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Special Report

Pathophysiologies of Dyspnea Explained: Why Might Opioids Relieve Dyspnea and Not Hasten Death?

James Hallenbeck, M.D.

Introduction

For many years palliative care clinicians have advocated for the use of opioids in the treatment of patients with dyspnea that is resistant to disease modification. And for at least as many years concern has been raised regarding possible respiratory suppression by opioids and the risk of hastening death. A number of studies have demonstrated evidence for significant improvement in dyspnea with opioid administration.[1–3] Studies suggest minimal clinical impact on respiration or associated blood gasses with proper use and no significant effects on life expectancy.[4–11] Although such studies are reassuring, an equally relevant question has often been neglected: If opioids are useful in the treatment of dyspnea, why do they work? What is the related physiology? This paper first reviews the pathophysiology of dyspnea and then discusses possible effects of opioids on this pathophysiology.

What Is Dyspnea?

The word "dyspnea" derives from Latin and Greek and refers broadly to abnormal breathing. It is curious that unlike words such as "pain" or "nausea" no one word in English captures the subjective experience of such difficulty. Rarely do patients present complaining of "dyspnea." Rather, patients have rather discrete sensations, such as air hunger, tiredness in breathing, awareness of the work of breathing, chest tightness, and feelings of suffocation, panic, or fatigue.[12] "Shortness of breath" is a term with some common usage, but this expression is of minimal help in identifying the more specific difficulties being experienced by the patient. These discrete sensations are correlated with pathophysiologies of specific disease processes.[13] Patients with bronchospasm, for example, will often complain about chest tightness, whereas patients with amyotrophic lateral sclerosis do not.[14,15] In assessing dyspnea it is important to get beyond general descriptors such as shortness of breath to more specific sensations.

The Physiologies of Dyspnea

The physiologies of dyspnea are multiple and complex. Our understanding of them lags behind our understanding of the physiologies of other common symptoms such as pain. Consideration of the role of dyspnea from an evolutionary perspective is a helpful way to organize and to understand these physiologies. The ability to breath effectively is critical to life; the inability to breath for even a few minutes is life-threatening. Thus, it makes sense that the physiologies of dyspnea are intricate and very sensitive to perceived threats to survival. The collective function of these physiologies is to ensure an adequate balance between supply and demand for gas exchange, to ensure an adequate response to variable respiratory demand, and to ensure the *sustainability* of respiratory function. The brain collects and analyzes information from a variety of sources to accomplish these goals. Current and projected needs for ventilation are assessed relative to perceived demand. Based on this, an "action plan" is developed and initiated. The adequacy of this action plan is rapidly assessed and reassessed in an iterative fashion and adjustments are made as necessary. Sustainability requires a careful adjustment of metabolic demand and responsive respiratory effort. Whereas respiratory effort should be robust enough to meet demand, it is also critical to guard against excessive respiratory fatigue, which can be life-threatening in and of itself.

The Role of Blood Gasses in Dyspnea

Blood gasses (oxygen [O_2], carbon dioxide [CO_2], and pH) are of great value in monitoring the severity of illness and responses to therapy, but many clinicians overestimate their value as markers of dyspnea. Whereas increased CO_2 production, lower pH, and to a lesser degree hypoxemia stimulate ventilation,[13] gross changes in CO_2 levels and associated falls in pH would be extremely late markers of an imbalance between metabolic demand and the ability to ventilate adequately, as such changes would usually be pre-terminal events prior to artificial ventilation and thus of minimal importance in promoting survival. More sensitive means of anticipating threats to ventilation would seem to be necessary if an organism was to have a reasonable chance of a successful response to a threat.

High CO_2 levels and other markers of increased metabolism, such as lower pH and higher body temperature, are indeed stimuli for increased ventilatory effort.[13,16–18] However, as long as a higher ventilatory rate is able to meet demand without undue tiring or other complication, dyspnea is not necessarily experienced. An excellent example of this is

School of Medicine, Department of Medicine, Division of General Medical Disciplines, Stanford University, Stanford, California.
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tachypnea of pregnancy.[19–21] Respiration may increase significantly and yet be out of consciousness for the woman. Dyspnea is not usually experienced. Dyspnea arises when there is either some perceived imbalance between the ability to ventilate adequately for a given demand or when there is a perception that the balance between demand and the respiratory response is unsustainable.

The relationship among oxygen, oxygen levels, and dyspnea is more complex.[5,22] Aerobic metabolism produces CO_2 and consumes oxygen. With diminished oxygenation anaerobic metabolism produces lactic acid, which stimulates ventilation by lowering blood pH, independent of CO_2. Rest hypoxia with otherwise adequate ventilation tends not to trigger dyspnea to the degree exertional hypoxia does. This makes some sense in that oxygen levels are minimally improved by increased respiratory efforts. From an evolutionary perspective (prior to medical disease modification or oxygen therapy) the major variable that may be adjusted when hypoxia is present is metabolic demand and thus dyspnea with exertion serves as a warning to decrease activity to the extent possible. A superb model for this can be found in high-altitude climbers, who may experience minimal dyspnea at rest, despite significant hypoxia, and yet who experience significant dyspnea with even minimal exertion. Clinically, exertional hypoxemia (and associated dyspnea) has generally been found to be more responsive to oxygen therapy than rest hypoxemia.[23]

Studies of oxygen therapy highlight the complexity of the relationship between oxygen and dyspnea. Oxygen also functions as a bronchodilator, thereby aiding ventilation.[24] Increased air/gas flow across the nasal mucosa may also reduce the sensation of dyspnea. That this effect is more a result of stimulation of receptors in the nasal mucosa than an effect of oxygen per se is suggested by a study by Liss and Grant, in which patients were randomized to receive oxygen or air via nasal prongs.[25] Dyspnea was equally relieved by both therapies, but was increased when the nasal mucosa was anesthetized.

Perceived Threats to Survival—An Integrated Response

If gross blood gas abnormalities reflect very late stages in the pathophysiology of dyspnea, what triggers dyspnea at earlier stages? Two major categories of threats to breathing and survival can be recognized: threats to the *ability* to ventilate and threats to a *sustainable balance* between supply and demand for gas exchange. Certainly, smaller changes in CO_2 levels, O_2, and pH provide important feedback to the respiratory centers regarding metabolic demand and ventilatory response. Beyond this, various peripheral receptors in the respiratory tree, nasal mucosa, skin, and musculature monitor the adequacy of air flow into and out of the lungs.[26] Skin and nasal receptors are sensitive to both air flow and temperature stimulation.[25,27–29] Lung and chest wall receptors measure stretch and movement.[30–32] Perception of robust and unimpeded airflow provides negative feedback to central nervous system (CNS) receptors. *Absence* or diminution of such signals provides a rapidly appreciated, potent stimulus to dyspnea. Threats to the sustainability of gas exchange, as described further below, are assessed by a complex array of sensors measuring ventilatory demand, adequacy of response, and projected response to this demand.

The Role of Other CNS Functions in Dyspnea

As a biologic function breathing is very unusual in that it is both "automatic," functioning out of consciousness, and yet subject to a degree of override and control by higher cortical processes. The ability to hold one's breath has obvious survival advantages. For better and for worse, there is an unusual level of integration between higher cortical, limbic (emotional), and more primitive medullary centers of the brain as relate to ventilation and dyspnea. These linkages are complex and appear to be bidirectional. Humans can consciously modulate breathing. Conversely, alterations in our breathing can affect our thoughts and feelings. A vigorous bout of exercise may be positively framed and interpreted as being pleasurable and good, despite resulting in a physiologic fatigue state that is remarkably similar to that found in certain diseases. However, relatively mild biologic stimuli of dyspnea may be cognitively and emotionally interpreted as serious threats to health and life, thereby giving rise to anxiety or frank panic and creating a positive feedback loop, which in turn may intensify ventilatory effort and associated dyspnea. Indeed, cognitive and affective framing of experience may give rise to dyspnea in the absence of any other physiologic stimuli. The hyperventilation and panic of a panic attack are not experienced as separate events.[33] They are one experience and build upon each other in a positive feedback loop. Thus, in addressing the suffering associated with dyspnea, we must consider the fact that the mind is not only an agent *through* which suffering is experienced or perceived, but it also is an active participant *in* the physiology of dyspnea. Therein lie clues both to conditions that give rise to associated suffering and potential means to alleviate such suffering.

Work-of-Breathing Dyspnea

When an organism perceives an imbalance between the current or a future ability to meet ventilatory demand, but where airflow into and out of the lungs is still occurring, "work-of-breathing" dyspnea develops. Various stimuli give rise to a perceived need for increased ventilation. Increased metabolic activity, production of CO_2, a lowered pH, increased body temperature, perhaps anxiety or panic, and increased sympathetic tone, among other things, signal the respiratory center to increase respiration. The aggregate intensity of such stimuli creates a signal to increase ventilation, much like stepping on a car's accelerator pedal, when going up a hill. The brain then monitors the body's response to this signal, much as the motorist evaluates the car's response by watching the speedometer and the engine's heat gauge, when stepping on the gas. It is theorized that a copy or "snapshot" of this motor stimulus and its intensity is sent to the sensory cortex. With this there is an awareness of an effort to increase respiration, a process called "corollary discharge," much as one is aware when the gas pedal is "floored."[13] If the signals coming back from the body suggest an adequate and sustainable response to this increased motor signal (increased ventilation to the desired degree), then dyspnea is minimal or not present. In healthy people the ability to control or titrate exercise to a sustainable level may be a major factor in mitigating dyspnea and avoiding suffering. A healthy runner can become short of breath while jogging, but not suffer because of a positive cognitive framing of the experience and an understanding that he or she can stop at any time—ventilation is

projected to be sustainable. However, when the expected "snapshot" of the body's projected response is compared with the *actual* response and found to be less than expected, then a "gap" is noted, referred to formally as "*efferent* (motor signal)-*reafferent* (return, afferent signal regarding ventilatory response) *dissociation.*"[34] This difference between drive and response is also sometimes called *neuromechanical dissociation.* Again, by metaphor, this is rather like when an underpowered car going up a hill fails to accelerate when the driver steps on the gas. When the expected response is compared with actual response, distress usually ensues. Studies in normal individuals designed to create such dissonance have supported this hypothesis.[35] Reafferent signals reflecting the adequacy of a response to increased ventilatory drive include resultant changes in chemical parameters, such as CO_2 levels and pH, as well as signals from mechanoreceptors and chemoreceptors. Both positive and negative feedback is provided. Negative feedback, inhibiting a dyspneic response from the respiratory tree and musculature, may signal adequacy of air flow. Positive feedback, for example via stretch receptors in the lungs, may warn of air trapping. Positive signals from tiring muscles may herald impending fatigue.The primary purpose of work-of-breathing dyspnea is to signal the body to *decrease* its metabolic activity, if at all possible. Whereas the signal to slow down can and should be overridden on rare occasions, as when running away from a tiger, clearly, the easiest way to resolve most such dyspneic crises in everyday life is to reduce the demand giving rise to a need for greater ventilatory effort.

Suffocation Dyspnea

From an evolutionary perspective the only thing worse than an imbalance in metabolic demand and respiratory response is not being able to breathe at all. Suffocation dyspnea results when a lack of airflow for whatever reason is perceived. Suffocation dyspnea can manifest in a pure form with sudden airway obstruction. Like work-of-breathing dyspnea, efferent-reafferent dissociation results from the gap between ventilatory drive and action. Suffocation in its pure form differs from work-of-breathing dyspnea in that fatigue is not a problem. The sensation of suffocation is associated with panic, which makes sense given the immediate life-threatening nature of true suffocation. The standard bodily response to suffocation dyspnea is the exact *opposite* of that seen in work-of-breathing dyspnea. Panic instills a last ditch, all-out effort to reestablish ventilation. This effort obviously *increases* metabolic demand, but given that true suffocation is immediately life-threatening, this is an acceptable trade-off.

In many cases of illness, however, a sharp distinction between work-of-breathing and suffocation dyspnea is artificial, as both processes are involved. For example, bronchoconstriction involves both obstructive processes, a form of incomplete suffocation, and ineffective, effort-intensive ventilation that gives rise to respiratory fatigue. Patients with amyotrophic lateral sclerosis, in contrast, typically have no respiratory obstruction, but they can experience severe muscular fatigue, decreased airflow, and a sense of suffocation due to decreased ventilation.

The initial trigger to suffocation dyspnea appears to be decreased perception of airflow and respiratory muscle movement. Decreased stimulation of related peripheral receptors results in decreased negative feedback to the brain. These signals are interpreted as inadequate ventilation. Where obstruction is involved, either of large or small airways, stretch and muscle receptors may signal pressure gradients, which are also interpreted as obstruction to flow. Interpretation of the situation as being life-threatening via higher cortical (cognitive) and limbic (emotional) processes, will contribute to a panic response and sense of dyspnea.

Blood gasses have little if any role in initiating pure suffocation dyspnea, as evidenced by a simple experiment. If a person holds his or her breath and then attends to when a perception first arises as a need to breathe, this impulse will be noticed in a matter of seconds—roughly when the natural ventilatory cycle is interrupted—well before any measureable change in blood gasses occurs. If the breath continues to be held, the desire to breathe rapidly builds. As long as breath-holding is voluntary, panic does not result. However, it is not hard to imagine how quickly air hunger and panic would grow if such a lack of airflow was involuntary, as in choking or in drowning. Changes in blood gasses would undoubtedly contribute to air hunger and dyspnea in such a circumstance, but only in the relatively late phase of this experience.

When a mix of work-of-breathing and suffocation dyspnea is present, the body is presented with a dilemma, as signals are present both to *increase* activity (via anxiety or panic) and *decrease* activity (via perception of work-of-breathing fatigue). Guided by higher cortical processes individuals may be able to strike a balance of sorts between these contradictory stimuli. Medications, such as opioids, may also be of assistance.

Opioids

Finally, we return to the question posed in the beginning. If opioids are helpful in treating dyspnea, *why* are they helpful? A number of studies have found that whatever the mechanism of action, with reasonable and proper use the mechanism does not appear to be as a result of a gross decreased ventilatory rate, overall ventilation, or sedation.[4–7,36,37] Understanding this is important because of the common and mistaken belief that opioids primarily work by decreasing this rate and almost, but not quite, killing the patient, or through simple sedation. Opioids certainly can depress respiration, but this appears primarily to be an effect of the *rate of rise* of the drug; steady-state levels have a negligible clinical effect on respiratory drive. The same holds true for sedative effects of opioids.[38] And yet, as for pain, steady-state opioid levels can provide continuing relief from dyspnea. In fact, it makes little sense that decreasing ventilation per se would reduce dyspnea. Such a decrease by itself might produce some relief from fatigue, but only at the cost of decreased airflow and worsening blood gasses, both of which typically stimulate ventilatory effort and associated dyspnea. What alternative explanations might exist for their efficacy?

Opioid receptors are found in a variety of locations in the CNS that have no direct association with pain.[39] Opioid receptors are also present in body organs important in monitoring respiration such as the carotid bodies. Respiratory centers in the medulla are studded with opioid receptors in animals as primitive as amphibians, suggesting some ancient and evolutionarily advantageous physiologic function.[40–42]In more advanced animals opioid receptors are also found in limbic and higher cortical areas. Recent clinical evidence

supports the role of endogenous opioids in ameliorating dyspnea in experimental subjects and patients with chronic obstructive pulmonary disease (COPD), as dyspnea tended to increase with naloxone administration during exercise and resistive load challenges.[43–46] Obviously, these receptors did not evolve in anticipation of our ingestion of exogenous opioids for the treatment of pain or inducement of pleasure, but for the purpose of binding endogenous opioids (endorphins, enkephalins) for some reason with a distinct survival advantage. What might that be? Before attempting to answer this question, let us consider more closely the physiologic effects of opioids on respiration.

The most direct effect of opioids on respiration is on inspiration, more specifically respiratory rhythm pattern generation by an area called the pre-Botzinger complex. This complex has not been definitively identified in humans, but it is clearly identified and well-studied in cats and other animals.[39] Opioids result in irregular, quantal inhibition of inspiratory signal transmission from this complex into the greater respiratory oscillating system. There is some debate among physiologists as to whether this effect is direct (opioids binding receptors in the pre-Botzinger complex) or indirect with some recent evidence suggesting the effect is indirect.[47–49] With opioid administration the pre-Botzinger complex continues its regular cycling rhythm, but generated action potentials are more likely to be subthreshold, resulting in irregular/skipped signals.[50] Pattinson has compared the generation of subthreshold action potentials to a Mobitz type-II second degree heart block.[39] In both cases the pattern generator tempo remains the same, but because of incomplete transmission the result is a slower net stimulus to inspiratory frequency. Opioids also appear to blunt responses to hypercapneic and hypoxic ventilatory drives both centrally and through peripheral chemoreceptors, particularly those in the carotid body, which is important in generating the hypoxic ventilatory response.[39] In the aggregate, multiple studies clearly demonstrate that binding of opioid receptors give rise to a net inhibition of respiratory inspiratory drive.

Balanced against all this is an evolving clinical literature, much of it from the palliative care community, demonstrating that in most cases when used judiciously (slow administration and upward titration) opioids do not significantly affect net ventilation and that relief from dyspnea is largely independent of any net slowing of ventilation.[9,51,52] It is important to note that the effect of opioids is primarily on inhibition of inspiratory *drive* in the CNS, not necessarily net respiration. Opioids work within a complex system of balances and counterbalances. For example, decreased respiratory drive from the CNS may result in transient decreased respiratory tidal volume, which will cause the partial pressure of carbon dioxide to rise, resulting in increased hypercarbic ventilatory drive, counterbalancing in part the decreased inspiratory stimulus. The presence of pain for which opioids are often prescribed, also has been found to stimulate respiration. In one study, experimentally induced pain was found to attenuate morphine-induced respiratory depression.[53]

More to the point, there is no evidence of a significant survival disadvantage to judicious use. Indeed, some recent studies raise the question of possible survival advantages to good symptom management (albeit not specifically the relief of dyspnea by opioids).[54] We have been acculturated to view "respiratory depression" as a bad thing, as it certainly can be. However, one cannot help but think that the evolutionary preservation of a system for inhibiting respiratory drive over millions of years in some way must be a good thing in terms of some survival advantage. Otherwise, why would this function exist?

At this point we leap from evidence to conjecture. As is true for pain, in respiration opioids appear to act as dampeners or modulators of a complex system, wherein a counterbalance is needed to offset particular response cascades. Under most circumstances these cascades (pain and dyspnea responses) are highly functional. However, in certain situations dampening of these responses appears needed in order to increase the probability of survival. This is most easily understood in pain. Unpleasant though it is, the survival advantage to pain should be obvious. It should also be clear that in certain circumstances there are advantages to suppressing pain—being wounded and running away from a tiger for example. What might be equivalent in respiration and dyspnea?

Dyspnea responses also have clear survival advantages in most situations, whether the drive is to decrease metabolic activity while intensifying the drive for ventilation, as in work-of-breathing dyspnea, or the panic response as in suffocation dyspnea. However, it should also be clear that in such circumstances, certain responses could be counterproductive, especially where the stimuli to such responses are other than of a transient duration. Extreme responses can produce deleterious effects. Such situations are common in advanced, chronic illness.

In chronic illness it may be inadvisable or impossible to further slow metabolic activity. One extreme response to dyspnea, total bed rest, may result in a vicious cycle of deconditioning, paradoxically contributing to worsening fatigue and progressive debilitation. The survival advantage of panic in true suffocation dyspnea should be obvious. However, in advanced disease where true suffocation is not present, a panic response may only serve to excessively increase metabolic demand, which similarly is not helpful, given limited reserves. Excessively strong respiratory drive in the weakened condition of advanced illness could give rise to overwhelming fatigue, which in turn could result in catastrophic respiratory failure and conceivably a hastened death.

How might this work physiologically in advanced illness? By way of example, imagine a chain of events starting with some increased metabolic demand, such as a patient trying to getting out of bed to go to the bathroom. The effect of resultant metabolic stimuli, such as rising CO_2 levels, is to increase respiratory drive. However, this effect might be dampened by opioids, with the result still being a higher net intensity of respiratory drive and rate, but *less* than might otherwise have occurred in their absence. Because of this blunted drive efferent-reafferent dissociation is lessened with secondary reduction in dyspnea. Extremes of a debilitating bedridden status, if the patient stays in bed, and respiratory exhaustion, if the patient pushes his or herself too hard, might be avoided.

Summary

We seem to have become so acculturated to our concern about the respiratory depressive effects of opioids that we may have overlooked the possibility that more common threats to survival from an evolutionary perspective might be grave debilitation at one extreme or catastrophic respiratory failure at the other, both of which would have the same lethal

outcome, death. Modulation between such extremes seems highly advantageous. Researchers have not teased apart the discrete roles of opioids in modulating dyspnea in advanced illness. However, it seems at least plausible that metaphorically speaking opioids may allow patients to "ease up on the gas pedal," when still trying to climb steep hills. They may get to their destinations a bit more slowly, but at least they get there. Relief of suffering is a secondary, albeit far from trivial, side benefit.

Our current understanding of the physiologic mechanisms of dyspnea and mechanisms of therapeutic action for many agents remains remarkably primitive. The discussion above is offered less as a definitive explanation of these mechanisms than an invitation and challenge to others to expand, refine, or refute this understanding. In the meantime, the practicing clinician is advised to consider what physiologic mechanisms may be a work in tailoring patient-specific therapeutic plans.

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Address correspondence to:
James Hallenbeck, M.D.
School of Medicine
Department of Medicine
Division of General Medical Disciplines
Stanford University
VA Palo Alto HCS
3801 Miranda Avenue
Palo Alto, CA 94304

E-mail: james.hallenbeck@va.gov