

# The neurophysiology of dyspnea

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## Abstract

**Objective** – To review the human and veterinary literature regarding the neurophysiology of dyspnea and to provide evidence for the beneficial effects of several novel therapies aimed at the alleviation of dyspneic sensations.

**Data Sources** – Data sources included scientific reviews, case reports, original research publications, and recent research conference proceedings.

**Human Data Synthesis** – The use of blood oxygenation level-dependent functional magnetic resonance imaging technology has revealed that the brain regions activated by air hunger in humans are also those activated by fear, pain, and thirst perception. In human subjects, it has been found that agents known to enhance the firing of pulmonary slowly adapting receptors (SARs) can alleviate the sensation of dyspnea without altering central respiratory drive. Several small studies have also shown that nebulized opioids can reduce the sensation of dyspnea apparently via activation of peripheral opioid receptors in the lung.

**Veterinary Data Synthesis** – There are several animal models relevant to both small and large animal clinical patient populations. Treatment of rats with a nebulized SAR sensitizing agent (furosemide) enhances SAR firing in response to lung inflation. Behavioral escape responses to airway occlusion are reduced in lightly anesthetized cats when treated with nebulized furosemide. Opioid agonists have been shown to inhibit the release of acetylcholine and other mediators from the airways of dogs and guinea pigs. Studies using a goat model with bilateral destruction of the pre-Bötzinger Complex do not support current paradigms of air hunger origination.

**Conclusions** – Veterinary patients may benefit from an approach to dyspnea that incorporates an understanding of the origins of the unpleasant sensations associated with the condition. Several novel therapies have shown promise in alleviating dyspneic sensations without altering respiratory drive. Further study is needed to determine the safety and efficacy of these therapies in veterinary patients.

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## Introduction

In veterinary medicine, dyspnea is an important clinical sign that has come to mean labored or difficult breathing. While dyspnea is also a symptom of disease in humans, the definition differs greatly from the veterinary usage. In human medicine, definitions of dyspnea are focused on the unpleasant sensory experience rather than the characteristics of the patient's respiratory efforts. The American Thoracic Society defines dyspnea as follows: 'dyspnea is the subjective experi-

ence of breathing discomfort that originates from interactions among various physiological, psychological, social, and environmental factors.'<sup>1</sup> The definition used in human medicine has evolved with the understanding that not all dyspneic patients have labored breathing and that not all patients with increased respiratory effort are experiencing dyspneic sensations.<sup>2</sup>

In 1956, a prominent physiologist suggested, 'it might be profitable to compare the symptom dyspnea with the symptom pain.'<sup>3</sup> Pain, dyspnea, nausea, thirst, and hunger are all subjective experiences that can be difficult to assess in any species when the patient is unable to communicate fully with caregivers. In recent years, the approach of focusing on the sensory experience has led to great strides in our understanding of pain in humans and animals alike. Current definitions of pain in animals bear far more resemblance to human definitions of symptoms than to veterinary definitions of clinical signs. Molony and Kent have defined animal

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pain as follows: 'animal pain is an aversive, sensory experience representing awareness by the animal of damage or threat to the integrity of its tissues (note that there might not be any damage). It changes the animal's physiology and behavior to reduce or avoid damage, to reduce the likelihood of its recurrence and to promote recovery. Nonfunctional (nonuseful) pain occurs when the intensity or duration of the experience is not appropriate for damage sustained (especially if none exists) and when physiological and behavioral responses are unsuccessful in alleviating it.'<sup>4</sup> A similar revised definition of dyspnea that addresses the sensory component may be of use in veterinary medicine. While pain represents a response to a threat to tissue integrity, dyspnea represents a response to a threat to adequate pulmonary ventilation. The focus of this review will be on the current understanding of the sensory experience of dyspnea in humans and animal models, rather than on causes of labored breathing.

### Importance

Dyspnea is an important source of morbidity and predictor of mortality in humans. Twenty-five percent of the general public over 40 years old report dyspnea when seeking medical attention and the presence of dyspnea predicts mortality with a relative risk of 2, which is equal to that of chest pain.<sup>5</sup> Dyspnea is a leading symptom of cardiopulmonary disease in humans and afflicts 50% of the patients in tertiary care facilities.<sup>6</sup> This is roughly equal to the symptom burden of pain (higher symptom burdens are associated with lower health-related quality of life). Dyspnea has been shown to overtake suffering from pain as the most difficult problem to address as terminal illness reaches the end stage.<sup>7,8</sup> In addition, dyspnea is reported as frequently as pain in seriously ill human patients.<sup>9</sup>

Patients with conditions that result in dyspnea often simultaneously experience other unpleasant sensory experiences (eg, pain, nausea, hunger, thirst). It has been found that dyspnea and pain interact at the perceptual level in humans. Painful stimuli can produce an increase in the perception of dyspnea, whereas dyspnea can result in a large (though variable) reduction in the perception of pain.<sup>10,11</sup> Dyspnea is thought to be a *counterirritant* that shares common neural pathways with pain. It has been suggested that such an arrangement may have evolved because under conditions that elicit dyspnea, temporary inattention to pain signals may favor survival.<sup>6</sup>

The lack of suitable animal models of the sensory aspects of dyspnea has led to dyspnea research lagging far behind studies of the pathophysiology of pain. It is not known at present if animal species experience dyspnea as humans do. It is known that animals exhibit

aversive behaviors under conditions that result in dyspnea in humans. The breathing of a gas mixture with an increased fraction of CO<sub>2</sub> is a commonly used model of producing air hunger (one type of dyspneic sensation) in human subjects. The innervation of the upper and lower airways and the processing of sensory inputs following carbon dioxide exposure are highly conserved between species (rats, humans, and other mammals).<sup>12</sup> This suggests, but in no way proves, that the perception of CO<sub>2</sub> stimulation is the same in rats and humans.<sup>2</sup> Carbon dioxide at an inspired fraction of 15% causes severe dyspnea in humans and the use of CO<sub>2</sub> chambers as a means of humane euthanasia in animals has been called into question.<sup>13</sup> Fasted rats will forgo food intake rather than remain in a chamber containing food and 15% carbon dioxide.<sup>14</sup> In this species at least, it appears that air hunger is more unpleasant than nutrient hunger. The interpretation of data from such animal studies is confounded by the fact that high ambient CO<sub>2</sub> levels can cause mucosal irritation and aversive behaviors may not solely be the result of dyspneic sensations.

It was long thought that hypoxia did not result in dyspnea. This concept was based on the finding that humans breathing at altitude under hypoxic conditions did not report experiencing dyspnea. However, under such conditions humans increase their minute ventilation substantially, which makes altitude exposure an unsuitable model of hypoxia-induced dyspnea. More recent work has shown that when minute ventilation is held constant then reductions in PaO<sub>2</sub> evoke strong sensations of dyspnea in human subjects.<sup>15</sup> Indeed, hypoxia and hypercapnia have equal potencies for producing air hunger.<sup>15</sup> Profound, abrupt hypoxia causes syncope rather than discomfort in both pigs and humans.<sup>16</sup> However, fasted rats will not enter chambers filled with argon (an inert gas) that contain food, suggesting that hypoxic environments are unpleasant to at least some animal species.<sup>12</sup>

The importance of dyspnea in clinical medicine is found not only in its perception but also in perception deficits. Failure to perceive dyspnea is thought to contribute to the risk of death due to asthma. Blunted perception of dyspnea may lead to inadequate use of medication, frequent rehospitalizations, and fatal or near-fatal asthma attacks.<sup>17-20</sup> Subgroups of asthmatics have been reported to have a blunted perception of dyspnea.<sup>17,21</sup> Studies have suggested that the deficits lie in the neuronal processing of sensory inputs.<sup>22,23</sup> Alternatively, chronic airway inflammation may lead to damage of sensory receptors in the lung.<sup>24</sup>

### The Neural Substrates of Dyspnea

As mentioned above, pain perception and dyspnea perception are interlinked. However, unlike pain there

are no specialized dyspnea receptors. Further, no cortical lesion has been identified that abolishes dyspnea perception. Typically, respiratory sensations cannot be linked to a single distinguishable stimulus as with pain (eg, thermal energy, tissue trauma). Dyspnea is composed of several qualitatively different sensations that may arise from distinct mechanisms. The identification of the contribution of sensory inputs from different airway receptor types to the perception of dyspnea remains an ongoing effort.

### Peripheral neural substrates (airway receptors)

The upper and lower airways contain a multitude of receptor types (see Table 1).<sup>25</sup> In this context, *receptor* is meant in the traditional sense of sensory fibers and organs rather than the alternative meaning of cell membrane receptor molecules. The contribution of airway receptors to the perception of dyspnea is an active area of research. Receptor types differ in the upper airways (laryngeal receptors) and lower airways (tracheobronchial receptors). The upper airways contain 5 generally accepted receptor types: pressure, drive, cold, irritant, and C-fibers. Irritant receptors are thought to mediate cough reflexes in response to laryngeal stimuli. The role of upper airway receptor inputs is uncertain in dyspnea. Current evidence suggests that a role may lie in modulating dyspnea perception. Upper airway and facial receptors modify the sensation of dyspnea. It has been shown that receptors supplying afferent signals via the trigeminal nerve influence the intensity of dyspnea.<sup>26,27</sup> Human patients with chronic obstructive pulmonary disease breathing cold air report a lessening of dyspnea.<sup>28</sup> Oral mucosal stimulation modulates the intensity of breathlessness induced in normal human subjects.<sup>27</sup> The role of

upper airway receptors in the origination of dyspneic sensations is thought to be limited.

Lower airway receptors (tracheobronchial receptors) are believed to be a major source of sensory input leading to the sensory experience of dyspnea. These receptors respond to both irritants and stretching. Afferent information from these receptors reaches the CNS via the vagus nerve. There are presently 5 distinct types of lower airway receptors recognized: slowly adapting receptors (SARs), rapidly adapting receptors (RARs), C-fibers, neuroepithelial bodies (NEB), and A $\delta$  nociceptors (see Table 1).

SARs are stimulated by inflation of the lung, although some may also respond to lung deflation. The SARs are typically found within airway smooth muscle layers and may respond to changes in smooth muscle tone, alterations in lung compliance, and direct actions on the receptor.<sup>25</sup> The SARs have very limited chemosensitivity. Reflex actions mediated by activation of this receptor type include the shortening of inspiration, the prolongation of expiration, and reflex bronchodilation.<sup>29</sup> SARs are responsible for the Hering-Breuer reflex (which inhibits further inhalation during large inspirations) and contribute to the normal respiratory sinus arrhythmia in dogs. The fibers are myelinated and are of the A $\beta$  and A $\gamma$  type.<sup>30</sup> SARs are not directly or substantially affected by hypoxia. Agents and interventions that *increase* SAR firing have been found to alleviate some sensations of dyspnea (Figure 1).<sup>31</sup>

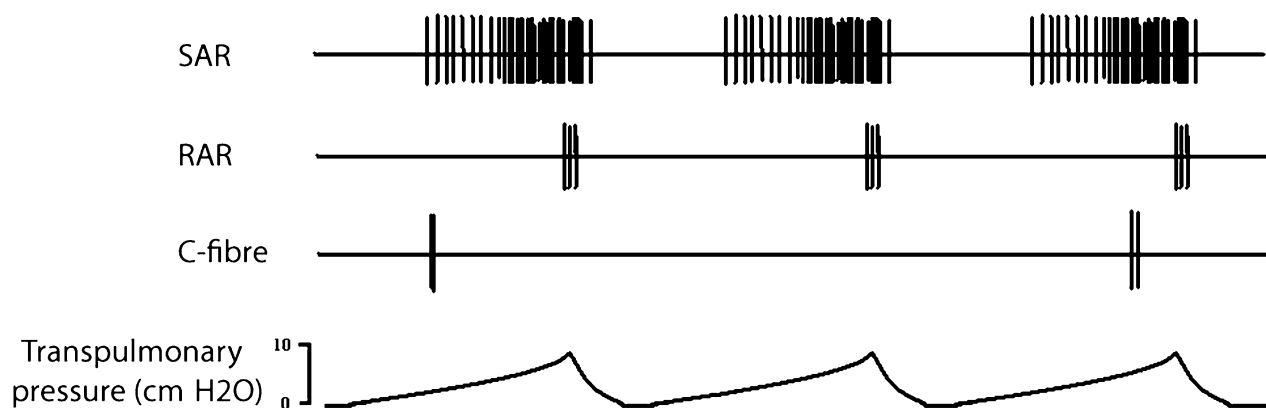
The RARs have a faster adaptation rate (they stop firing quickly after stimulation by lung inflation) than the SARs (which continue firing at a substantial rate with sustained stretch). The RAR also has myelinated fibers, but is thinner than the SAR. The RAR is polymodal and chemosensitive with terminals in the epithelium and submucosa. This receptor type is absent (or exceptionally sparse) in ferrets and mice, species that lack a cough reflex. RAR stimulation typically results in effects on bronchomotor tone and pattern of breathing opposite to those seen with stimulation of the SAR (Figure 1). They are stimulated by increases in extracellular fluid volume, lung lymphatic obstruction, and increases in pulmonary capillary pressure.<sup>32,33</sup> In vivo stimulation of RARs can occur by increases in tidal volume or respiratory rate and by decreases in lung compliance.<sup>34</sup> This receptor type can be sensitized by ozone and histamine.<sup>35,36</sup> In contrast to the SAR, agents and interventions that *decrease* RAR firing can reduce some of the sensations of dyspnea (Figure 1).

C-fibers are found in both the airways and the alveolar walls. They are polymodal and nociceptive. Branching C-fibers can be localized throughout the mucosa. C-fiber responses are thought to contribute to the pathogenesis of neurogenic pulmonary inflammation.<sup>37</sup> Reflex

**Table 1:** Sensory receptors involved in the regulation of airway function and minute ventilation

Upper airway receptors
Pressure
Drive
Cold
Irritant
C-fiber
Tracheobronchial receptors
Slowly adapting receptors (SAR)
Rapidly adapting receptors
C-fibers
Neuroepithelial bodies (NEB)
A $\delta$ nociceptors
Chest wall receptors
Intercostal muscle and diaphragm mechanoreceptors
Chemoreceptors
Peripheral and central chemoreceptors

Receptor subtypes are grouped according to anatomic location.



**Figure 1:** An illustration of the typical differences in action potentials (AP) recorded from individual vagal nerve fibers carrying afferent signals from 3 types of airway receptors. During lung inflation, slowly adapting receptor (SAR) produces a steady and increasing afferent output while rapidly adapting receptor (RAR) stimulation produces a brief burst of AP activity near the end of inspiration. APs from C-fibers appear sporadically and appear to be independent of changes in transpulmonary pressure. Interventions that increase the firing of SARs and decrease the firing of RARs can reduce dyspnea in humans.

actions include bronchoconstriction, mucus secretion, hypotension, bradycardia, and laryngospasm. The respiratory response to C-fiber activation includes apnea and rapid, shallow breathing patterns (Figure 1).<sup>38</sup>

NEBs are groups of neuroepithelial endocrine cells. Unlike SARs, RARs, and C-fibers, the NEB receptor type is directly sensitive to hypoxia. Under hypoxic conditions, the NEBs release an array of bioactive substances that can stimulate nearby nerve endings. NEBs are thought to serve as hypoxia sensors.

$\delta$  nociceptors are also found within the respiratory tract. The role of these pain receptors in the pathophysiology of dyspnea is largely unknown. As mentioned above, pain and dyspnea share common neural substrates at some levels and the perception of one is modified by the perception of the other.

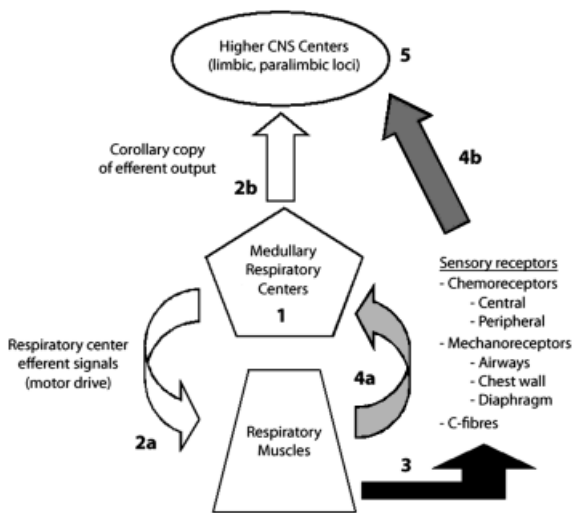
In addition to upper and lower airway receptors, sensory organs in other locations may influence the sensory experience of dyspnea. Among these are mechanoreceptors in the chest wall, central chemoreceptors, and peripheral chemoreceptors. A variety of afferents in the joints, tendon organs, and muscle spindles can be identified in the respiratory muscles of the thoracic cavity. Receptors in the intercostal muscles and diaphragm signal information regarding length-tension relationships and respiratory muscle displacement and have been shown to be involved in the perception of dyspnea.<sup>39,40</sup> Mechanical vibration of the chest wall can reduce dyspnea.<sup>39,41</sup> Such vibrations likely stimulate chest wall muscle spindles although one cannot rule out an effect on pulmonary stretch receptors (eg, SARs, RARs).<sup>42,43</sup>

Central chemoreceptors in the medulla and peripheral chemoreceptors in the aorta and carotid bodies

serve as sensory organs for alterations in the composition of blood gases. Hypercapnia and hypoxemia result in increased afferent signals from these chemoreceptors that may be perceived directly or secondary to increased medullary respiratory motor drive subsequent to the increased afferent signals.<sup>15,44</sup>

#### Central neural substrates

As described above, the afferent inputs involved in dyspnea perception are many and complex (Figure 2). The CNS receives inputs from airways, lung parenchyma, and chest wall receptors as well as afferent signals from chemoreceptors monitoring respiratory gas levels in the arterial blood and pH of the CSF (Figure 2). Another active area of research involves investigations into how the CNS processes this varied afferent input and how such processing leads to sensations of dyspnea. The most widely accepted model at present revolves around the comparison of vagal afferent signals with current motor drive (Figure 2). The medullary respiratory centers continuously produce an efferent motor drive signal based on afferent signals, which act as markers of present ventilatory need. It is thought that a *corollary copy* of medullary motor drive ascends through the midbrain where comparisons are made at higher centers (Figure 2).<sup>45</sup> This processing at higher CNS levels has been thought of as a comparison between *ventilation demanded* (corollary copy of motor drive) and *ventilation achieved* (vagal afferent signals from the peripheral receptors described above). This process has been described as *efferent-reafferent matching* and imbalances as *neuroventilatory dissociation*.<sup>46</sup> At times the motor drive may originate from cortical centers (motor cortex) rather than brainstem centers. Such



**Figure 2:** An overview of the most widely accepted model of the generation of dyspnea sensations. (1) Medullary respiratory centers generate a level of respiratory motor drive based on the current level of ventilator need, (2a) this efferent output is sent to the respiratory muscles and (2b) a *corollary copy* of this efferent output is sent to higher CNS loci in the limbic and paralimbic regions, (3) the blood gas, CSF pH, and degree of chest wall/lung expansion achieved by this motor activity will be detected by sensory receptors, and (4a) sensory afferent input will be carried to the medullary centers to signal current, ongoing ventilatory demand and (4b) also to the higher CNS centers. (5) Lastly, in the limbic/paralimbic sites a comparison will be made between the corollary copy of efferent output and the subsequent afferent signal. If the afferent signals do not match the anticipated pattern for a given level of prior efferent output then dyspnea will develop.

higher cortical respiratory centers have not yet been found in the human cortex, but have been found in cats in which sensory thalamic nuclei were activated by corollary discharges.<sup>47,48</sup> It has been suggested that the source of the motor drive may alter the character of what is perceived.<sup>49</sup> Regardless of the source of the motor drive, dyspnea is thought to occur when a mismatch between the 2 sets of signals is perceived. Under any given set of conditions, it appears the brain has a preset pattern of ventilation and subsequent afferent feedback that is anticipated and that when this preset pattern is not achieved dyspnea will arise or intensify. The experimental evidence does not uniformly support the present model. Studies using a goat model with bilateral destruction of the pre-Bötzinger Complex have challenged the model of *efferent-reafferent matching*.<sup>50</sup> In this model, goats appear to be dyspneic while lacking a respiratory pattern generator from which the *corollary copy* is derived. However, one cannot be certain that such goats are truly experiencing dyspnea.

Where the comparison between efferent and reafferent signals is made remains unclear, but recent advanced imaging studies are beginning to shed light on the process and the brain regions involved. Blood oxygen level-dependent functional magnetic resonance imaging performed on human subjects experiencing air hunger (a form of dyspnea, see below) revealed limbic and paralimbic loci activation within the anterior insula, anterior cingulate, operculum, cerebellum, amygdala, thalamus, and basal ganglia.<sup>51</sup> Loci within the anterior insula were also identified in studies using H<sub>2</sub><sup>15</sup>O positron emission tomography and the insular cortex appears to be particularly important in producing the unpleasant sensations of dyspnea.<sup>13,52,53</sup> The limbic/paralimbic system is thought to aid survival by integrating behavior with the perception of physiologic needs.<sup>54–56</sup> It has been suggested that the anterior insula may serve either as a nonspecific alarm center for identifying nonspecific physiologic threats or that there may be specific insular neurons that are activated by different types of threats (eg, air hunger, thirst, nutrient hunger, pain).<sup>51,57</sup>

### The Perception of Dyspnea

Dyspnea is a term applied to a set of distinct sensations that may occur independently. At present, dyspnea in humans has been subdivided into 3 types of unpleasant sensory experiences: air hunger, increased work/effort, and tightness. While these sensations may arise independently, more than one may be present in an individual and their perception may have additive effects on the overall feeling of dyspnea experienced.

#### Air hunger

Air hunger, or an uncomfortable urge to breathe, has a normal protective role in conscious behavior. For instance, air hunger ensues during breath-hold diving and triggers behaviors that lead to an animal seeking access to air once again. The nature of air hunger has been compared with other essential sensations such as thirst and nutrient hunger.<sup>13,52</sup> The sensation of air hunger is increased by afferent inputs signaling a greater need for ventilation (eg, hypoxemia, hypercapnia) and decreased by afferent signals reporting thoracic cavity and lung expansion. Within the context of the prevailing comparator model, air hunger arises when the CNS perceives there to be a mismatch between these 2 sources of inputs. Recent work suggests that air hunger depends on the perception of an increased drive to breathe rather than a direct effect of the stimulus (ie, not directly caused by effects of hypoxemia on cortical centers themselves).<sup>15</sup> As described above, there are a large number of sensory inputs that

are used to compare expected ventilation to achieved ventilation. In the case of air hunger, inputs from pulmonary stretch receptors and chemoreceptors appear to be of particular importance.<sup>31</sup> This differs from the generation of the sensation of increased work/effort in which signals from muscle mechanoreceptors and C-fibers appear to be of primary importance. The sensation of air hunger is reported to be more unpleasant than that of increased work/effort.<sup>58</sup> In the face of hypercapnia or hypoxemia or both, the sensation of air hunger can be alleviated by vagal inputs signaling greater lung inflation (SAR inputs in particular).<sup>59</sup> Air hunger is not alleviated by chest wall vibration.<sup>39,41</sup>

It is important to remember that it is the relative balance of ventilation achieved and ventilation demanded that determines if air hunger will develop, not the absolute value of blood gases. If minute ventilation is reduced, but end-tidal CO<sub>2</sub> is maintained at a constant level, human subjects report a marked increase in breathlessness.<sup>60,61</sup> The rate of stretching (lung inflation) will influence afferent inputs as well. When normal subjects are made to breathe at inspiratory flow rates lower than those they have deemed most comfortable, air hunger ensues.<sup>62</sup> Thus, patients on mechanical ventilators may *buck* the ventilator when inspiratory flow rates are too low even when blood gases are considered within normal ranges.

### Increased work/effort

Eupneic breathing is not normally consciously perceived. When ventilation is obstructed, stimulated, or challenged, cognitive awareness of breathing occurs and can reach distressing levels. The term increased work/effort is used to describe unpleasant sensations that arise when greater than usual respiratory muscle activity is required to maintain ventilation.<sup>63-65</sup> Whereas air hunger is thought to arise from altered ventilatory chemical loads (hypoxemia/hypercapnia relative to present respiratory efforts), increased work/effort sensations are thought to arise due to increased mechanical loads. Gas trapping and lung hyperinflation induce a perception of increased work/effort (but not tightness, discussed below).<sup>66</sup> Currently, it is thought that hyperinflation leads to sensations of increased work/effort due to decreased pulmonary compliance, alteration of respiratory muscle resting length, or both. The most widely accepted theory is that increased work/effort sensation arises from simultaneous activation of the sensory cortex at the time that the outgoing motor command is sent to the respiratory muscles.<sup>67</sup> The sense of increased work/effort is related to the pressure generated by the current breath relative to the maximum pressure generating capacity of the respiratory system.<sup>68</sup> Thus the sense of increased work/

effort will intensify when the respiratory muscles must generate greater pressure *or* if the maximum pressure generating capacity of the respiratory system is diminished.<sup>67</sup> Inputs from the respiratory muscles are important to the development of the increased work/effort type of dyspnea and this sensation can be relieved by chest wall vibration.

### Asthmatic tightness

A feeling of chest tightness is the third distinct sensation reported by humans experiencing dyspnea. Chest tightness is thought to occur as a result of bronchoconstriction and is reported primarily in asthmatics.<sup>66,69,70</sup> An alternative hypothesis that chest tightness arises secondary to hyperinflation has been proposed, but currently there is little evidence to support this mechanism.<sup>71</sup> The principle afferent signals involved in the generation of a sensation of asthmatic tightness are intrapulmonary afferents rather than respiratory muscle afferents.

### Therapeutic Alleviation of Dyspnea

Advances in the alleviation of dyspnea in veterinary medicine have been slowed by difficulty in recognizing both the presence of dyspnea and the mechanism underlying its development. As noted above, it is not known at present whether animal species experience the unpleasant sensations of dyspnea as humans do. However, as is the case with pain, patients will likely benefit if their caregivers work under the assumption that they do experience the sensory aspects of dyspnea. The first principle in managing a patient that is, or may be, dyspneic is to address the underlying problem. However, not every cause of dyspnea can be addressed immediately or ever. There are a number of measures that may be taken to alleviate the unpleasant sensations associated with dyspnea in man. These measures include both pharmacologic (nebulized furosemide, opioids, corticosteroids) and nonpharmacological (chest wall vibration) means.

### SAR sensitizers

It has been noted above that sensations of air hunger may be alleviated by increased vagal inputs from airway SARs. In recent years studies have been performed to evaluate the efficacy, duration of effect, and mechanism of action of agents that increase SAR afferent signaling when delivered via the inhalational route. Such research has revealed a previously unrecognized effect of a widely used drug, furosemide.

Furosemide is typically given via the IV or oral route as a diuretic. However, studies have shown that *aerosolized* furosemide protects against bronchoconstriction

and inhibits the cough reflex in addition to reducing pulmonary edema when absorbed systemically.<sup>72,73</sup> These studies do not explain the efficacy of aerosolized furosemide in patients whose dyspnea is not due to congestive heart failure or asthma. A case report describing the use of aerosolized furosemide for dyspnea relief in terminal cancer patients as an alternative to opioid sedation was first reported in 1994.<sup>74</sup> Subsequent case series have reported the successful use of inhaled furosemide for dyspnea relief in cancer patients.<sup>75</sup>

The original case report stimulated researchers to investigate the effect of inhaled furosemide on dyspneic sensations under laboratory conditions. Nishino et al,<sup>76</sup> demonstrated that inhaled furosemide reduced the perception of discomfort due to breath holding or resistive loading in healthy human subjects (a reduced sense of work/effort). Diuretic or bronchoprotective actions were unlikely to explain the effect in healthy subjects because neither pulmonary edema nor bronchospasm was induced. It was later found by this same group that aerosolized furosemide stimulates SARs and desensitizes RARs in rats.<sup>77</sup> As has been described above, both increased SAR afferent signals and decreased RAR inputs reduce the sensation of dyspnea in humans. It is not known by what mechanism furosemide increases SAR sensitivity. It has been proposed that furosemide's known inhibitory action on the Na-K-2Cl cotransporter may increase local sodium ion concentrations in the airways following aerosol delivery.<sup>76,78</sup> The increased local sodium ion concentration may increase sodium influx, which is thought to increase pulmonary stretch receptor activity.<sup>79</sup> Inhaled furosemide has been shown not to affect CO<sub>2</sub> chemosensitivity or breathing patterns at rest.<sup>80</sup>

A later study using healthy human subjects has since shown that inhaled furosemide reduces air hunger perception and not just increased work/effort sensations.<sup>81</sup> In this study, the effect was brief, lasting only 2 hours. Inhaled furosemide has been shown to inhibit behavioral responses to airway occlusion in lightly anesthetized cats.<sup>82</sup> The effect in this study lasted for >3 hours.

### Opioid receptor agonists

Pulmonary opioid receptors are concentrated in the bronchioles and parenchyma. Traditional  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors as well as nonconventional opioid binding sites have been identified in lung tissue of humans and animals.<sup>83</sup> The role of lung opioid receptors in normal pulmonary physiology is unclear, but they may play a role in the origin or modulation of dyspnea sensation.<sup>83</sup> A 1981 study by Woodcock et al<sup>84</sup> is generally thought to be the first report of a clinical investigation of the effects of an orally administered opioid on dyspnea. Oral opioid therapy is now a standard

treatment for dyspnea in human cancer patients.<sup>85</sup> At present, 17 studies or clinical reports have been published on the use of opioids for the relief of dyspnea in human patients.<sup>83</sup> Both inhaled and systemic opioid receptor agonists have been shown to be effective for dyspnea relief. The site of action is unknown.<sup>86,87</sup> It has been shown that inhaled opioids can provide dyspnea relief even in patients already receiving much higher doses via other routes for analgesia. This suggests that the site of action is not central, as central opioid receptors would presumably be occupied in patients already receiving systemic analgesic doses of these agents.<sup>88,89</sup> Opioid receptor antagonists increased dyspnea in one study, but not in another.<sup>90,91</sup>

The mechanism of action of opioids in dyspnea is unknown. Opioid agonists inhibit the release of acetylcholine and other mediators from the airways of dogs and guinea pigs.<sup>92-94</sup> Opioids may also alter the activity of alveolar C-fibers.<sup>95</sup>

### Corticosteroids

Corticosteroids may influence dyspnea perception. Proposed mechanisms include reduction of airway inflammation, restoration of epithelial structure, and CNS effects.<sup>96</sup> Airway inflammation may damage sensory receptors in the airways and corticosteroids may reduce this damage.<sup>24</sup> Nine studies have been performed to assess how inhaled corticosteroids may alter dyspnea perception. Six studies showed enhanced dyspnea perception.<sup>24,96-100</sup> However, 3 studies have shown contrary results.<sup>101-103</sup> In addition to studies focused on inhaled corticosteroids, 1 study found that a single IV dose of methylprednisolone reduced dyspnea perception.<sup>104</sup> Oral corticosteroids were found to have no effect on dyspnea perception in a single study.<sup>105</sup> At present, no firm conclusions can be drawn regarding the influence of corticosteroids on dyspnea perception.

### Chest wall vibration

Mechanical vibration of the chest wall can reduce the perception of some forms of dyspnea. Mechanical vibration is thought to stimulate chest wall muscle spindles or pulmonary stretch receptors.<sup>42,43</sup> Under experimental conditions of combined hypercapnia and an increased resistive load, chest wall vibration reduces respiratory discomfort.<sup>39,41</sup> Limited studies in human patients with chronic obstructive pulmonary disease suggest that chest wall vibration may have clinical utility.<sup>106</sup> It must be noted, however, that mechanical chest wall vibration does not appear to reduce perception of air hunger, but rather only the sensations of increased work/effort and tightness.<sup>107</sup> Furthermore, the effect of chest wall vibration depends on both the location and the timing of the stimulus. Chest wall vibration can

actually increase respiratory discomfort when it is applied out of phase (eg, vibrating inspiratory muscles during expiration).<sup>43</sup>

### **Application to Veterinary Emergency and Critical Care Medicine**

While great strides have been made in recent years in the management of animal pain, similar advances in the approach to dyspnea in animals have yet to be realized. The findings that animals exhibit aversive behaviors under conditions that cause dyspnea in humans and that sensory processing following CO<sub>2</sub> exposure is highly conserved among mammalian species suggest that dyspnea in animals is experienced in a fashion similar to how it is perceived in humans. As such, the application of new methods of dyspnea relief may lead to both increased patient comfort and improved outcomes in veterinary patients.

General applications of the information presented above to veterinary medicine could include the introduction of new measures to alleviate dyspnea in patients suffering from conditions associated with dyspnea in humans (eg, cardiopulmonary disease, cancer) particularly in cases for which no effective treatment exists for the underlying cause. The use of SAR-sensitizing agents such as aerosolized furosemide in this context may reduce morbidity as well as the risk of handling dyspneic patients for physical examinations, diagnostic procedures, sampling, and instrumentation.

Specific applications include the use of newer dyspnea alleviating measures in veterinary patients with dynamic upper airway obstruction (eg, laryngeal paralysis in canine patients). In such cases, patient anxiety and rapid respiratory rates may increase the severity of the obstruction. In these patients it is common for light to moderate sedation to be administered. In severe cases, general anesthesia, intubation, and mechanical ventilation may be required. Each of these approaches carries considerable risk to the patient. Sedation can reduce postural airway guarding and increases the risk of the development of complete obstruction. Some patients may also develop hypotension secondary to the administration of sedatives. In a subset of patients requiring mechanical ventilation the institution of ventilatory support may be a terminal exercise with the patient unable to be weaned successfully. It would be preferable if dyspnea in this setting could be alleviated while avoiding the risks associated with sedation, anesthesia, and mechanical ventilation. The use of SAR sensitizing agents such as inhaled furosemide may be of particular value in these cases if it is found that such therapy can alleviate dyspnea without the need for sedation or anesthesia.

Another appropriate specific application of new dyspnea relief measures would be in patients afflicted with pulmonary thromboemboli (PTE). In humans, no mechanism clearly explains the magnitude and character of the dyspnea seen with PTE.<sup>62</sup> The intensity of the dyspnea is thought to be out of proportion to any alterations in respiratory gas exchange. C-fibers or cardiovascular pressure receptors may mediate the origination of dyspnea sensations in the setting of PTE. It is likely that PTE-induced dyspnea is as intensely unpleasant in animals as it is in humans. As such, the development and application of new dyspnea therapies may be of particular benefit to veterinary patients with PTE or pulmonary infarction.

### **Conclusions and Recommendations for Future Studies**

Veterinary patients would likely benefit from a working definition of dyspnea in animals that included a consideration of the likely unpleasant sensory components and the behaviors elicited by dyspneic sensations. Such a change in focus away from considering merely whether breathing is labored should lead to the institution of novel approaches to dyspnea management. Dyspnea in humans consists of at least 3 distinct types of sensations: air hunger, increased work/effort, and asthmatic tightness. It is important to recognize that the individual therapies for dyspnea discussed above do not provide effective dyspnea relief for each type of dyspnea sensation when used alone. Thus, a multimodal approach to dyspnea that incorporates the use of SAR sensitizers, judicious use of opioids or corticosteroids or both, and chest wall vibration may provide the greatest improvements in patient comfort.

Much work remains to be done to determine if the therapies discussed herein are safe and efficacious in veterinary patients. SAR sensitizers have been found to reduce aversive behaviors in cats with airway obstruction,<sup>82</sup> but the clinical utility of these agents in large and small animals remains to be demonstrated. In addition, if *inhaled* furosemide is found to be efficacious for dyspneic veterinary patients, then optimal dose, nebulized droplet size, and dosing frequency need to be established.

At present, the use of aerosolized opioids is not advised. While these agents may prove to be efficacious, the risk of chronic, low-dose exposure of personnel to opioids likely outweighs potential benefits. Concerns have already been raised about environmental second-hand exposure to opioids contributing to addiction in human medicine even when these agents are not being nebulized.<sup>108</sup> However, the use of nonnebulized opiates to address dyspnea in veterinary patients is a field that



would benefit from additional study. The development of quantifiable behavioral and physiological markers of dyspnea would allow for comparisons of the effectiveness of different opioids to be made.

Chest wall vibration therapy needs to be explored as a potentially beneficial therapy for dyspneic large and small animal patients. It remains to be seen if current models of commercially available chest wall vibration devices are suitable for use in veterinary patients. If proven efficacious, then further studies to explore the feasibility of chest wall vibration being applied by owners in an out-of-hospital setting should be performed. In some conditions such as dynamic airway collapse (eg, tracheal collapse), the stress of the hospital environment can contribute greatly to clinical signs and therapeutic options are needed that can be applied in the home environment to avoid hospitalization when possible.

Further study will be needed to determine if newer therapies for dyspnea should be part of the chronic management of cardiorespiratory disease or just during acute disease exacerbations. As discussed above, reduced perception of dyspnea in human asthmatics is thought to contribute to asthma morbidity and mortality in a subset of patients. It might be found that owner adherence with therapy instructions could be reduced if the patient seemed to be improved following dyspnea relief measures. It would need to be stressed to caregivers that dyspnea relief therapies are meant to supplement current treatments, not substitute for them.

In summary, the recent advances in veterinary pain recognition and management are laudable achievements. However, in human medicine the symptom burden of dyspnea is equal to that of pain; it must be considered that veterinary patients may undergo similar negative sensory experiences under conditions that produce dyspnea in humans. Dyspnea is a primal threat signal of a similar nature to pain, thirst, nausea, and nutrient hunger. Imaging studies in man suggest that these varied primal threat signals may all be processed in a similar manner in the CNS. Current veterinary definitions of dyspnea are inadequate and need revision. A number of novel dyspnea therapies are currently being explored in human and animal studies and may be applicable to veterinary clinical practice.

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