung disease vulnerable to acute respiratory distress syndrome (‘ARDS’) presents a special air hunger problem. The lungs of these patients have reduced compliance, and are vulnerable to damage if inflation pressures are too high; therefore ‘lung protective ventilation’ is usually practiced. To avoid ventilator-induced lung injury (‘VILI’), tidal volumes are reduced, often to the point at which arterial PCO_2 rises (‘permissive hypercapnia’). As the reader of this chapter will understand, this is a recipe for air hunger. One study found that half of mechanically ventilated critically ill patients report dyspnea, and the majority of these described experiencing air hunger (210). The most effective intervention to reduce dyspnea in these patients was to increase ventilator tidal volume (not all these patients were deemed at high risk for VILI). In cases where it is not deemed safe to increase tidal volume, opiates provide a good alternative.

Conclusion

Air hunger is the consciously perceived manifestation of inadequate gas exchange – a critical threat to homeostasis. Homeostasis of oxygen and carbon dioxide is ordinarily satisfied by reflex adjustment of the respiratory and cardiovascular systems. However, there are occasions when reflex changes are not adequate to maintain homeostasis, and more complex behaviors are necessary. These circumstances include: a) interruption or limitation of breathing in the service of other acts – eating, drinking, speaking, breath hold diving; b) obstruction of breathing by external objects, etc.; c) gas exchange demand that exceeds the capacity of the respiratory or cardiac pump – either through intense exercise in healthy subjects, or through impaired pumping due to respiratory or cardiovascular disease. In such circumstances, behaviors involving systems other than the cardiovascular and respiratory systems are necessary – whether to leave a hostile environment, remove an external airway obstruction, stop drinking in order to breathe, reduce running speed to a sustainable level,

or in today's world, seek medical help. These responses require a decision on the best course of action, perhaps suppressing a competing but less urgent demand, and altering motor command to the appropriate systems. It has even been proposed that awareness of homeostatic needs such as air hunger, hunger, and thirst gave rise to consciousness (71, 72).

Air hunger results from ventilation inadequate for ventilatory demand – i.e., a comparison of two afferent inputs. Information about ventilatory demand is relayed to the cortex from medullary respiratory centers, where the various stimuli for ventilation (blood gasses, exercise inputs, etc.) are integrated to produce motor output, and a copy of motor output (termed 'corollary discharge) projects to limbic and paralimbic cerebral cortex. Information about ventilation, or the lack thereof, arises from mechanoreceptor afferents sensing tidal inflation of the lungs (pulmonary stretch receptors). The resulting air hunger sensation is immediately unpleasant, and gives rise to anxiety, frustration and fear. These emotions are important in motivating behavioral change to address the problem.

Air hunger can be measured using psychophysical methods during controlled, quantifiable laboratory stimuli. Most subjects are able to provide reliable ratings (high correlation between rating and stimulus intensity within subject), and the across-subjects variance in stimulus-response slope is similar to the across-subjects variance in reflex ventilatory response. If ventilation is held near resting levels, intolerable air hunger occurs at an average $PETCO_2$ 13 Torr above resting; if ventilation is doubled at that $PETCO_2$, the intensity of air hunger will be halved. Hypoxia is much less effective in generating air hunger: when ventilation and $PETCO_2$ are held near resting levels, pronounced hypoxia ($PETO_2$ near 50 Torr) is needed to generate air hunger, and severe hypoxia – beyond ethical limits – is required to generate severe air hunger. When subjects breathe freely, the lower PCO_2 and increased mechanoreceptor discharge inhibits air hunger until hypoxia is profound, altering consciousness.

Air hunger is a central component of clinical dyspnea, generating an emotional response that causes patients to seek care, but when unrelieved severely impacts quality of life. Although much has been learned about air hunger in the past few decades, much remains to be discovered, ranging from fundamental questions about neural mechanisms to adequate and safe methods to mitigate air hunger in clinical situations.

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DIDACTIC SYNOPSIS

- Air hunger is the conscious appreciation of an uncomfortable urge to breathe.
- Air hunger is the most uncomfortable, most prominent, and most common of the sensations comprising clinical dyspnea.
- Air hunger can be reliably scaled by most people using various psychophysical rating scales. Although non-human vertebrates presumably sense air hunger, there is currently no accepted experimental model to scale air hunger in animals.
- Air hunger is a primal sensation, alerting the animal to a threat to homeostasis that requires a behavioral response more complex than increasing respiratory muscle output or cardiac output.
- Air hunger activates limbic and paralimbic regions in the brain giving rise to anxiety and fear.
- Air hunger arises when minute ventilation is less than desired minute ventilation. Current understanding is that a copy of motor activity in medullary respiratory centers (‘corollary discharge’) projects to sensory cortex, and is compared to signals of tidal lung inflation arising mainly in pulmonary stretch receptors.

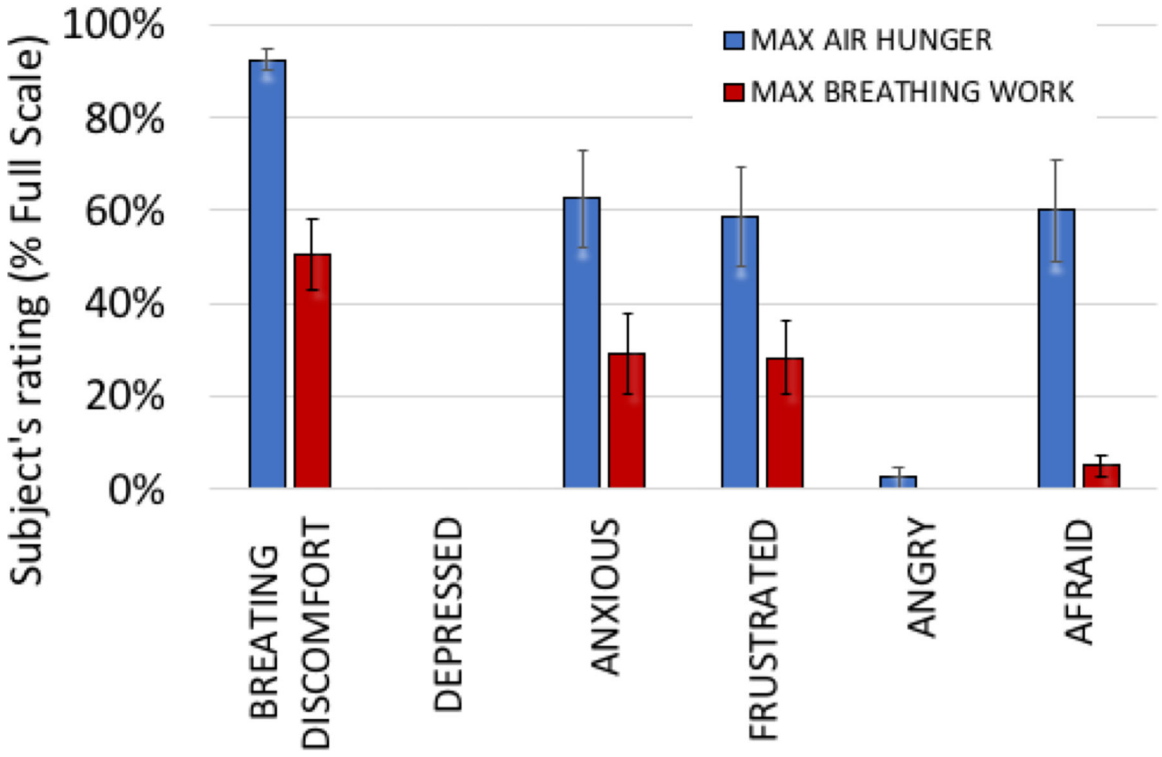

Figure 1.

Air hunger provokes strong emotional response compared to maximal breathing work. Data from Reference (20) Figs 5&6. Healthy naïve subjects were exposed to the maximum tolerable air hunger stimulus (blue bars) and were required to do the maximal amount of inspiratory work of breathing (red bars). Data plotted are group mean ±SE. The air hunger stimulus comprised mild hypercapnia ($PETCO_2$ 6 Torr above resting) combined with progressively decreased ventilation until the tolerable limit was reached. The work stimulus comprised constant eucapnia while the subject breathed against moderate resistance and progressively higher ventilation target until task failure. Mild hyperoxia prevailed throughout; FIO_2 was 30%. Adapted with permission of the American Thoracic Society (ATS). Copyright © 2020 ATS. All rights reserved. *Am J Respir Crit Care Med* 177:1384–1390. The Am J Respir Crit Care Med is an official journal of the ATS. Readers are encouraged to read the entire article for the correct context at [doi: 10.1164/rccm.200711-1675OC]. The authors, editors, and The ATS are not responsible for errors or omissions in adaptations.

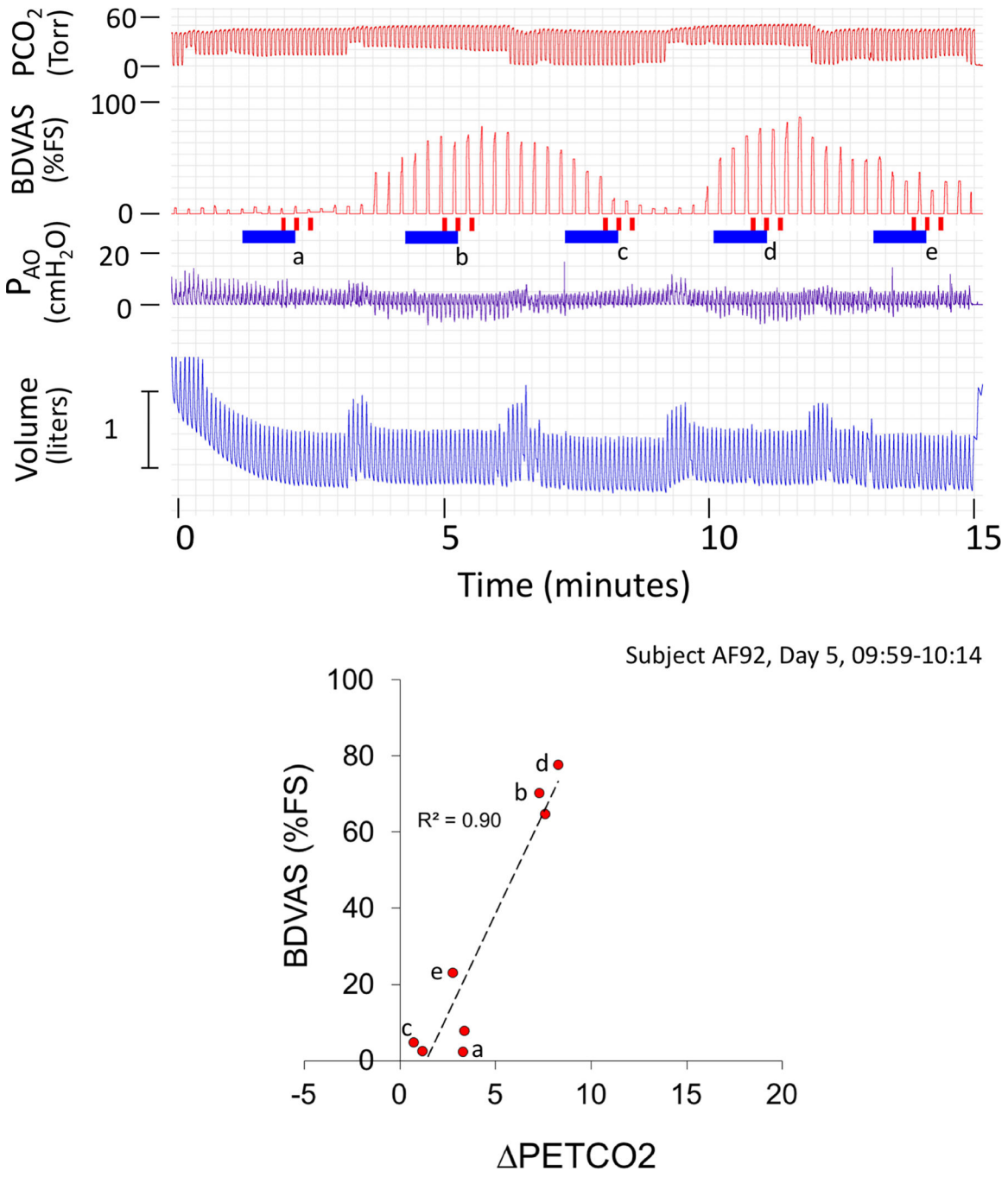

Figure 2.

Methodology. **Upper panel:** Time tracing of physiological variables during one run of a typical air hunger study in a healthy volunteer, together with resultant stimulus response plot (Subject AF92 in reference 21). Traces from top: Tidal PCO_2, Visual Analog Scale rating of Breathing Discomfort (BDVAS) at 15 sec intervals, pressure at the mouthpiece (P_{AO}), volume derived from integrated flow signal (the initial transient is due to the start-up effect of a high-pass filter). Inspired fraction of CO_2 was varied manually to achieve desired $PETCO_2$. Five large breaths were delivered at the time of each PCO_2 step in order to speed

gas change and to give the subject momentary relief when at high discomfort. Red bars indicate times of collection of BDVAS ratings; blue horizontal bars below BDVAS tracing indicate periods for collection of physiological data. As explained more fully in the text, the air hunger response lags changes in end-tidal PCO_2 and changes in tidal volume (14); therefore air hunger measurements are offset in time to account for the slow air hunger dynamic response. **Lower panel:** The 90 sec average $PETCO_2$ plotted against the average of 3 BDVAS ratings comprise one data point. This run resulted in 5 of the data points on this plot of breathing discomfort rating *vs* $\Delta PETCO_2$ expressed as torr above mean resting $PETCO_2$ (42.5 Torr in this subject). Each data point is labelled in both panels. Mild hyperoxia prevailed throughout; FIO_2 was 30%. Adapted with permission License #4834191357251.

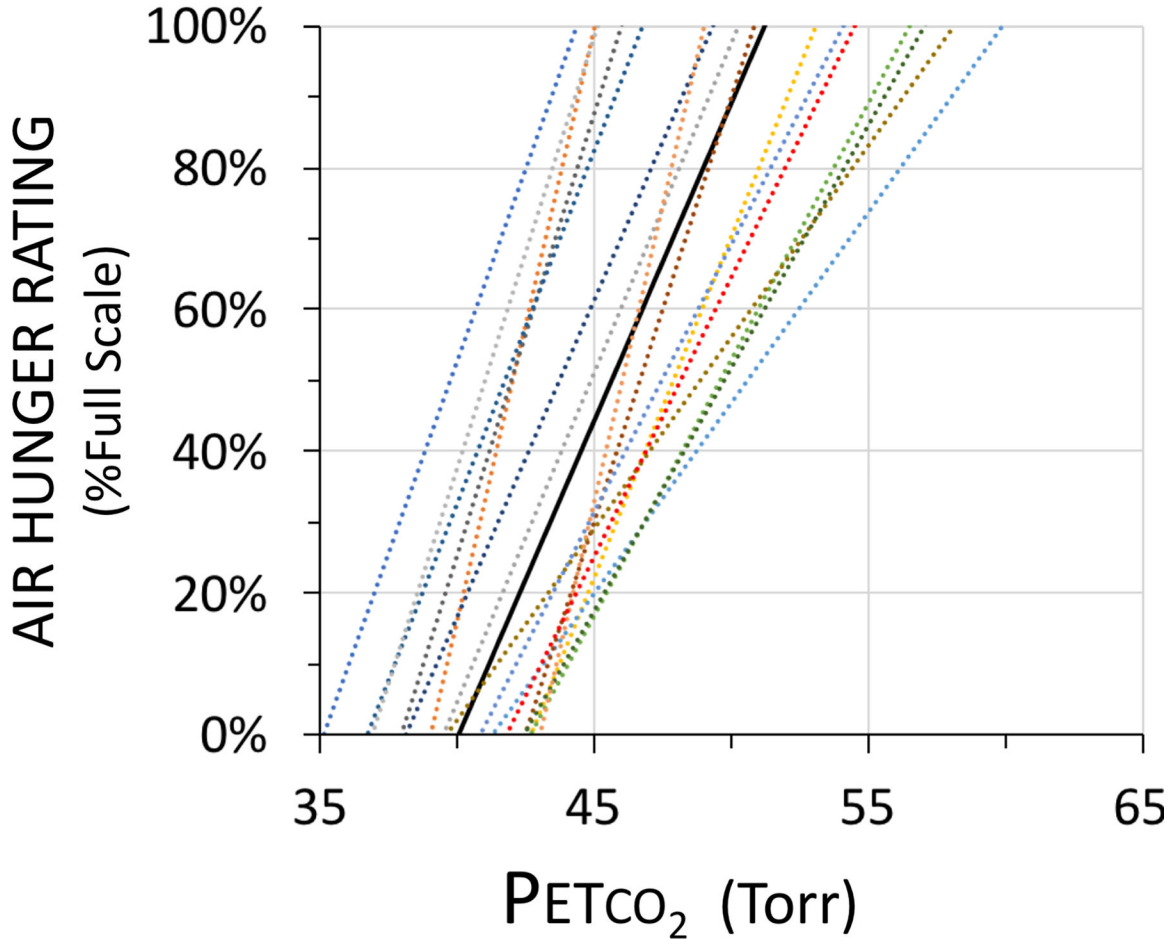

Figure 3.

Normative data of the air hunger response vs CO_2 stimulus showing variance in air hunger stimulus-response among 16 normal subjects. Data re-plotted from reference (12), Table 2. This figure depicts a regression line for each subject, as well as the mean of all subjects (heavy black line). In this study subjects rated air hunger on a 7-point ordinal scale implemented with an electronic box with 7 evenly spaced buttons ranging from no air hunger intolerable air hunger. It was later determined that subjects treated this scale in the same way as they treated a VAS with the same scale definitions(136). Ventilation was determined by a volume-control ventilator that delivered constant frequency and tidal volume resulting in minute ventilation of at 0.16 liters•min^{-1}•kg^{-1}; inspired gas contained 50% O_2 and a variable fraction of CO_2 manually controlled to achieve desired $PETCO_2$. Because air hunger is a very distressing sensation, subjects were told that if they rated 100% of scale (i.e., intolerable) we would immediately reduce the stimulus, reducing discomfort in 2 to 5 breaths, or they could remove the mouthpiece and experience immediate relief. The variance of this perceptual response among subjects is similar to that reported for the reflex-driven hypercapnic ventilatory response (HCVR).

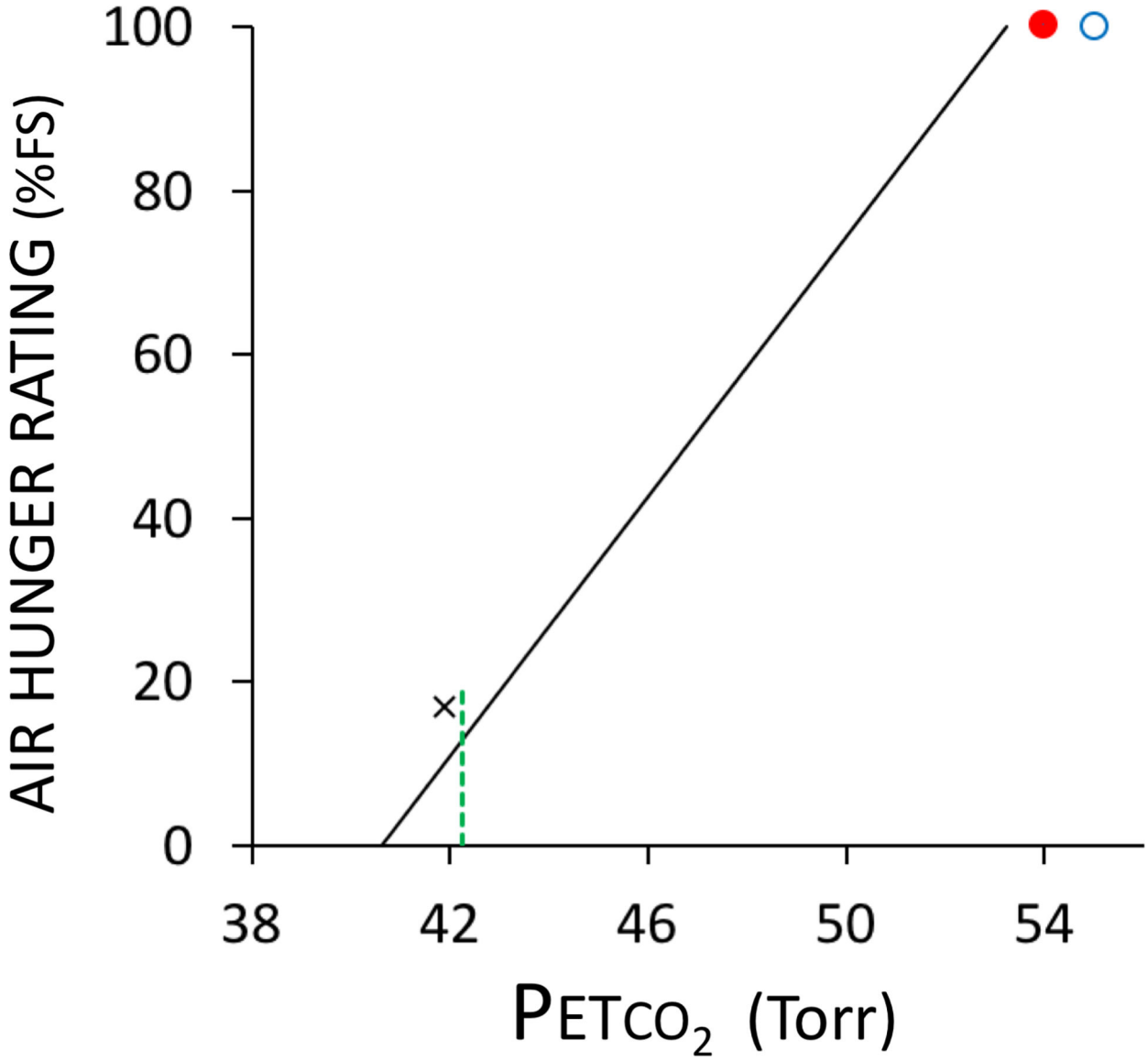

Figure 4.

Normative data of the air hunger response vs CO_2 stimulus, summarizing data from several studies in which ventilation was near resting level with background hyperoxia. The Y axis is the subject rating expressed as percent full scale (%FS), top of the scale defined as intolerable, $PETCO_2$ = end-tidal PCO_2. The solid line represents the mean regression line from 5 studies using rating scales that defined the upper end of the scale as 'intolerable' as shown in Table 1. The solid red circle represents data from Remmers et al (203), showing the $PETCO_2$ at which subjects could not tolerate breathing to the ventilation target of 10 $L \cdot min^{-1}$ (we infer that this is the same as a rating of intolerable). The open blue circle represents data from Mithoefer et al, including the data supplement, (154) showing the PCO_2 in the rebreathing bag at the point where subjects could no longer tolerate rebreathing, utilizing the average of hyperoxic runs with ending ventilation closest to 10 $L \cdot min^{-1}$. The vertical dotted green line shows data from Castele et al, (44) and represents the $PETCO_2$

at which subjects first reported that ventilatory needs were not satisfied (they did not give a rating). One of the studies in Table A, reference (12), used a discrete scale, the lowest point of which is comparable to the threshold – this is indicated by X. The small $PETCO_2$ difference between the BD0 intersection and the threshold points is probably due to the subject's 'decision criterion': i.e., there must be some finite sensation before a subject will decide to report the presence of sensation.

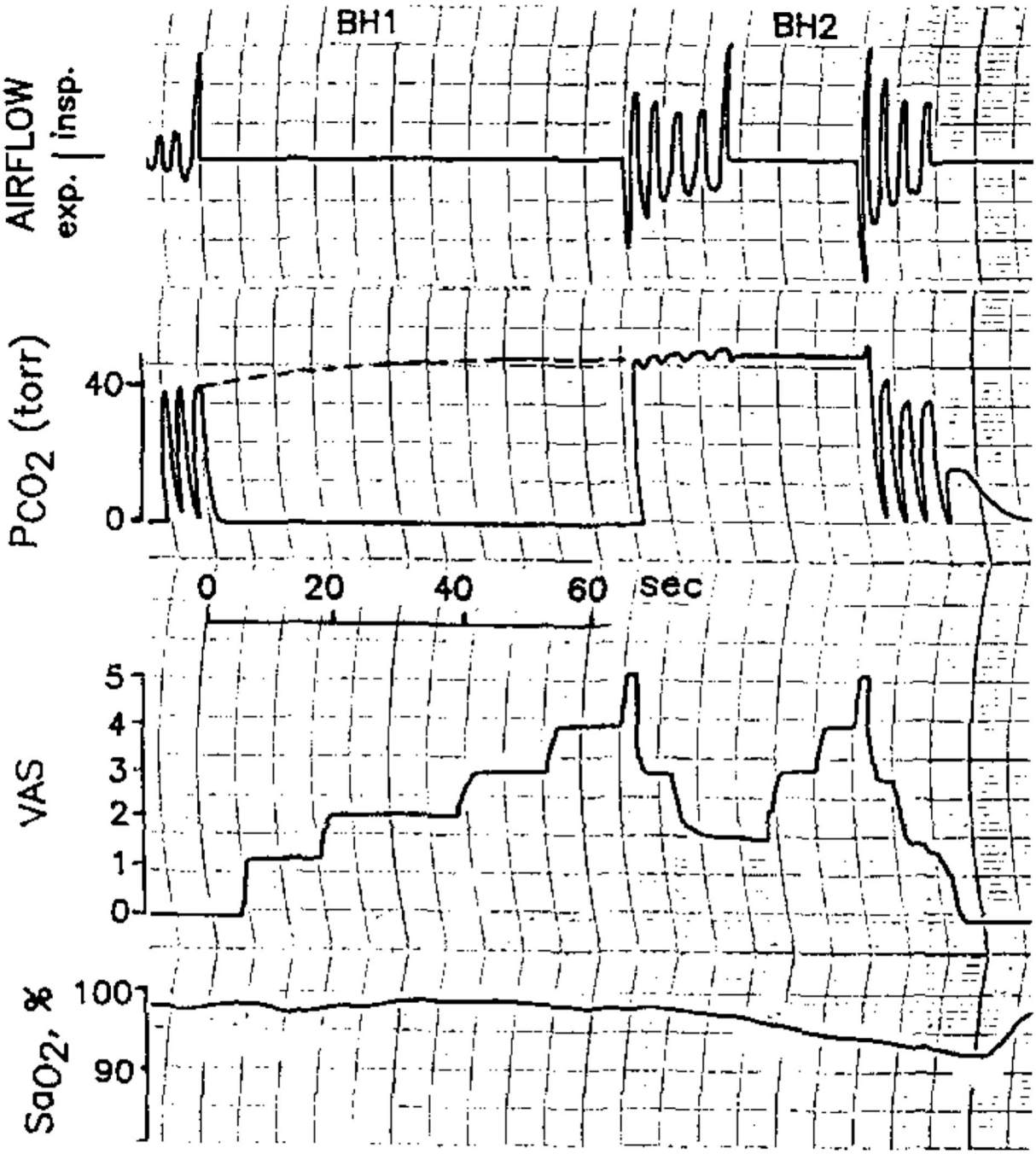

Figure 5.

Time course of air hunger during breath hold to break point, followed by rebreathing of alveolar gas, and second breath hold. This shows the relief of air hunger from mechanoreceptors sensitive to lung inflation is sufficient to permit a second breath hold with no improvement of blood gasses. Recordings in one subject of respiratory airflow, airway PCO_2, O_2 saturation (SaO_2), breathing 'discomfort' was reported using a visual analog scale (VAS) where the top of the scale was defined as the sensation at breakpoint of a maximal breath hold; subjects described this sensation in terms equivalent to air hunger (see text).

The subject performed a maximal duration breath hold at total lung capacity (BH 1), then rebreathed five breaths of 8.2% O2 and 7.5% CO_2, and then performed a second breath hold (BH2). There were progressive increases in air hunger during breath hold and a rapid, but not instantaneous relief when breathing resumed. Dashed lines represent the estimated rising $PaCO_2$ during breath hold. Note substantial relief of air hunger during rebreathing despite increased PCO_2 and decreased SaO_2. (with permission from reference 91); license #4823800766466.

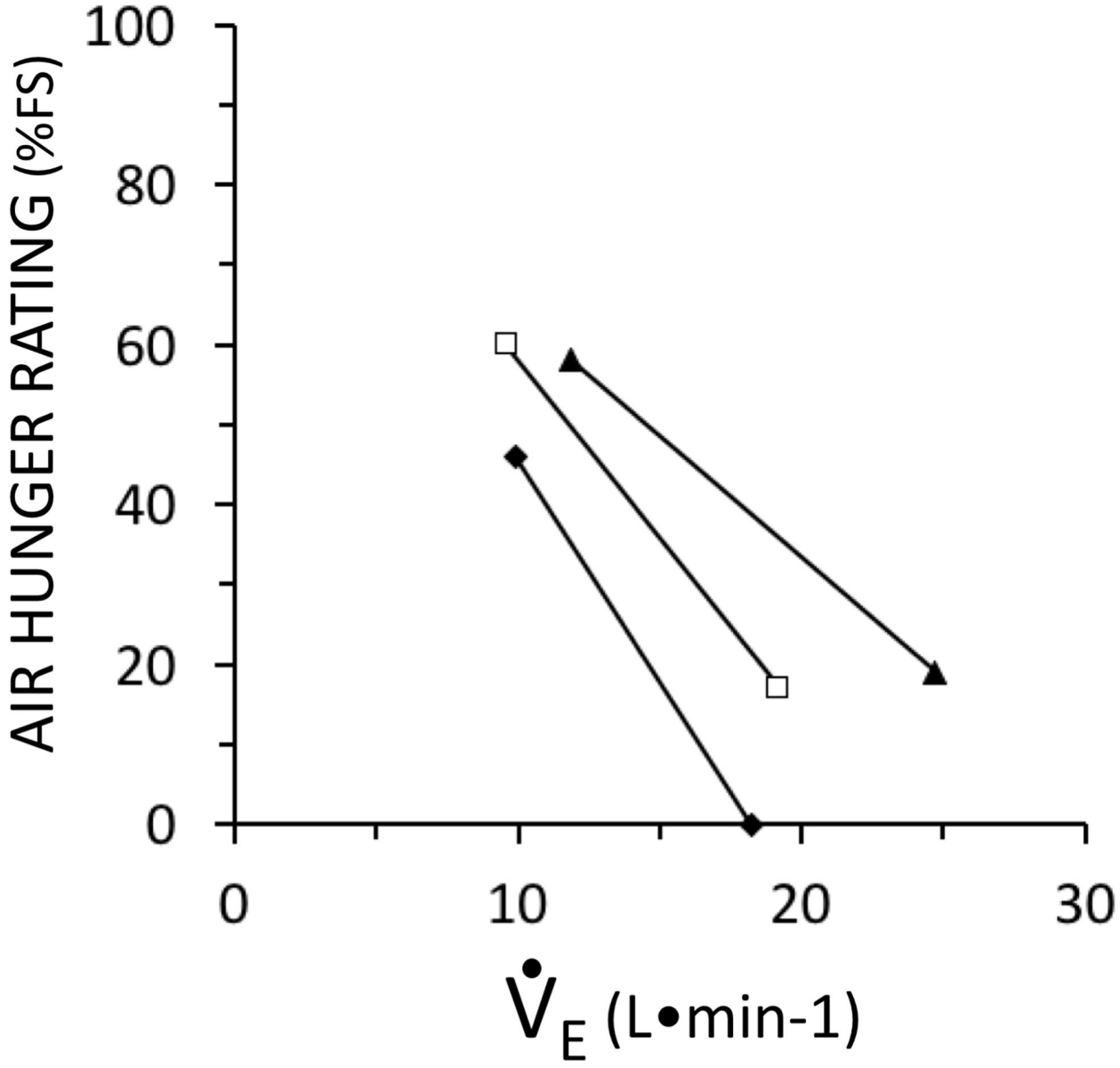

Figure 6.

Effect of increased ventilation on air hunger in healthy subjects, quantifying mechanoreceptor relief. In all cases $PETCO_2$ was kept the same in both ventilation conditions by raising inspired PCO_2 as ventilation was increased. Solid triangles show data from reference (105) Experiment 3 during mechanical ventilation; solid diamonds show data from reference (85) during mechanical ventilation; open squares show data from reference (162) during bag-limited ventilation. All studies were done under mild hyperoxia. Given the somewhat different methods, starting points, and individual subjects, the responses are quite similar, and show a profound inhibition (relief) of air hunger at the higher ventilation.

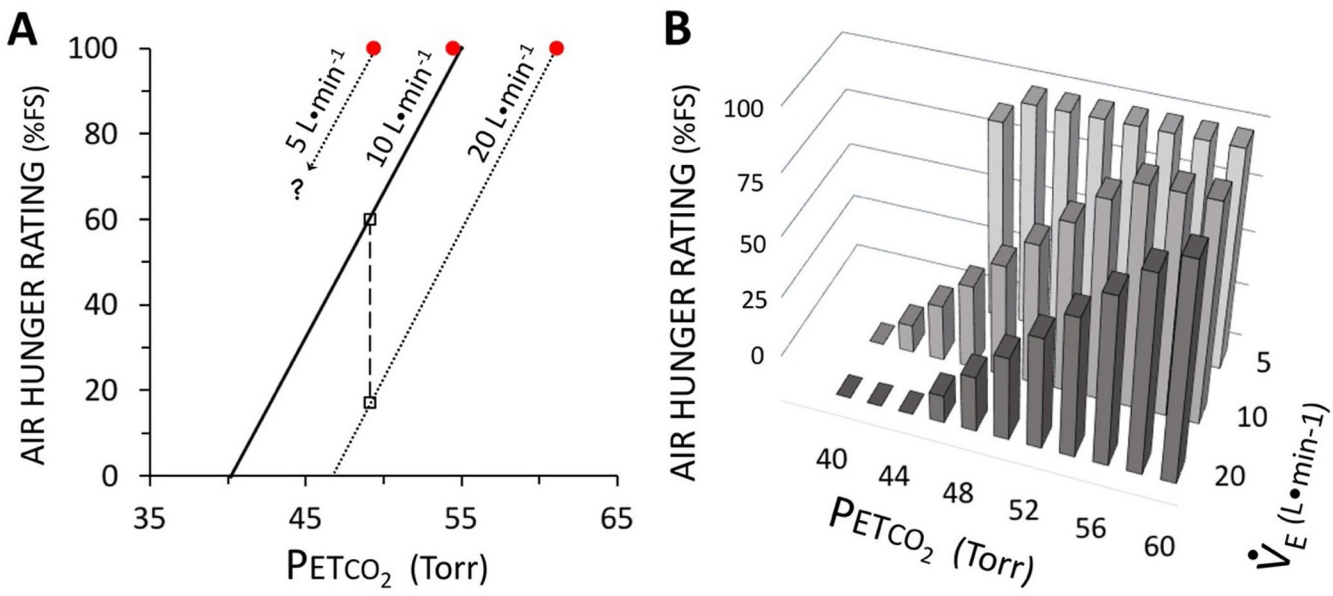

Figure 7.

Effect of minute ventilation on air hunger. Composite graph of two studies using widely different methodologies in which $PETCO_2$ and tidal volume were varied against a background of constant hyperoxia. Panel **A**: The solid line indicates the mean air hunger response of 12 subjects to alterations of $PETCO_2$ when ventilation was restricted to mean of 10 L•min^{-1} by a bag-limit device combined with a metronome set at 14 breaths•min^{-1}; the hollow square points connected by the dashed line are from the same subjects when the ventilation limit was increased from 10 to 20 L•min^{-1} by increasing flow to the bag (162). The filled red circles are from a different study in which 4 subjects breathed to targets of 5, 10, and 20 L•min^{-1} and a metronome set at 14 breaths•min^{-1} as $PETCO_2$ was slowly raised until the subject reported that the sensation was intolerable (203). Tolerance limit is assumed to be 100%FS air hunger. The dotted lines are hypothetical; the right dotted line is constructed from data points from the two studies, and the left dotted line is assumed to have the same slope extending from one data point, but the region below the question mark on the 5 L•min^{-1} line cannot be explored in steady state without extraordinary methods such as extracorporeal exchange to reduce $PETCO_2$ at low ventilation. Panel **B**: An approximate 3-D representation of the same data.

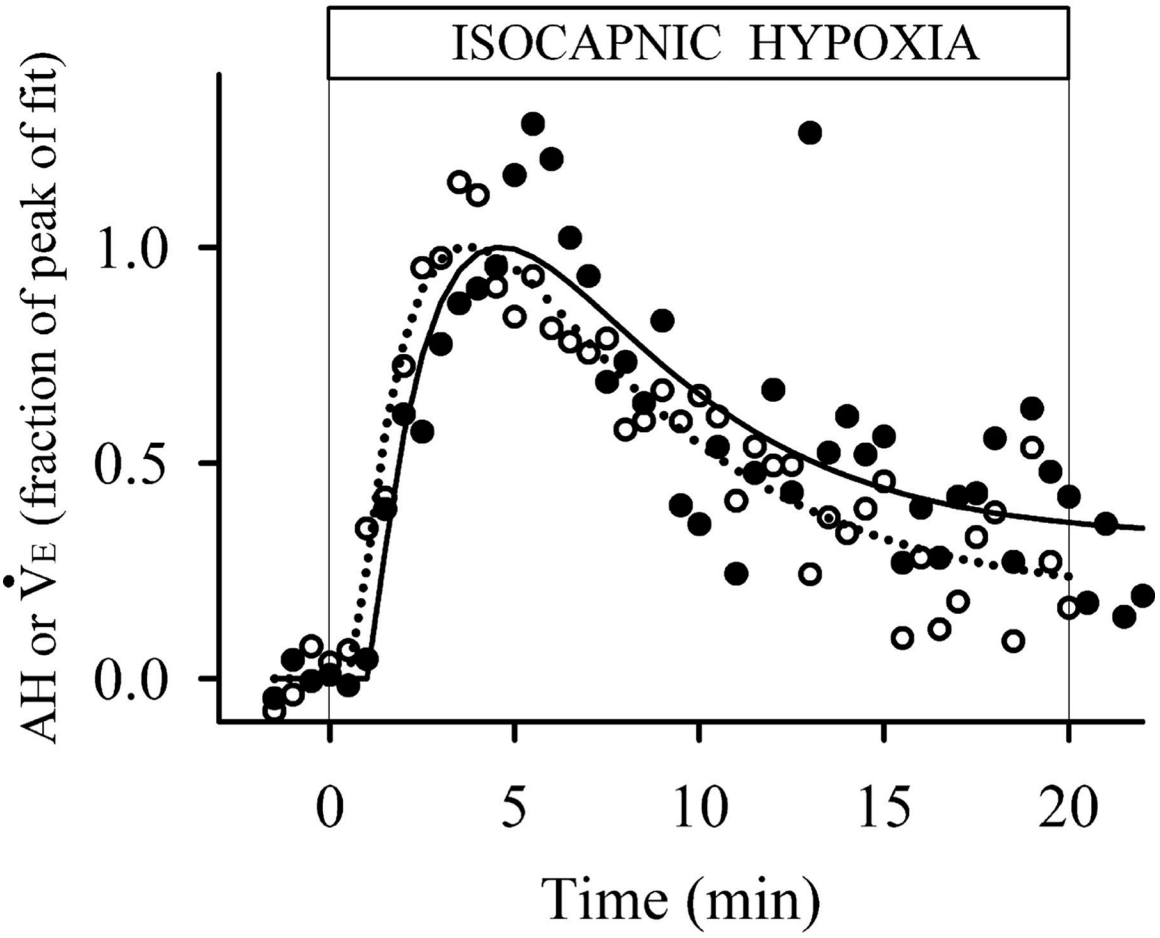

Figure 8.

Time course of air hunger response to onset of hypoxia shows the same biphasic response as the hypoxic ventilatory response. Solid circles represent the average air hunger response to a step reduction in $PETO_2$ during constant mechanical ventilation at eucapnia. For comparison, the open circles depict the average response of ventilation during free breathing to a step reduction in $PETO_2$ during constant $PETCO_2$ at eucapnia during a separate session in the same subjects. From reference (157), with permission RightsLink.

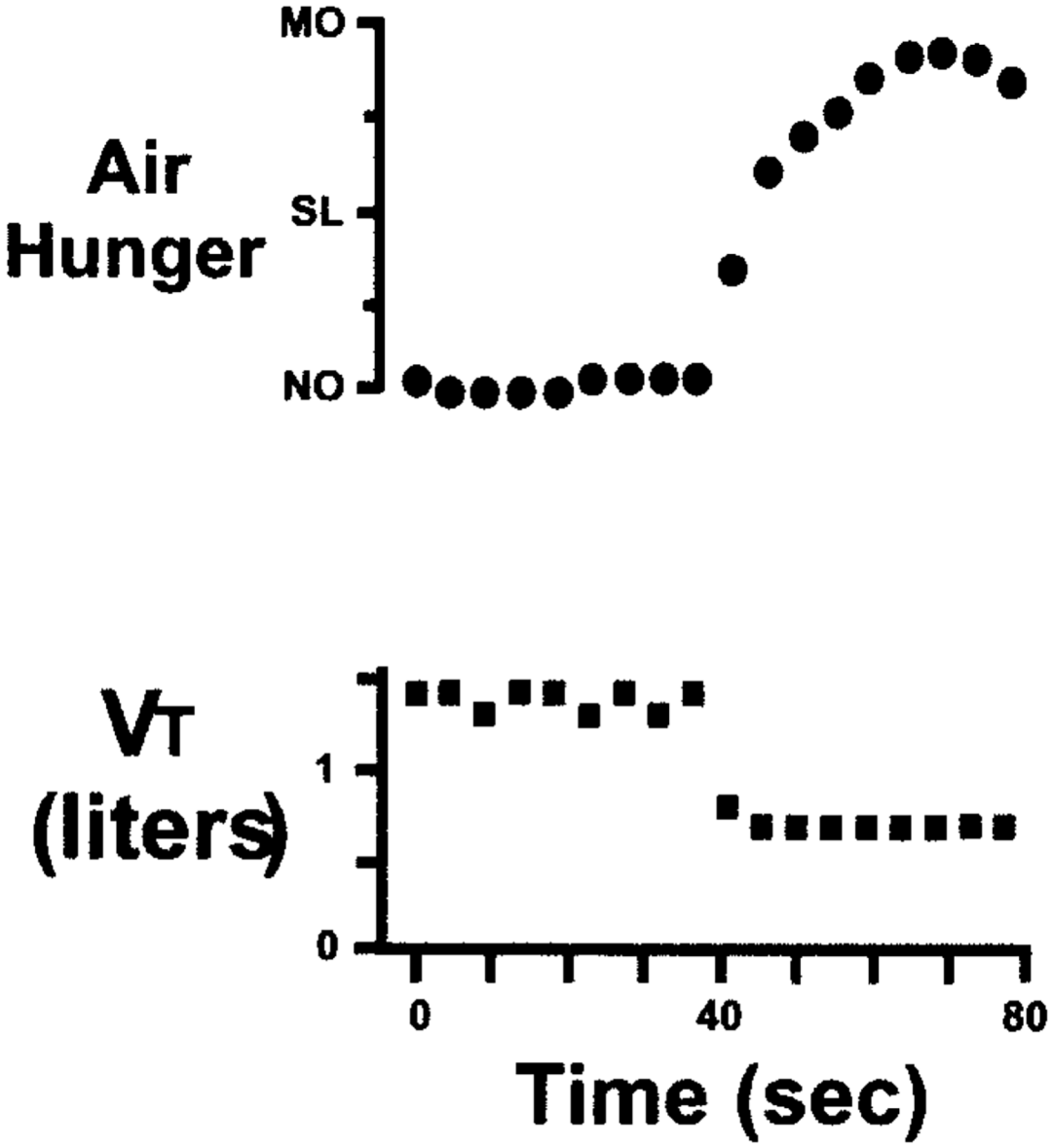

Figure 9.

Time course of air hunger response to a step change in tidal volume at constant $PETCO_2$ and $PETO_2$. Although mechanoreceptors respond fully on the first breath, central neural processes act as a low-pass filter, slowing the perceptual response. Step changes in tidal volume were effected during mechanical volume-control ventilation, while $PETCO_2$ and $PETO_2$ were held constant by altering inspired gasses. Breath by breath mean tidal volumes (VT) and air hunger ratings were averaged from 30 steps in 6 healthy subjects. Breaths were aligned with respect to the step change in tidal volume. This experiment was conducted under mild hyperoxia ($PETO_2$ approximately 160 Torr) (reprinted reference 85) with permission RightsLink.

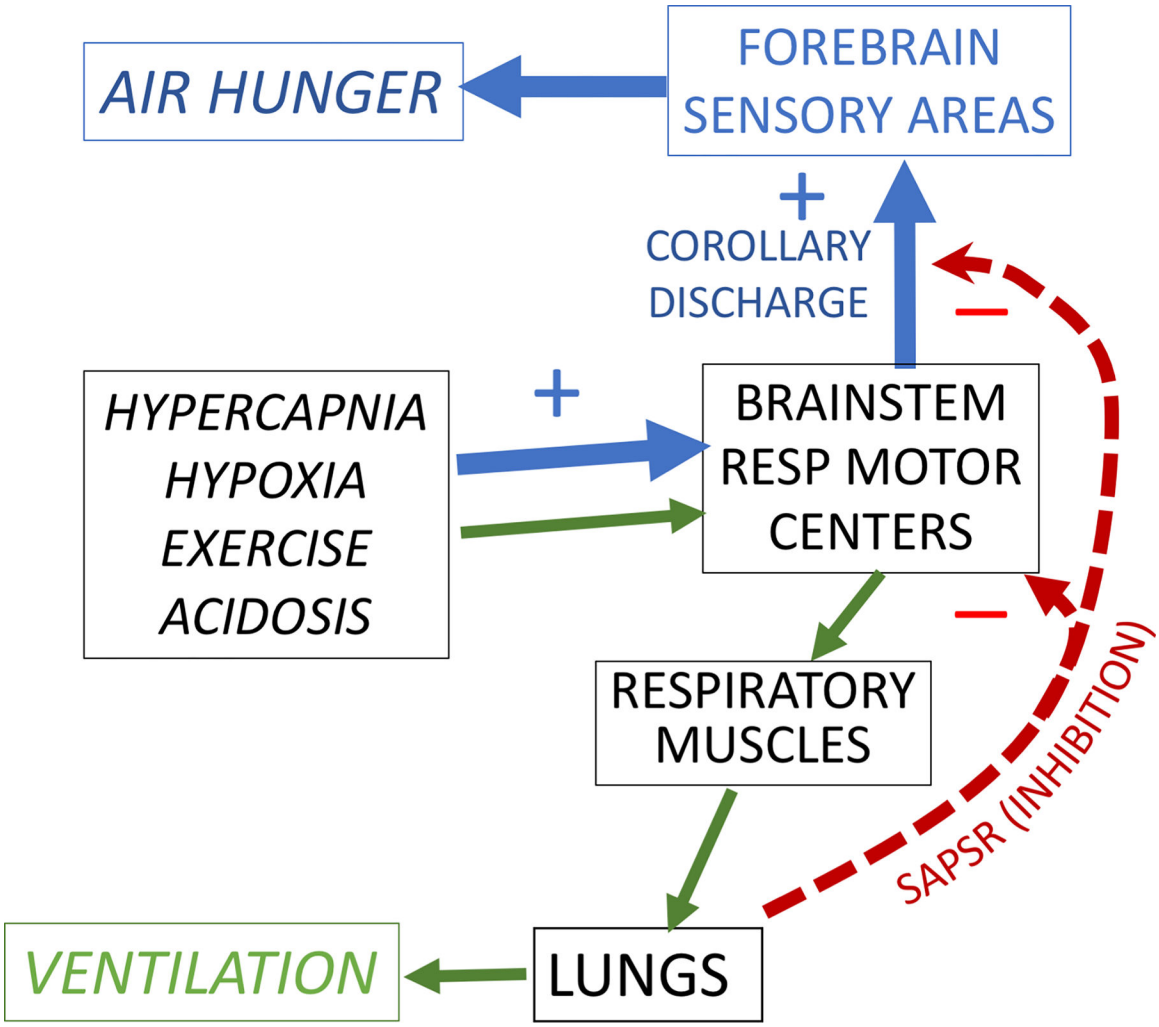

Figure 10.

Likely neural pathways for air hunger based on current information. Inputs and outputs are in italics, structures are normal font. The heavy blue arrows indicate the currently favored pathway for air hunger sensation; green arrows indicate the generally accepted pathway for reflex ventilatory response; black indicates structures and stimuli in common for air hunger and ventilatory responses; red dashed arrow indicates the pathway for relief (inhibition) of air hunger sensation by mechanoreceptor input coming from slowly adapting pulmonary stretch receptors (SAPSRs). SAPSR input projects both to brainstem neurons and to cortical neurons – the level at which air hunger relief is effected is currently unknown.

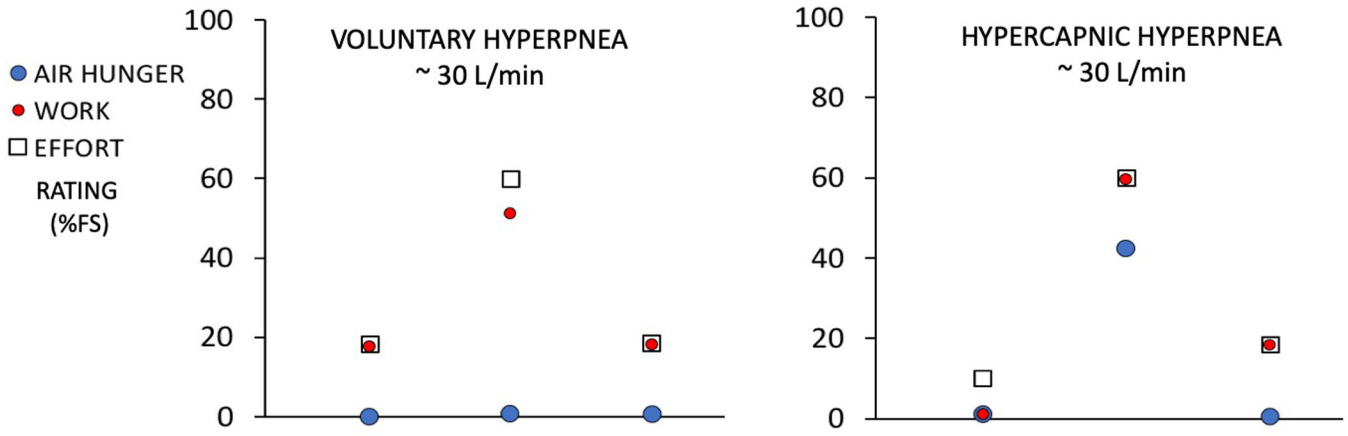

Figure 11.

Differential effect on respiratory sensations of partial neuromuscular block with short-acting agent (mivacurium). These data show that air hunger and work/effort sensations are distinct, driven by different neural mechanisms. Air hunger ratings = blue filled circles; work ratings = red filled circles; breathing effort ratings = open squares. **Upper panel**: Subjects breathed to a 30 liter•min^{-1} target while eucapnic $PETCO_2$ was maintained by altering inspired PCO_2. In the upper panel it can be seen that during volitional hyperpnea partial paralysis had a large effect on perceived work and effort of breathing, which increased as more voluntary (cortical) motor command was needed to maintain the ventilation target. In contrast air hunger remained at zero throughout because the prevailing level of reflex (medullary) drive was low throughout. **Lower panel**: Ventilation was stimulated by hypercapnia to achieve approximately 30 liter•min^{-1}. In the lower panel it can be seen that during CO_2-driven hyperpnea air hunger increased in concert with work and effort because medullary motor command was elevated (implying greater medullary corollary discharge). The degree of partial paralysis was sufficient to reduce vital capacity by 40% compared to control (and reduced handgrip strength by 60%); full vital capacity had returned at the time of recovery measurements. (Data re-plotted with permission from Figure 2 in Reference 160); license # 4826560010506.

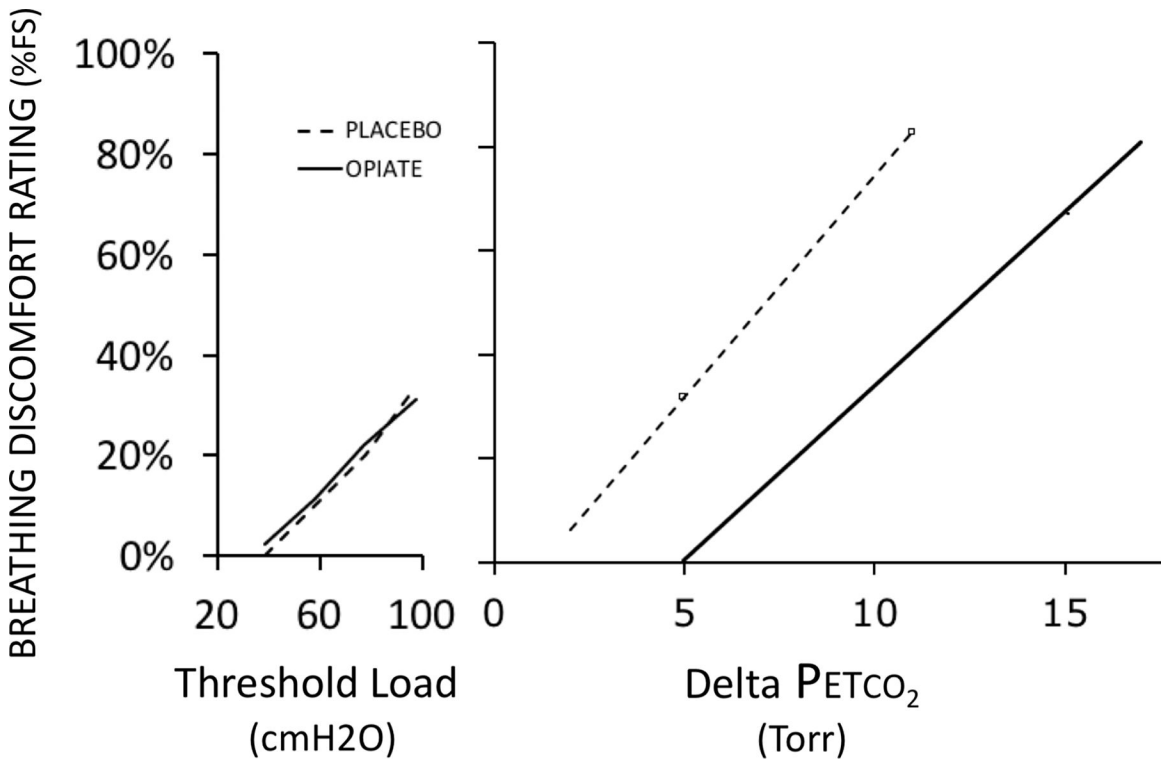

Figure 12.

Lack of effect of opiate on work/effort breathing discomfort (left panel) contrasts with pronounced effect of opiate on air hunger breathing discomfort (right panel). This is another demonstration that air hunger is distinct from work/effort sensations because they can be separately manipulated. The **left panel** shows data re-plotted from Figure 1 of Supinski et al (232). Subjects breathed against large inspiratory threshold loads, but respiratory rate and tidal volume were well maintained, from which we infer that blood gasses were not compromised (there were no measures of arterial or end-tidal gasses). Ratings of "discomfort" are expressed as percent of full scale (%FS). The minimum and maximum ends of the scale were not defined, but seven descriptors were placed along the scale. The maximum discomfort elicited by the largest threshold load (74% of maximum static inspiratory pressure) was equivalent to the verbal scale label "unpleasant"; the low ratings of discomfort in this experiment probably reflect the fact that respiratory work tasks are not very unpleasant in the absence of air hunger (20). Breathing discomfort following opiate was not different in this work/effort model. The **right panel** shows data replotted from reference (15). In this experiment subjects rated "breathing discomfort" on a visual analog scale, where the scale maximum was defined as "unbearable"; these ratings are expressed as %FS. Inspired PCO_2 was varied while ventilation was restricted to approximately 0.13 l•min^{-1} with a background of constant hyperoxia (FIO_2 = 30%). Ratings were obtained over a range of $PETCO_2$. Regression lines were obtained for each subject in each condition, then averaged to obtain the mean regressions shown here. The large decrease in breathing discomfort with opiate was statistically significant in this air hunger model. The drug, dosage, and route of administration differed between studies, but we assess them as roughly equivalent opiate doses. Supinski et al confirmed effective

analgesia following oral codeine using a cold pressor test. (Data replotted from references 15, 232). Adapted with permission of the American Thoracic Society (ATS). Copyright © 2020 ATS. All rights reserved. *Am Rev Respir Dis* 141: 1516–1521 and *Am J Respir Crit Care Med* 184: 920–927. The Am J Respir Crit Care Med and Am Rev Respir Dis are official journals of the ATS. Readers are encouraged to read the entire articles for the correct context at [https://doi.org/10.1164/ajrccm/141.6.1516%20 & https://doi.org/10.1164/rccm.201101-0005OC]. The authors, editors, and The ATS are not responsible for errors or omissions in adaptations.

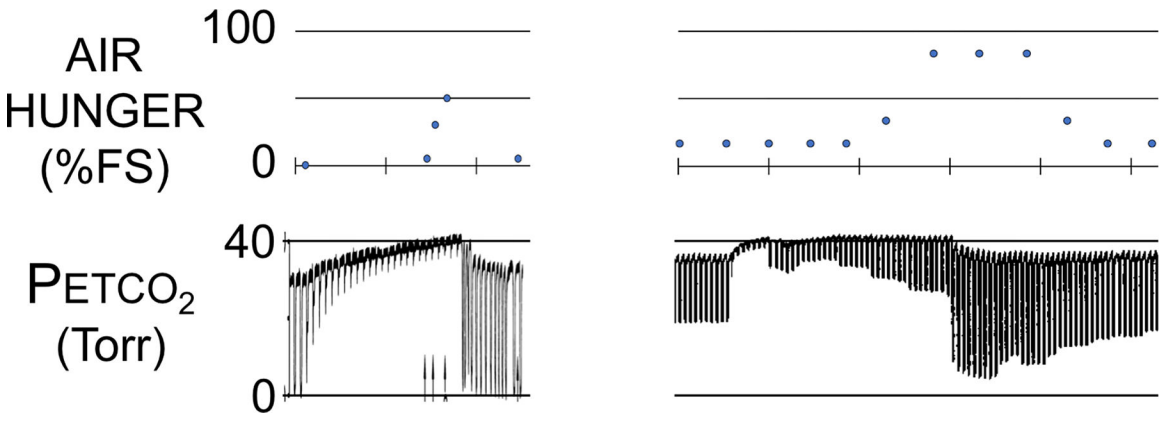

Figure 13.

Air hunger during complete paralysis, showing that respiratory muscle contraction is not necessary for air hunger. Because this experiment disproved a long-held tenet, it was repeated by a completely independent laboratory. Left panel shows data extracted from Figure 3 in reference (95); right panel shows data extracted from Figure 3 in reference (16). In both cases the subject (both authors of their respective studies) was totally paralyzed with curariform neuromuscular block and mechanically ventilated at constant tidal volume and frequency (Left VT = 1.0 L, f = 8.8, SpO_2 >98%; right VT = .92 L, f = 12.5, FIO_2 >90%). Time ticks in both panels are at 100 sec intervals. As explained more fully in the text, the air hunger response lags changes in end-tidal PCO_2 and changes in tidal volume (14, 85); therefore, air hunger measurements are offset in time to account for the slow air hunger dynamic response. Subjects were told to rate “respiratory discomfort” (left panel) or “air hunger” (right panel); both subjects chose the descriptor “urge to breathe” in debriefing. Rating scale on left was marked “severe” at 50% Full Scale and “maximal” at 100%FS; Rating scale on right was marked “slight plus” at 50% Full Scale and “extreme, intolerable” at 100%FS. From references (16) and (95) with permission; license #4823790296315 & #4826560802572.

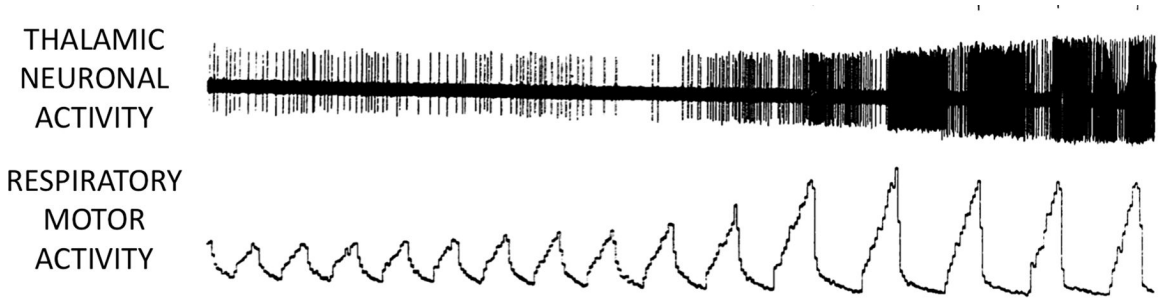

Figure 14.

Putative ‘respiratory corollary discharge’ recorded in the thalamus of a decorticate, paralyzed cat. This is one example of thalamic neurons that responded to increased respiratory motor activity. Just before the beginning of the record mechanical ventilation was paused. As PCO_2 rose during the ‘breath hold’, brainstem ventilatory motor output (reflected in phrenic nerve activity) increased. About midway through the record a threshold appears to be reached, and there was a profound progressive increase in thalamic activity. This mirrors the rise of air hunger sensation seen during a breath hold starting at low $PETCO_2$ in human subjects (91, 173). Similar responses have been observed in midbrain neurons (46). These observations suggest a neural substrate in accord with the theory that air hunger arises from corollary discharge carrying information about medullary motor activity to cortical sensory regions (Hypothesis 3). (adapted with permission from Fig 1 in reference 47) license #4826561235292.

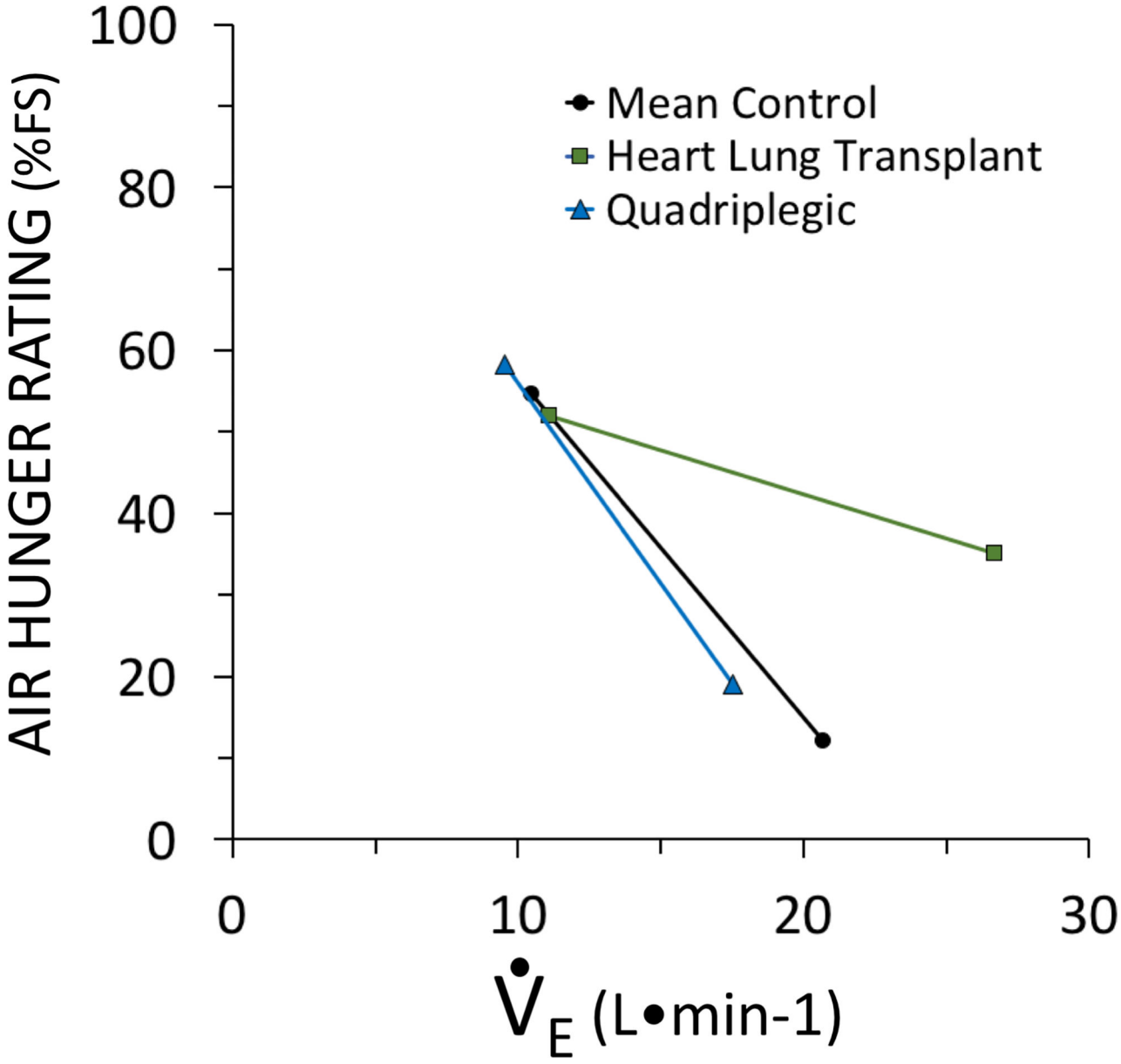

Figure 15.

Effect of neural lesions on mechanoreceptor relief of air hunger (effect of ventilation on air hunger). This graph demonstrates the predominant effect of pulmonary mechanoreceptors compared to rib cage and diaphragm mechanoreceptors. In all cases moderate air hunger was evoked by elevating $PETCO_2$ above resting level while holding ventilation constant at about 10 $L•min^{-1}$ with a background of mild hyperoxia (FIO_2 30–50%); this is the left-hand point on each line. Tidal volume was increased while $PETCO_2$ was held constant by elevating inspired PCO_2. The black line with filled circles shows the mean reduction of air hunger in healthy normal subjects (averaged from the 3 studies depicted in Figure 4) (85, 105, 162). The blue line with filled triangles shows the response of quadriplegics having complete spinal cord lesions at the cervical 1 to 2 level (29); Quadriplegic subjects are presumed to have no chest wall sensation, but pulmonary stretch receptor innervation via the vagus

nerve is presumed intact. The green line with filled squares shows the response of heart lung transplant patients is less than normals and quadriplegics, suggesting that chest-wall afferents provide less relief (Experiment 3, in reference 105); transplant patients have intact rib cage and diaphragm innervation but were presumed to have no pulmonary innervation (although later work showed that some pulmonary innervation returns in such patients (38)).

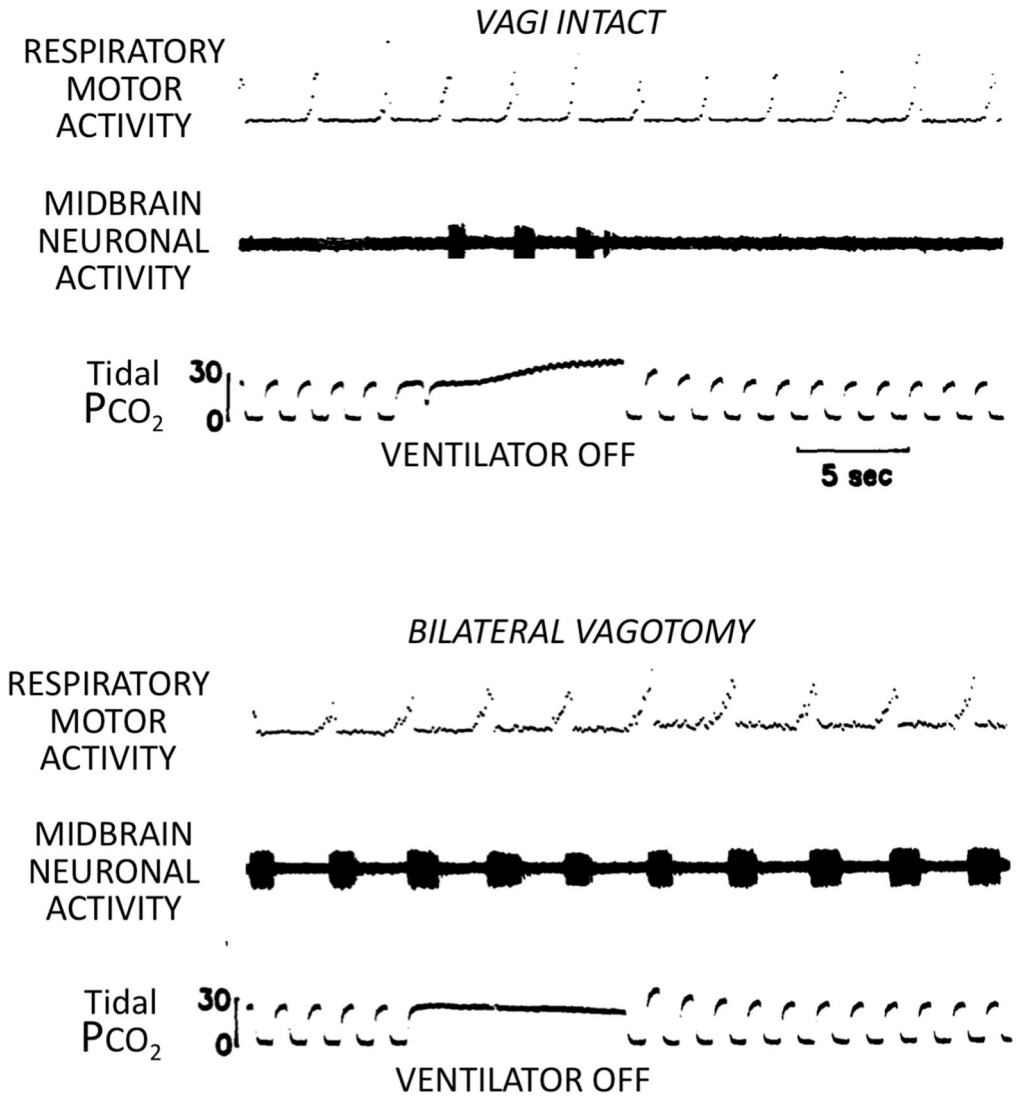

Figure 16.

Mechanoreceptor inhibition of putative respiratory corollary discharge by vagal pulmonary mechanoreceptor afferents in decerebrated paralyzed cats (78). In the upper panel the vagus nerves are intact, and the midbrain neuron is silent during mechanical ventilation; when the ventilator is paused (‘breath hold’) activity appears in the midbrain neuron. Midbrain activity is once again inhibited when ventilation is resumed. In the lower panel, following bilateral vagotomy, the midbrain neuron is active regardless of whether the mechanical ventilator is cycling. Vagal cooling data suggested the inhibition was mediated by slowly adapting pulmonary stretch receptors (SAPSRs). This is consistent with experiments in humans with neural lesions described in the text (92, 105, 145). Adapted with permission from reference (78) license #4826561496041.

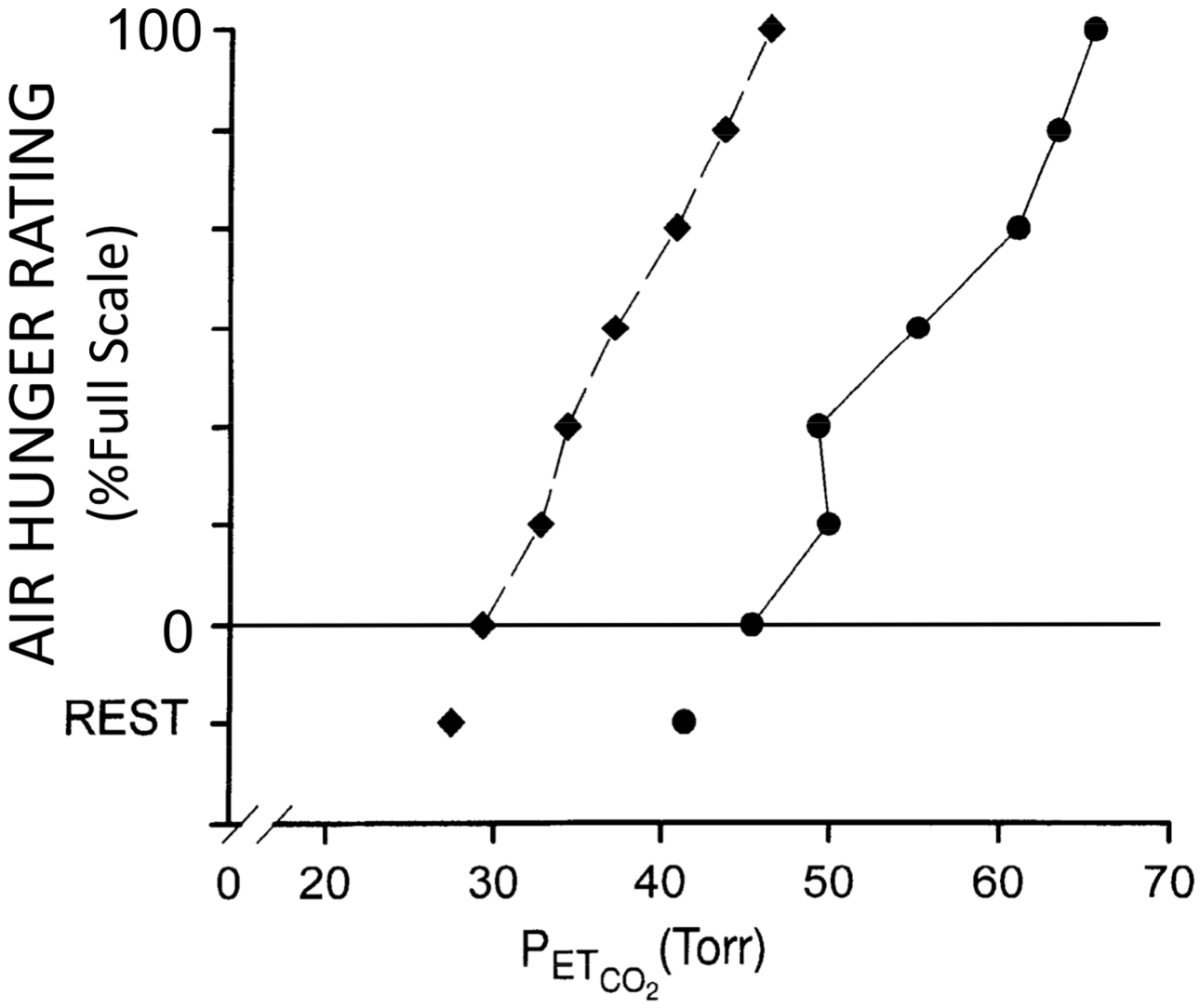

Figure 17.

Adaptation of air hunger response to prevailing level of $PETCO_2$ (from reference 28). Four ventilator dependent patients were adapted from a baseline "resting" 27 Torr $PETCO_2$ to 41 Torr $PETCO_2$ by slowly increasing inspired PCO_2 over the course of 1–3 days. Ventilator-delivered tidal volume and respiratory rate were held constant throughout. The acute air hunger response to a CO_2 stimulus was assessed before during and after adaptation. Filled diamonds with dashed line represent the average air hunger response to acutely elevated $PETCO_2$ before and after the adaptation period; solid circles with solid line represent the air hunger response to acutely elevated $PETCO_2$ during chronically elevated $PETCO_2$. Adaptation and acute testing were performed during normoxia (FIO_2 21%). Figure modified with permission from reference (28) with permission RightsLink.

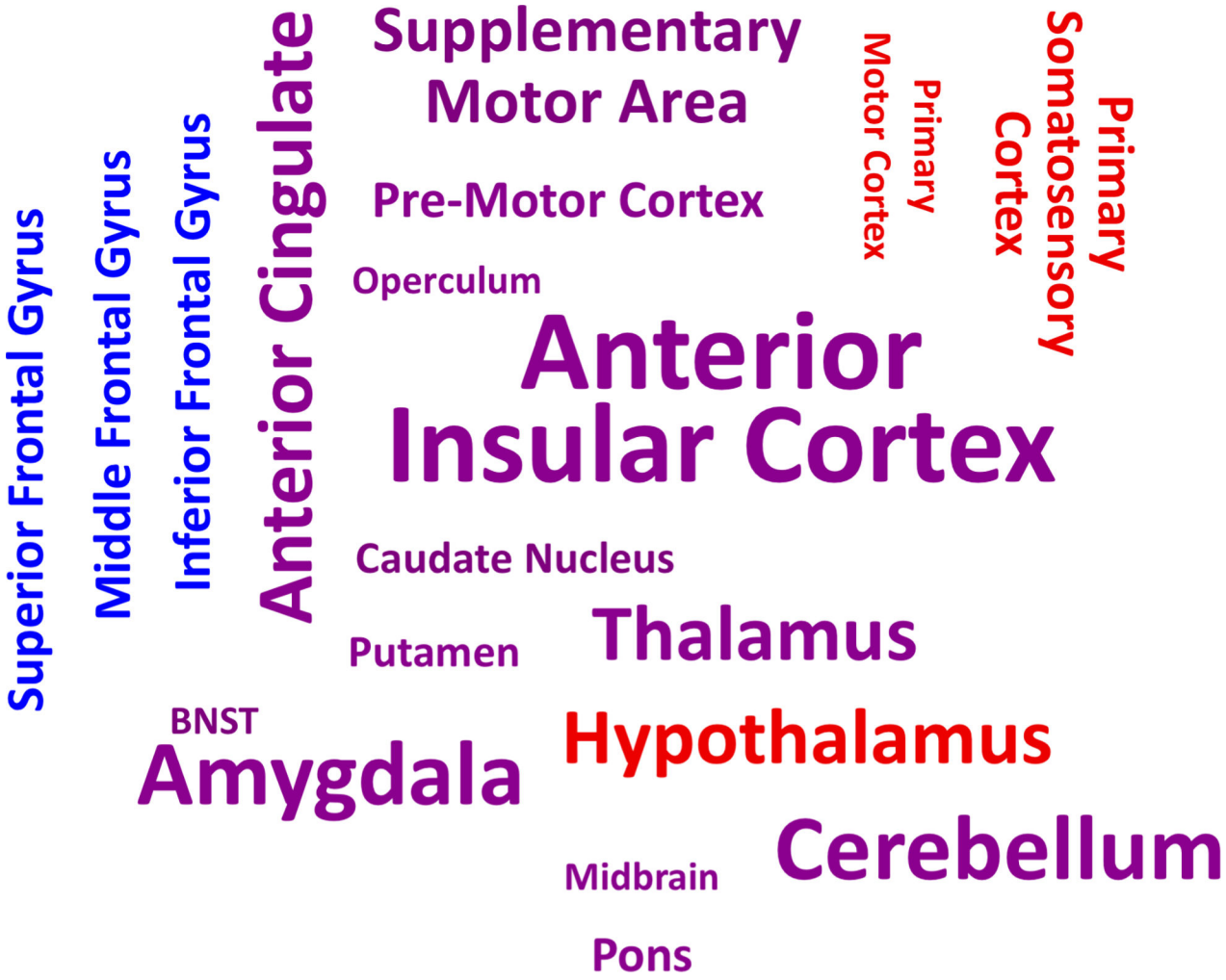

Figure 18.

Word Cloud summary of brain activations during respiratory discomfort. Numerous functional imaging studies have observed regional brain activations associated with dyspnea. These studies employed either a) mild to moderate resistive loads or b) mild hypercapnia combined with tidal volume restriction and so likely produced different qualitative forms dyspnea. The former stimulus evokes mainly work/effort sensation, while the latter evokes air hunger sensation. The composite results of 16 studies are represented with the regional activations associated with the distinct stimuli being differentiated by font color; activations exclusive to air hunger (3 studies) are shown in blue, those exclusive to work/effort (13 studies) are shown in red and activations common to both air hunger and work effort are shown in purple. The font size represents the number of studies in which each particular regional activation was observed. All studies observed activation of the insular cortex. BNST = Bed Nuclei of the Stria Terminalis.

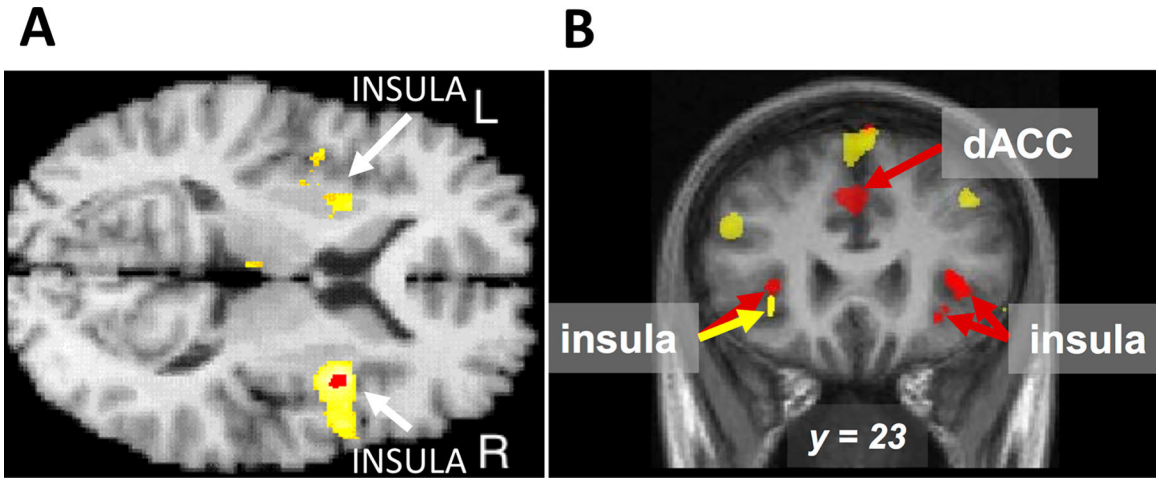

Figure 19.

Activation of the anterior insular cortex is observed in PET and fMRI studies that induce air hunger by tidal volume limitation. Panel A (adapted from reference (18)) shows a transverse PET image (8mm rostral to AC-PC baseline) from the first published brain imaging study of air hunger. Panel B (adapted from reference (26)) shows a coronal fMRI image of the same region (centered on the AC line) with red arrows indicating activations associated with the onset of air hunger and yellow arrows indicating areas associated with steady state air hunger. The insular cortex is involved in the perception of other homeostatic warning signals (e.g. pain, thirst, and food hunger) and is the most commonly observed regional activation in brain imaging studies of respiratory discomfort. The fMRI study (Panel B) also shows activation of the dorsal anterior cingulate cortex (dACC), an area involved with integration of emotional responses to adverse stimuli. From references (18) and (26) with permission; license #4825931387868 and #4830231140126

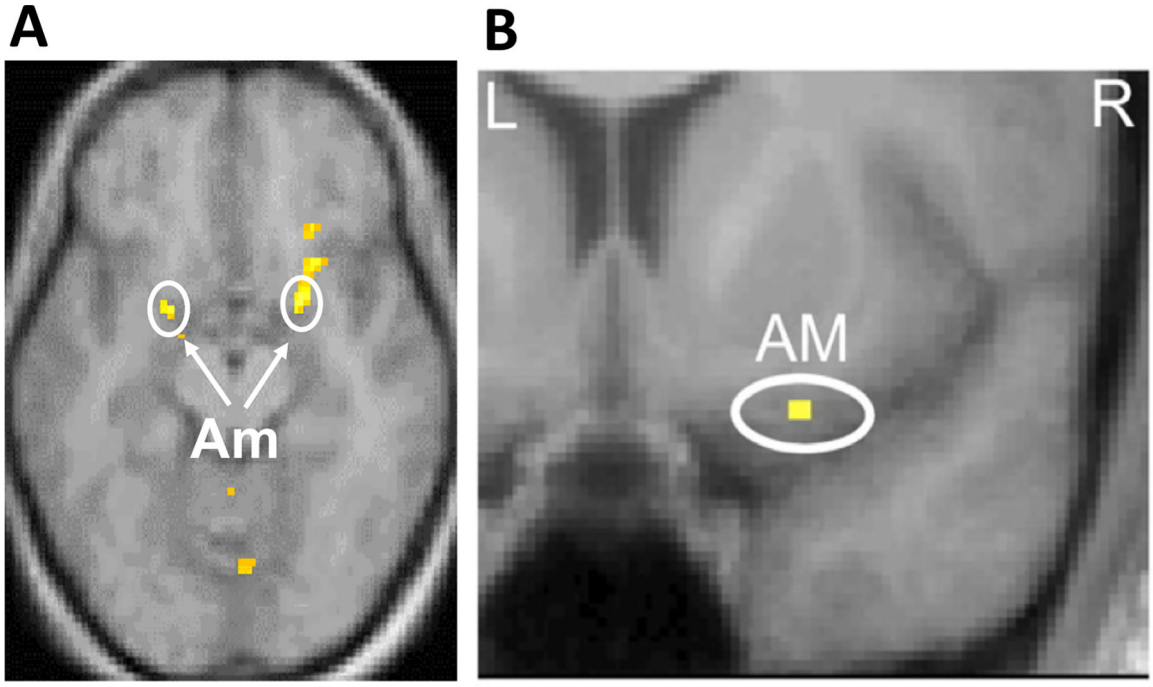

Figure 20.

Functional MRI images of activation in the amygdala during respiratory discomfort. The amygdala is a component of the limbic system associated with emotional responses, particularly fear. It is activated by air hunger induced by tidal volume limitation, as observed in the fMRI study by Evans et al (Panel A, Am, transverse view at z-plane =14, adapted from reference 85). Von Leupoldt et al also observed amygdala activation associated with the 'unpleasantness' of uncomfortable breathing induced by resistive respiratory loads (Panel B, AM, coronal view at y=9, adapted from reference 238). From reference (85) with permission (RightsLink) and reference (238) Adapted with permission of the American Thoracic Society (ATS). Copyright © 2020 ATS. All rights reserved. *Am J Respir Crit Care Med* 177: 1026–1032. The Am J Respir Crit Care Med is an official journal of the ATS. Readers are encouraged to read the entire article for the correct context at [https://doi.org/10.1164/rccm.200712-1821OC]. The authors, editors, and The ATS are not responsible for errors or omissions in adaptations.

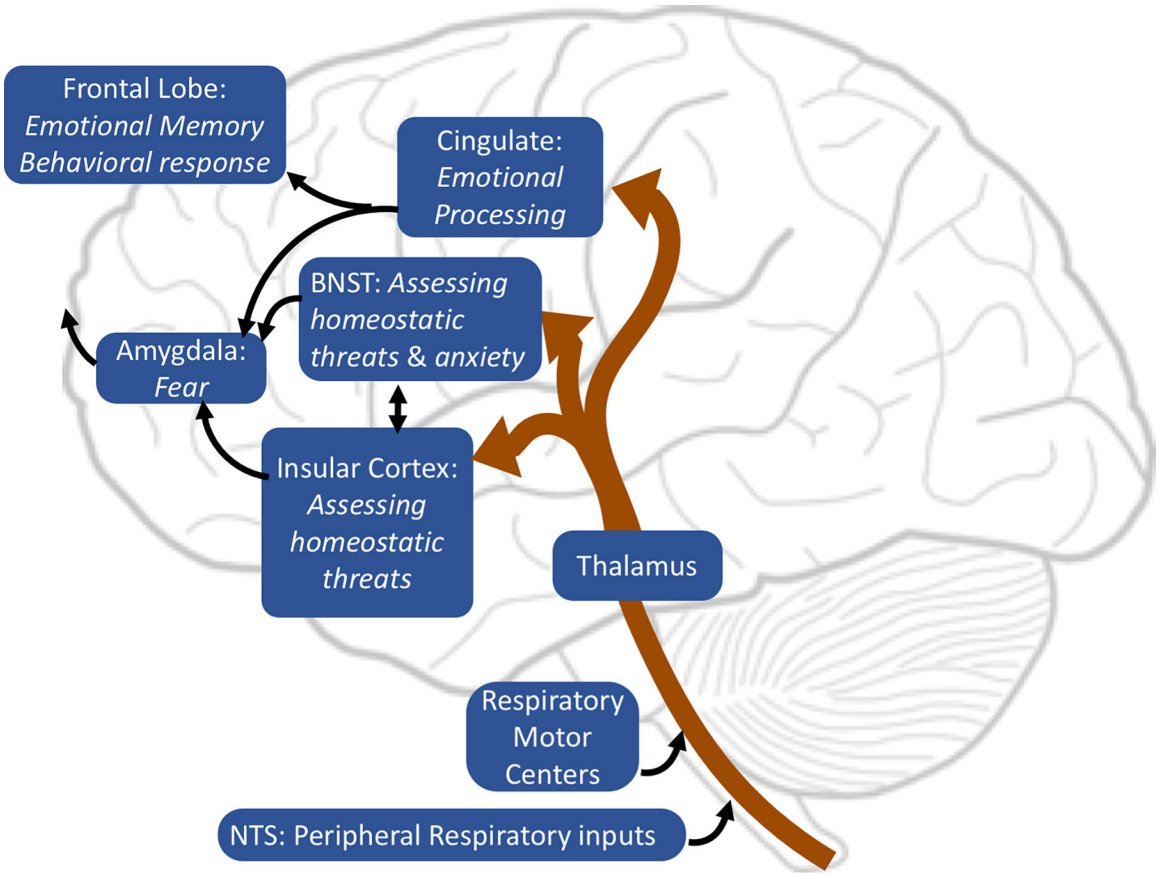

Figure 21.

Proposed central network for air hunger and the emotional and behavioral responses to it. The brown lines depict the interoceptive pathway and black arrows represent known connections. BNST = bed nuclei of the stria terminals. NTS = nucleus tractus solitarius.

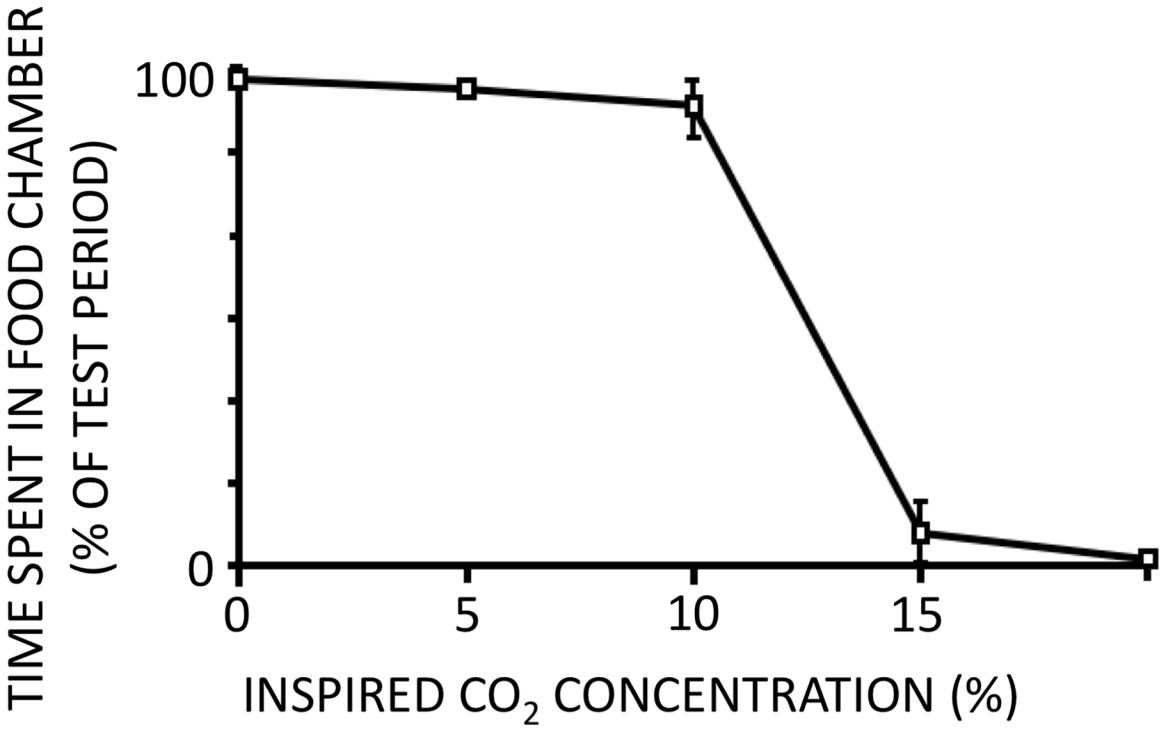

Figure 22.

Rats avoid CO_2 - induced discomfort rather than eat. The study by Neil and Weary shows that rats given 5 min of access to a chamber that contains a food reward, avoid that chamber when CO_2 in the chamber rises above 10% (171). The measurable change in behavior provides proof of concept that complex integrated processes can be included in an animal model of air hunger. Developing an animal model of air hunger presents novel issues. Because air hunger is an amalgam of integrated afferent inputs that lead to emotional and behavioral responses, a robust model cannot simply measure reflex responses, but should encompass higher cortical processes. Inspired CO_2 concentrations above 10% are rarely used in human studies, but the rats in this study were free breathing and afforded the mechanoreceptor relief that it brings (see Section on the quantitative relationship between stimulus and air hunger Part B – changing ventilation while holding ventilatory drive constant.). The rats were being encouraged to tolerate hypercapnia through the enticement of a food reward, whereas positive rewards have not been used in human studies of air hunger. There may also be important species differences in chemoreception, which is a fundamental physiological aspect that should be considered in animal model development. From reference (171) with permission. License #4825940537868.

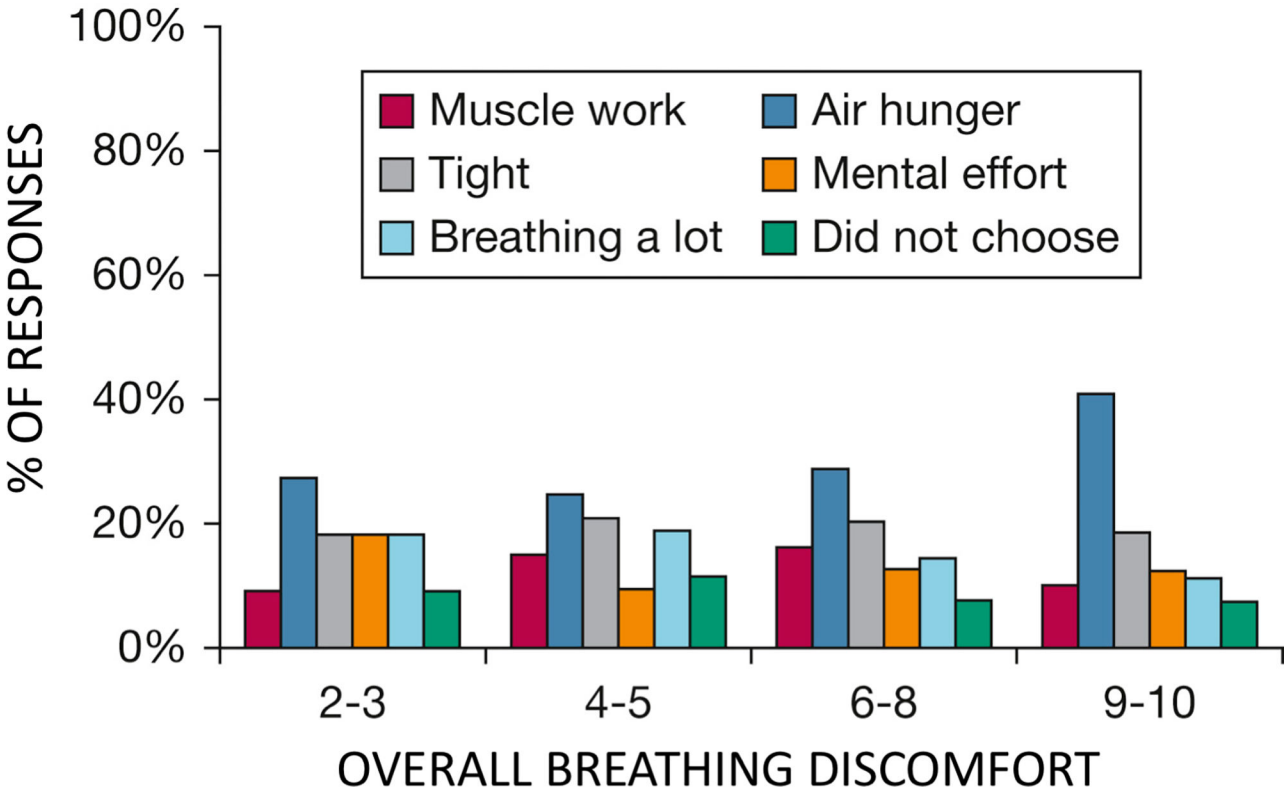

Figure 23.

Air hunger is the dominant sensory quality of breathing discomfort in hospitalized patients. Graph depicts the frequency with which sensory qualities are chosen by hospital inpatients as the most apt description of their dyspnea. The prominence of air hunger sensation increases as clinical dyspnea worsens. Responses are grouped by the overall level of breathing discomfort on a scale of 0 to 10 where 10 is ‘unbearable’. Graph summarizes 460 responses from 156 patients interviewed repeatedly during the hospital stay utilizing the Multidimensional Dyspnea Profile. Reprinted from reference (225) with permission. License #4830241184265.

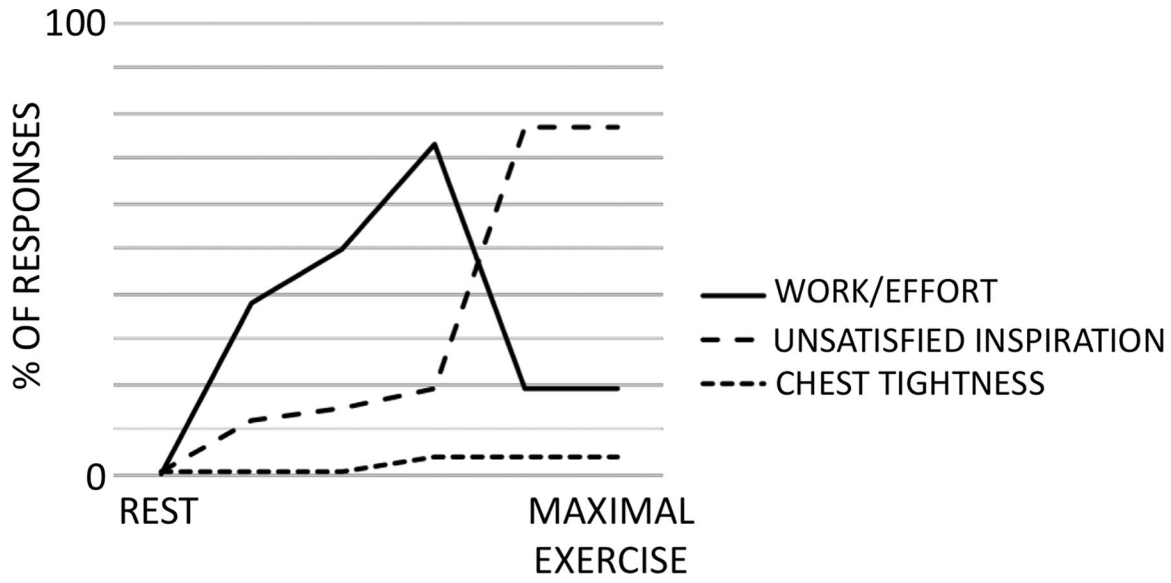

Figure 24.

Air hunger (also termed ‘unsatisfied inspiration’) becomes the dominant sensory quality of breathing discomfort in pulmonary patients undergoing progressive exercise. Graph depicts the frequency with which sensory qualities are chosen by patients with pulmonary hypertension (n=26) as the most apt description of their dyspnea during symptom-limited incremental cycle exercise. The sudden rise in selection of air hunger coincides with the point at which tidal volume becomes limited by declining inspiratory capacity. From reference (32); reproduced with permission of the © ERS 2020: European Respiratory Journal 55 (2) 1802108; DOI: 10.1183/13993003.02108-2018 Published 12 February 2020.

Table 1.

Summary of normative air hunger response to CO_2 stimulus.

'Mech vent' = mechanical ventilation at set tidal volume and frequency, Bag limit = set tidal volume and frequency using anesthesia bag and metronome. Ordinal = 7 point verbal scale upper anchor 'intolerable', VAS = 10cm visual analog scale upper anchor 'intolerable', AH= air hunger, BD= breathing discomfort (but where subjects rated BD, they identified air hunger as the quality of their discomfort). %FS= percent of full rating scale, BD0 = $PETCO_2$ at which the regression line intersects zero air hunger, BD60 = $PETCO_2$ at which subjects rating equals 60%FS, BD100= $PETCO_2$ at which the regression line predicts intolerable air hunger. *Italicized variables* have been calculated from information available in the publications cited. BD0 (the X intercept) is the $PETCO_2$ at which air hunger theoretically begins to be perceived; in reality, some finite level of perceived sensation must be reached before the subject will report air hunger – the 'decision criterion'.

	Reference (12)		**Reference (159)**		**Reference (15)**		**Reference (175)**		**Reference (162)**		**Mean value across studies**	**Mean SD across studies**
N	16		11		6		5		12			
Ventilation scheme	Mech Vent		Mech vent		Bag Limit		Bag Limit		Bag Limit			
Minute Ventilation $L \cdot min^{-1} \cdot kg^{-1}$	0.16		0.15		0.13		0.13		0.13			
Sensation Rating Scale	Ordinal AH		VAS AH		VAS AH		VAS BD		VAS BD			
	mean	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**		
R^2, subject rating vs PCO_2	0.88	±0.1	0.96	N/A	0.76	N/A	*0.79*	*±0.2*	N/A		0.87	±0.14
Slope (Rating %FS/$PETCO_2$ torr)	*9.9*	*±3.4*	7	±4	7.5	±2.1	*11.3*	*±3.0*	6.8	±2.3	8.5	±3.0
BD0 Absolute $PETCO_2$ (torr)	*40.0*	*±2.5*	38	±4	42.1	±4.4	*42.4*	*±3.6*	*40.2*	N/A	40.6	±3.5
BD60 Absolute $PETCO_2$ (torr)	*46.7*	*±3.8*	*46.5*	N/A	50.6	±5.8	*48.1*	*±2.9*	*49.1*	N/A	48.2	±4.2
BD100 Absolute $PETCO_2$ (torr)	*51.2*	*±5.1*	*51.9*	N/A	56.3	±7.0	*51.8*	*±2.7*	*55.0*	N/A	53.2	±4.9
BD0 $\Delta PETCO_2$ (torr)	*.9*	*±2.4*	N/A		0.7	±2.9	*0.8*	*±4.0*	−0.3	±5.8	0.5	±3.8
BD60 $\Delta PETCO_2$ (torr)	*7.6*	*±3.4*	N/A		9.2	±3.9	*6.4*	*±3.6*	8.6	N/A	8.0	±3.6
BD100 $\Delta PETCO_2$ (torr)	*12.1*	*±4.5*	N/A		*14.9*	*±5.0*	*10.2*	*±3.5*	*14.5*	N/A	12.9	±4.3

The upper and lower ends of the regressions are less certain because 1) data at $PETCO_2$ below perceptual threshold would skew the bottom of the line, schemes to avoid inclusion of these data are imperfect; 2) not much data is available at the top of the line because repeatedly causing intolerable discomfort reduces subject retention. Furthermore, regressions are by nature more certain in the center of the data – we thus often use the BD60 to assess changes in perception, for instance with treatment.

Resting $PETCO_2$ was determined without mouthpiece, but stimulus-response data were obtained with mouthpiece, which has been shown to increase drive to breathe.

Not all studies measured or reported all variables – mean values are calculated from available data without weighting for subject number. Data from reference (162) are averaged from pre-intervention data for both pre-furosemide and pre-saline conditions. Data from reference (175) were calculated from graphed data points for pre-intervention. Data from reference (15) are pre-intervention, Data from reference (159) are taken from Experiment 1. Data from reference (12) are calculated from values in Table 2 of that publication, assuming correspondence of ordinal and VAS scales as shown by Lansing et al (136). All studies shown were done under conditions of mild hyperoxia: reference (12) FIO_2=50%;reference (159) $PETO_2$=146 Torr; References (15, 162, 175) FIO_2=30%.

Table 2:
Behavioral responses of different species to hypercapnic atmospheres.

Aversion to hypoxia also varies across species. Hens avoid 7% O_2 (199), whereas mice have no apparent behavioral response to it (222). Rats avoid a feeding chamber when it contains less than 10% O_2 (171), but turkeys and pigs do not show signs of distress in an anoxic environment (198, 201). In general, hypoxia appears to be less aversive than hypercapnia and some species lose consciousness before signs of distress are apparent; pigs keep feeding on apples placed in an anoxic environment until losing consciousness, but abandon this prized food when it is placed in 30% CO_2 (197). This lack of aversion to hypoxia prior to unconsciousness is similar to that described in humans (see Section Hypoxia as a Stimulus for Air Hunger). Like hypercapnia, hypoxia has also has physiological effects beyond generating air hunger as cerebral hypoxemia may modify behavioral responses, so again caution must be exercised if hypoxia is implemented in an animal model.

Species	Reference	% CO_2 used	Response
Mink	(55)	>80%	Avoidance despite competing motivation to investigate a novel object.
Pigs	(200)	30% and 90%	Abandon food reward to escape 90% CO_2, but no aversion to 30% CO_2
Rats	(120, 171)	0–20%	Abandon food reward to escape 14–15% CO_2
Rats	(128)	1–5%	Avoidance of 3% CO_2
Rats	(235)	8–15%	Operant escape behavior at 8% CO_2
Rats	(244)	Gradual infusion of 100%	Abandon preferred (dark) chamber when CO_2 was added.
Hens	(199)	0–10%	Avoidance seen above 7.5% CO_2
Turkeys	(198)	72%	No aversion