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Introducing breathlessness as a significant animal welfare issue

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Review Article

Introducing breathlessness as a significant animal welfare issue

NJ Beausoleil*§ and DJ Mellor*

Abstract

Breathlessness is a negative affective experience relating to respiration, the animal welfare significance of which has largely been underestimated in the veterinary and animal welfare sciences. In this review, we draw attention to the negative impact that breathlessness can have on the welfare of individual animals and to the wide range of situations in which mammals may experience breathlessness. At least three qualitatively distinct sensations of breathlessness are recognised in human medicine – respiratory effort, air hunger and chest tightness – and each of these reflects comparison by cerebral cortical processing of some combination of heightened ventilatory drive and/or impaired respiratory function. Each one occurs in a variety of pathological conditions and other situations, and more than one may be experienced simultaneously or in succession. However, the three qualities vary in terms of their unpleasantness, with air hunger reported to be the most unpleasant. We emphasise the important interplay among various primary stimuli to breathlessness and other physiological and pathophysiological conditions, as well as animal management practices. For example, asphyxia/drowning of healthy mammals or killing those with respiratory disease using gases containing high carbon dioxide tensions is likely to lead to severe air hunger, while brachycephalic obstructive airway syndrome in modern dog and cat breeds increases respiratory effort at rest and likely leads to air hunger during exertion. Using this information as a guide, we encourage animal welfare scientists, veterinarians, laboratory scientists, regulatory bodies and others involved in evaluations of animal welfare to consider whether or not breathlessness contributes to any compromise they may observe or wish to avoid or mitigate.

KEY WORDS: *Breathlessness, dyspnea, animal welfare, affective states, respiration*

Introduction

Breathlessness, in its various manifestations, has been studied extensively in human beings who report that it can be extremely unpleasant and distressing. Breathlessness incorporates a set of potentially negative experiences relating to respiratory sensations. Here, we provide a brief integrated account of the neural and other physiological mechanisms underlying the generation and conscious awareness of such sensations (excluding other respiratory sensations such as cough and irritation), as these are currently understood in human medicine. Inferences are made about possible experiences of breathlessness in non-human mammals, based on similar neural and respiratory anatomy and physiology and similarities in brain and behavioural responses to similar stimuli. Our consideration of breathlessness is restricted to mammals.

Our main aims in this review are to draw attention to the negative impact that breathlessness can have on the welfare of individual animals and to the wide range of situations in which mammals may experience breathlessness. To these ends, we illustrate the important interplay among various primary stimuli to breathlessness and other physiological and pathophysiological conditions, as well as animal management practices. We encourage readers to consider the full breadth of possible situations and conditions leading to breathlessness in mammals.

Definition and characterisation of breathlessness

The human medical literature most commonly uses the term dyspnoea to refer to sensations and experiences associated with respiratory discomfort. The American Thoracic Society proposed a comprehensive definition:

"Dyspnoea is a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, social and environmental factors, and may induce secondary physiological and behavioural responses" (Parshall *et al.* 2012).

It is clear that the current medical concept of dyspnoea, like pain, incorporates both physical sensory and affective experiences related to altered respiratory function (Wade *et al.* 1996; Lansing *et al.* 2009). A consequence of animals being unable to directly communicate their affective experiences is that terms like dyspnoea, respiratory discomfort, respiratory distress and breathlessness used in animal-based studies and clinical reports reflect only the observable respiratory signs. For example, in the veterinary literature, the term dyspnoea is almost exclusively defined as "difficult, laboured breathing" (Mellema 2008). To highlight the fact that respiration is associated not only with physical sensations but also with affective experiences, here we use the term breathlessness rather than dyspnoea when discussing the related experiences of animals.

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The sensory dimension of breathlessness is characterised by the quality, intensity and time course of the respiratory stimulus. In humans, the affective dimension constitutes immediate feelings of unpleasantness (A1 experiences) and subsequent emotions associated with the unpleasant sensation (A2 experiences) (Peiffer 2008; Lansing *et al.* 2009). Because animals are unable to communicate emotions such as fear, anxiety or depression, and because they may not project some present experiences into the future, it is unknown whether or not they have A2 experiences (Lansing *et al.* 2009). However, from an animal welfare perspective, the differentiation of A1 and A2 experiences relating to respiratory sensations may not be relevant. An animal's experience of A1 unpleasantness alone is likely to be sufficient to potentially compromise welfare, i.e. animals could suffer without A2 experiences.

Like humans, other mammals appear to experience A1 unpleasantness associated with altered respiratory function. Conscious experience of A1 unpleasantness generates a sense of urgency to engage in specific behaviours to rectify situations that threaten survival (Denton *et al.* 2009). For example, various mammalian species show withdrawal, escape attempts, struggling and other aversion behaviours to stimuli similar to those that cause dyspnoea in humans, e.g. inspiration of high carbon dioxide tensions (hypercapnic gases) (Niel and Weary 2007; Dalmau *et al.* 2010), airway occlusion and drowning (Gilbert and Gofton 1982; Nehashi *et al.* 2001). At present, the interpretation of responses to inhalation of strongly hypercapnic gases as reflecting the unpleasantness of breathlessness *per se* may be confounded by the experience of unpleasant sensations other than dyspnoea, e.g. airway/eye irritation, aversive taste/smell (Hawkins *et al.* 2006; Niel and Weary 2007). However, animals, like humans, also appear to avoid engaging in behaviours that trigger or exacerbate dyspnoeic sensations, probably because they are unpleasant, e.g. reduced exercise tolerance in dogs and humans with chronic obstructive airway conditions (O'Donnell *et al.* 2009; Packer *et al.* 2012).

Brain imaging studies in humans, along with electrophysiological and gene expression studies in non-human mammals, support the behavioural evidence (reviewed by Buchanan and Richerson 2009; Davenport and Vovk 2009; Evans 2010). In humans, stimuli associated with at least two qualities of breathlessness – air hunger and respiratory effort (loaded breathing) – activate similar cortico-limbic regions to those activated by other interoceptor-elicited sensations such as thirst, hunger and pain, i.e. the anterior insular cortex, cingulate gyrus and amygdala (Banzett *et al.* 2000; Peiffer *et al.* 2001; Evans *et al.* 2002; von Leupoldt *et al.* 2008). These regions are known to play an important role in generating the immediate sensation of unpleasantness associated with sensory inputs and, in humans, are part of the systems that motivate actions designed to rectify the cause of the sensation (Davenport and Vovk 2009). Thus, various lines of evidence support the notion that non-human mammals experience A1 unpleasantness associated with altered respiratory function.

Multiple qualities of breathlessness

At least three different qualities of breathlessness are currently recognised in the medical literature. They are respiratory effort, air hunger and chest tightness. Each of these is described differently by human subjects, can be varied independently with physiological interventions, is sub-served by a distinct afferent pathway, and likely causes a different pattern of activation in the forebrain, i.e. the cortex and limbic system (reviewed by Davenport and Vovk 2009; Lansing *et al.* 2009; Evans 2010).

In human ill health, breathlessness is usually studied in relation to various cardiopulmonary diseases in which two or more qualities of breathlessness often occur and increase together (Schwartzstein and Adams 2010). In non-human mammals, however, there may be more situations in which a single quality of breathlessness is manifest, e.g. air hunger due to killing by asphyxia or drowning. In addition, one such quality may replace another if the stimulus to breathlessness is not mitigated, if it intensifies or if it is combined with other stimuli (see the section on Interplay). As is described below, different qualities of breathlessness vary in terms of their unpleasantness (Banzett *et al.* 2008). Thus, it will be informative from an animal welfare perspective to make distinctions among qualities and to have a clear understanding of the likely affective implications of each quality.

Control of respiration

Central command

The respiratory system is unusual in that it is under both automatic/brainstem and voluntary/cortical motor control (Corfield *et al.* 1998). Automatic or reflex control of breathing is due to the collective activity of various nuclei in the medulla. These brainstem respiratory centres stimulate pools of inspiratory motor neurons, which, in turn, influence the frequency, strength and timing of contractions of the respiratory muscles. The activity of these medullary centres is sufficient to generate the normal spontaneous rhythm of breathing (Bianchi *et al.* 1995). However, their activity, and therefore the pattern of breathing, is influenced by afferent inputs of four major types: (1) inputs from central and peripheral chemoreceptors responding to the partial pressures of oxygen and carbon dioxide, the acid/base balance and many other factors in arterial blood and cerebrospinal fluid; (2) respiratory afferent feedback (see below); (3) inputs from working locomotor muscles; and (4) afferents from various higher brain centres (Buchanan and Richerson 2009; Jensen *et al.* 2009; Widdicombe 2009). Voluntary control of breathing depends on efferent signals from the primary motor cortex and is involved in activities that interrupt the normal rhythm of breathing such as vocalisation and breath-holding, as well as controlling ventilation during increased exertion (el-Manshawi *et al.* 1986; Gandevia 1987; Jensen *et al.* 2009).

Afferent feedback from respiratory structures

Afferent feedback that signals the response of the respiratory apparatus to central motor command is integral to both the control of breathing and the conscious awareness of respiratory sensations (Figure 1). Information from a variety of receptors in the airways, lungs, respiratory muscles and chest wall is transmitted to the cortex and limbic structures and thereby plays a key role in generating or modulating sensations of breathlessness (Widdicombe 2009; Parshall *et al.* 2012). The effect of respiratory afferent feedback on the quality and intensity of breathlessness depends on which receptors are stimulated, or in some cases not stimulated, and how strongly, and on the source of central motor command to which respiratory response is compared, i.e. automatic or voluntary (Manning and Schwartzstein 1995).

Conscious awareness of respiratory sensations

During normal breathing at rest, we are not usually aware of sensations relating to ventilation. However, when respiration is stimulated, challenged, obstructed or attended to, we may become conscious of our breathing (Davenport and Vovk 2009). This conscious awareness of respiratory sensations arises when afferent inputs ascend to the cerebral cortex. It is important to our consideration of breathlessness in non-human mammals to recognise that much of the data informing current understanding of the underlying neurophysiology come from studies of rodents, cats and other mammalian species (see, e.g. Buchanan and Richerson 2009; Davenport and Vovk 2009; Evans 2010 and references contained therein). Figure 1 shows a simplified depiction of the mechanisms underlying the three most commonly recognised qualities of breathlessness as they are currently understood in human medicine.

The intensities of both unpleasant respiratory effort and air hunger appear to be proportional to the mismatch between respiratory motor command and afferent signals reflecting ventilatory response. This is summed up well by Manning and Schwartzstein (1995): "Under a given set of conditions, the brain "expects" a certain pattern of ventilation and associated afferent feedback, and deviations from this pattern cause or intensify the sensation of dyspnoea". Tightness appears to relate specifically to constriction of the airways and therefore relies only on respiratory afferent feedback.

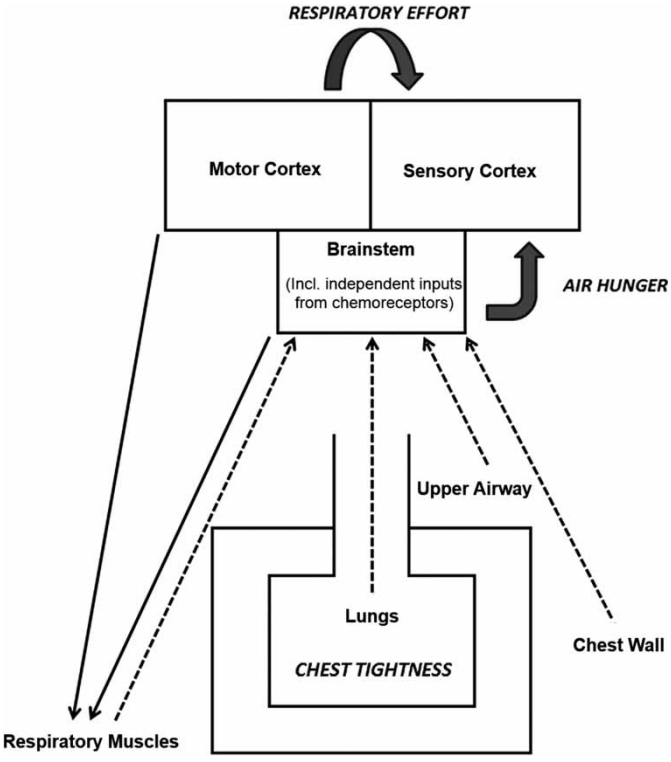

Figure 1. A simplified representation of the neurophysiological mechanisms underlying the three most commonly recognised qualities of breathlessness as they are currently understood in human medicine: respiratory effort, air hunger, chest tightness. Solid arrows indicate motor output to respiratory muscles, dashed arrows indicate afferent feedback, block arrows indicate corollary discharge of motor output. Afferent feedback from various structures projects to the sensory cortex via the brainstem. Modified from Manning and Mahler (2001).

Respiratory effort

Respiratory effort is defined as the conscious awareness of the respiratory muscle force required to achieve the necessary or desired ventilation (Gandevia 1987; Parshall *et al.* 2012). This sensation is described in terms of the work, effort or heaviness of breathing (Jensen *et al.* 2009). A sensation of increased effort occurs whenever voluntary motor command to the respiratory muscles must be increased to achieve the necessary level of ventilation. This occurs in two particular situations. First, when there is an increase in the depth and frequency of breathing during normal exertion, and second, when the motor command needed to elicit a given level of ventilation is greater than normal, such as occurs in many pathological states (el-Manshawi *et al.* 1986; Manning and Schwartzstein 1995; O'Donnell *et al.* 2009). The unpleasantness of respiratory effort experienced in each case may differ (e.g. O'Donnell *et al.* 2009).

Normal exertion

During sub-maximal exertion in healthy humans, the intensity of perceived effort is proportional to the increase in rate and depth of breathing, measured as minute ventilation in L/min (el-Manshawi *et al.* 1986). As long as the ventilatory response is appropriately matched to cortical motor command, this sensation is not inherently unpleasant in healthy subjects (Banzett *et al.* 2008; Jensen *et al.* 2009; O'Donnell *et al.* 2009).

When exercise begins, voluntary motor command from the primary motor cortex to the locomotor muscles may also be copied to the brainstem respiratory centres to increase ventilation. As well as sending parallel output to the brainstem, the motor cortex likely also sends a copy of its output to the somatosensory cortex (Figure 1); this corollary discharge mechanism facilitates conscious awareness of the increased effort of muscles, including the respiratory muscles, required during exercise (Gandevia 1987; Jensen *et al.* 2009). The perception of respiratory effort is also informed by afferent feedback from various receptors in the respiratory apparatus. Muscle spindles, Golgi tendon organs and metaboreceptors in the diaphragmatic, intercostal and abdominal muscles provide information on the length and tension generated by muscle contraction and muscle metabolic status (Gandevia 1987; Zhang and Davenport 2003). These sensory afferents ascend to the somatosensory cortex and other forebrain regions and their combined input is compared to outgoing voluntary motor command to assess its effectiveness in producing the necessary respiratory response (Gandevia 1987).

After the initial phase of exercise, automatic drive to breathe may be enhanced by increased activation of peripheral chemoreceptors and muscle metaboreceptors (Prabhakar and Peng 2004; Lindinger and Heigenhauser 2012) (see Air Hunger for details). As exercise intensity approaches the aerobic threshold, the stimuli to automatic breathing increase markedly, minute ventilation rises steeply with increasing work rate and respiratory effort becomes increasingly intense (O'Donnell *et al.* 2009; Lindinger and Heigenhauser 2012). If a mismatch between total central command (sum of voluntary and automatic) and respiratory response develops during normal exertion, a different quality of breathlessness may arise, i.e. air hunger (O'Donnell *et al.* 2009) (see below).

Mismatched voluntary motor command and respiratory muscle response.

An unpleasant sensation of increased effort can occur when the response of the ventilatory apparatus, in particular the respiratory muscles, is smaller than expected at a given level of motor command (Jensen *et al.* 2009; O'Donnell *et al.* 2009). This can

arise because the respiratory muscles must generate greater airway pressure, e.g. to overcome mechanical loading, or when the maximum pressure-generating capacity of the respiratory system is diminished (Manning and Mahler 2001; O'Donnell *et al.* 2009).

Mechanical loading is increased by resistance to air flow, as occurs in many obstructed airway conditions as well as asthma, loss of elasticity in lung and chest wall structures (decreased compliance), and externally applied restrictions to thoracic movement (Manning and Schwartzstein 1995; O'Donnell *et al.* 2009). Maximal pressure-generating capacity is reduced when the respiratory muscles are fatigued or otherwise weakened, or when they are placed at a length disadvantageous for contraction, or when the flow of efferent signals to the respiratory muscles is compromised (Table 1), e.g. by paralysis, or neurological or

Table 1. Examples of pathological and other conditions that may impair respiratory function or afferent feedback about respiratory function in humans and other mammals[a].

Type of impairment	Conditions	Potential examples relevant to animal welfare
Decreased respiratory muscle function	Neuromuscular or neurological disease or injury	Motor neuron disease, myasthenia gravis, muscular dystrophies, myopathies, polyneuropathies, high spinal injury
	Muscle fatigue or weakness	Metabolic exhaustion, severe under-nutrition, metabolic disorders, infectious disease, prolonged hyperventilation, drugs
	Thoracic or abdominal pain or injury	Road accidents, back-snap traps, handling, yarding, transport, rodeo, racing, steeplechase, show jumping, predation
	Factors leading to early onset metabolic acidosis during exercise	Muscle deconditioning, obesity, old age, reduced perfusion, metabolic disorders
	Tissue hypoxia	Breathing hypoxic gases, anaemia, haemoglobin dysfunction/competitive binding, inadequate gas exchange during exercise with cardiopulmonary disease, circulatory impairment
	Respiratory muscle paralysis caused by natural or artificial toxins	Pest poisoning, research, poisonous plants, snake/spider bites, chemical warfare
Increased resistive loading	Airway narrowing due to:	
	Chronic inflammation and tissue remodelling	Chronic bronchitis, asthma/allergic bronchitis
	Conformational defects or exercise-induced injuries	Brachycephalic obstructive airway syndrome in cats/dogs, laryngeal hemiplegia in dogs/horses, pulmonary haemorrhage in race horses
	Respiratory muscles placed at length disadvantageous for contraction	Dynamic lung hyperinflation due to chronic airway obstruction (emphysema), abdominal distension due to late pregnancy, obesity, ascites, bloat in ruminants
Increased external loading	Tight strapping around thorax	Saddle girths, research equipment
	Overlying/overcrowding	Large litters, transport, high density in yards/pens
Acute airway occlusion	Drowning	Killing unwanted animals, underwater trapping of furbearers, marine mammals tangled in nets
	Asphyxia	Suffocation, strangulation, neck-hold/noose traps, physiological research
Decreased lung/chest wall compliance	Acute or chronic pulmonary disease	Interstitial lung disease (e.g. pneumonia) and sequelae (e.g. fibrosis) Pleural space disease Emphysema Obesity Kyphosis/scoliosis Thoracic neoplasm Pulmonary damage e.g. gas fumigants, mechanical ventilation, research-induced, toxins
Reduced feedback from respiratory afferents	Neurological disease affecting sensory nerves	Sensory neuropathies, high spinal injury
	Neuro-inhibitory substances used in research	
Mechanical ventilation inadequate to meet ventilatory drive		Mainly research

[a]Based on information from Manning *et al.* 1992; Manning and Schwartzstein 1995; Ludders *et al.* 1999; O'Donnell *et al.* 2000; Manning and Mahler 2001; Iossa *et al.* 2007; Johnson and Martin 2008; Leduc *et al.* 2008; Mellema 2008; Jensen *et al.* 2009; Lansing *et al.* 2009; O'Donnell *et al.* 2009; Bannasch *et al.* 2010; Tomczak *et al.* 2011; Hoareau *et al.* 2012; Lindinger and Heigenhauser 2012; Manens *et al.* 2012; Parshall *et al.* 2012.

neuromuscular disease (el-Manshawi *et al.* 1986; Manning and Mahler 2001; Jensen *et al.* 2009).

In humans with any of these conditions, increased effort is perceived at lower levels of exertion and minute ventilation than in healthy subjects, or even at rest, and effort becomes severe more rapidly with increasing exertion/ventilation (el-Manshawi *et al.* 1986; Jensen *et al.* 2009; O'Donnell *et al.* 2009). Increased effort due to impaired respiratory function is immediately unpleasant in humans, as evidenced by activation of limbic structures (reviewed by Davenport and Vovk 2009).

Air hunger

Air hunger is the sensation experienced at the end of a long breath hold. It is often described as "increased urge to breathe", "shortness of breath", "needing more air", "unsatisfied inspiration", "smothering" or "suffocating" (Schwartzstein and Adams 2010; Parshall *et al.* 2012). It is always reported to be unpleasant, and even moderate air hunger is more unpleasant than maximal respiratory effort (Banzett *et al.* 2008).

Air hunger arises primarily from a mismatch between automatic motor command and the degree of lung inflation, i.e. tidal volume (Banzett *et al.* 1990; Lansing *et al.* 2009; O'Donnell *et al.* 2009). The automatic drive to breathe is increased by any condition that raises arterial carbon dioxide tension (hypercapnia/respiratory acidosis), reduces arterial oxygen tension (hypoxaemia) or causes a systemic metabolic acidosis (Lindinger and Heigenhauser 2012). Table 2 outlines general situations in which each stimulus can occur and provides specific examples that are relevant to animal welfare. In addition, other stimuli such as hypotension, hyperthermia and altered plasma osmolality may contribute to automatic drive (Kumar and Prabhakar 2012; Lindinger and Heigenhauser 2012).

Such changes are detected by central and peripheral chemoreceptors and stimulate increased activity in brainstem respiratory

Table 2. Stimuli that increase automatic command to breathe, general situations in which each stimulus can occur, and specific examples of each of relevance to animal welfare.[a] Hypercapnia refers to a rise in arterial carbon dioxide tension. Hypoxaemia refers to a drop in arterial oxygen tension. Metabolic acidosis refers to a drop in arterial pH. Ketoacidosis occurs due to high rates of fat oxidation when inadequate carbohydrate substrates are available to cells.

Stimulus	Situation	Examples
Hypercapnia/respiratory acidosis	Inhalation of gas mixtures containing high CO_2 tension	Routine stunning or killing of pigs for food production, farmed fur-bearers, rodents in research, unwanted cats and dogs
		Ventilator malfunction in indoor housing systems
		Emergency killing of some production species for disease control
	Impaired ventilation-perfusion matching in lungs	Various cardiopulmonary diseases
		Other conditions that impair breathing, alveolar diffusion and/or perfusion
Hypoxaemia	Inhalation of gas mixtures containing low O_2 tension	As above for inhalation of hypercapnic gases
	Impaired ventilation-perfusion matching in lungs	As above for hypercapnia
Metabolic acidosis	Lactacidosis	
	Insufficient oxygen to support cellular aerobic metabolism	Heavy exercise
		Significant hypoxaemia
		Impaired circulation
		Impaired haemoglobin function due to anaemia, competitive binding of haemoglobin (e.g. carbon monoxide, other toxins)
	Cells unable to use available oxygen	Cyanide poisoning
		Mitochondrial disorders
	Ketoacidosis	Uncontrolled diabetes mellitus
		Silage/grain (butyric acid) toxicosis in ruminants
		Severe under-nutrition and/or high metabolic demands (e.g. multiple pregnancies in sheep or high milk production in dairy cows)
		Note: Exercise or obesity may exacerbate ketoacidosis
	Ion imbalances	Renal failure
		Metabolic diseases (e.g. hypocalcaemia)
		Endocrine diseases (e.g. hypoadrenocorticism)
		Loss of bicarbonate and sodium ions due to severe diarrhoea (e.g. scouring calves or piglets)

[a]Based on information from Anonymous 1993; 1997; Sherwood *et al.* 2005; Biondo and De Morais 2008; Bruss 2008; Schenck and Chew 2008; De Morais and Dibartola 2009; Foster and Smith 2009; Anonymous 2010; Lindinger and Heigenhauser 2012; Anonymous 2013.

nuclei, which alter their efferent output to respiratory muscles. In addition, during exercise, information about the metabolic activity of working skeletal muscles is sensed by metaboreceptors and transmitted to the medullary respiratory centre to influence ventilation (Jensen *et al.* 2009; Lindinger and Heigenhauser 2012). Both corollary discharge of brainstem respiratory neurons and direct inputs from chemoreceptors to the cortex and limbic system subserve conscious perception of this increased chemical drive to breathe (Buchanan and Richerson 2009) (Figure 1).

Afferent signals produced by the motion of the lungs and chest wall during breathing inform the cortex of the appropriateness of the ventilatory response to heightened automatic command (Schwartzstein *et al.* 1989). In healthy subjects, mild or moderate air hunger can usually be relieved by an appropriate increase in ventilation, which is signalled by afferent feedback from respiratory structures. In particular, increased activity of slowly adapting pulmonary stretch receptors, which detect lung inflation, relieves air hunger (Widdicombe 2009). On the other hand, decreased input from these receptors when tidal volume is restricted leads to more intense air hunger at a given chemical drive (Manning *et al.* 1992). In addition, the activity of mechanoreceptors in respiratory muscles and chest wall and various airway receptors may influence air hunger (Widdicombe 2009).

Thus, air hunger occurs when there is a mismatch between automatic command and the ventilatory response to that command, and the greater the mismatch, the more intense is the sensation (Parshall *et al.* 2012). The ventilatory response may be insufficient for two reasons: (1) because command exceeds the normal functional respiratory capacity, as may occur during continuous inhalation of high tensions of carbon dioxide or, occasionally, exercise above the aerobic threshold (Adams *et al.* 1985), or (2) because respiratory function, in particular tidal volume, is restricted so that even normal command cannot be satisfied (Banzett *et al.* 1990; Manning *et al.* 1992; Tomczak *et al.* 2011). The mismatch, and therefore air hunger, is more intense when increased command and restricted tidal volume occur simultaneously (Schwartzstein *et al.* 1989; O'Donnell *et al.* 2000), as is common in many cardiopulmonary diseases (O'Donnell *et al.* 2009; Schwartzstein and Adams 2010; Parshall *et al.* 2012). More detail on these conditions and other situations that can lead to restricted tidal volume are discussed in the section on Interplay, below.

Chest tightness

Tightness appears to relate specifically to bronchoconstriction, which occurs in inflammatory airway diseases such as asthma (Widdicombe 2009; Parshall *et al.* 2012) or allergic bronchitis (Johnson and Martin 2008; Reinero 2011). Tightness has been suggested to reflect afferent input from irritant receptors in the airways and lungs ascending to the cerebral cortex. Activation of airway and lung C fibres by inflammatory substances leads to both parasympathetically controlled airway constriction and the sensation of tightness (Undem and Nassenstein 2009). This is usually the first symptom described during an asthma attack, and often progresses to increased respiratory effort which is required to overcome airflow resistance, and because lung hyperinflation due to trapped air puts inspiratory muscles at a mechanical disadvantage (Manning and Schwartzstein 1995). Air hunger may occur if tidal volume is restricted by this process and/or if gas exchange is impaired.

Interplay among stimuli to breathlessness

While the different qualities of breathlessness may occur individually, interactions among various factors may lead to more intensely unpleasant sensations and/or to the simultaneous experience of multiple qualities of breathlessness. Several examples are presented below to illustrate how combinations of increased command and restricted response interact, leading to sensations with greater potential to impact negatively on animal welfare. Clearly, many other combinations of individual factors are possible, and readers are encouraged to consider them independently of this review using examples in Table 1 as a guide.

Increased automatic drive and impaired respiratory response intensify air hunger

As noted above, any factor that impairs respiratory function will intensify air hunger at a given level of automatic drive (Schwartzstein *et al.* 1989; O'Donnell *et al.* 2009; Parshall *et al.* 2012). In practice, this means that any animal with impaired respiratory function, in particular, reduced tidal volume, will experience more intense air hunger when exposed to gases resulting in hypercapnia or hypoxaemia, during metabolic acidosis or perhaps when hyperventilation is automatically driven by other stimuli such as hyperthermia. In addition, the intensity of work/exercise that can be achieved without air hunger may be diminished (see below). Respiratory function can be impaired by numerous pathological conditions as well as by other externally induced conditions (Table 1).

Annually, many millions of mammals are deliberately drowned or asphyxiated for the purposes of pest control, harvesting of fur, or to eliminate unwanted individuals, and others die this way accidentally (see Table 1 for examples) (Iossa *et al.* 2007). During both drowning and asphyxia, airflow is occluded and thoracic volume expansion is impossible. Pulmonary gas exchange stops and carbon dioxide and oxygen tensions equilibrate between blood and static air (or water) in the lungs (Ludders *et al.* 1999). Cellular metabolism continues, first using up the available oxygen and producing an accumulation of carbon dioxide; progressive hypoxaemia and hypercapnia will stimulate automatic drive to breathe. As oxygen is depleted, cells switch to glycolysis which generates a lactacidosis, further enhancing drive to breathe. The complete lack of afferent feedback from pulmonary stretch receptors, superimposed on rapidly rising automatic drive to breathe will produce severe air hunger before loss of consciousness (Ludders *et al.* 1999).

Altered respiratory mechanics can cause unpleasant respiratory effort and air hunger during exertion

During exertion in healthy humans, ventilatory response is usually sufficient to meet the combined voluntary and automatic drives to breathe, and increased respiratory effort is not reported to be unduly unpleasant even at high exercise intensities (Jensen *et al.* 2009). However, any factor that impairs respiratory mechanics will increase the effort of breathing, especially during exertion. Various cardiopulmonary, neurological and neuromuscular diseases, as well as conformational defects, exercise-induced injuries and management-related conditions, increase the voluntary motor drive required to overcome mechanical loading or to otherwise bring about adequate respiratory muscle contraction (Table 1). Of interest, in humans, pregnancy, obesity and old age also affect respiratory mechanics and increase the sense of breathing effort at a given level of exertion (Jensen *et al.* 2009; Lindinger and Heigenhauser 2012).

It is conceivable that similar effects could occur in non-human mammals (e.g. Manens *et al.* 2012), as could specific conditions such as ascites (Leduc *et al.* 2008) and ruminant bloat.

In terms of animal welfare, yarding, mustering, riding, racing, driving or exercising animals with any condition that impairs ventilatory capacity may cause an unpleasant sense of effort. Brachycephalic obstructive airway syndrome illustrates how impaired ventilation can lead to unpleasant respiratory effort and, perhaps, air hunger during exertion in animals. Brachycephalia refers to the shortened muzzle phenotype of some dog and cat breeds (Schlueter *et al.* 2009; Packer *et al.* 2012). This condition results from a mutation that shortens the muzzle bones of the cranium without reduction of the associated soft tissues of the nasopharynx (Bannasch *et al.* 2010). Essentially, these animals have too much soft tissue compressed inside a too-small cranium, which obstructs the upper airways and causes turbulent airflow (Hoareau *et al.* 2012).

In order to overcome the increased resistance to airflow in the upper airways of such animals, greater negative pressure must be generated using the inspiratory muscles, leading to the perception of increased respiratory effort (Bernaerts *et al.* 2010). Complicating this primary response, chronically increased negative pressure creates widespread inflammation, oedema, and airway tissue remodelling, which can further exacerbate airflow resistance (Fasanella *et al.* 2010). Some studies also suggest pathological changes occur in lower airway and lung structures, including alveolar and pulmonary capillary damage which can reduce gas exchange efficiency, and fibrosis of the elastic tissues leading to reduced pulmonary compliance (elastic recoil) (Bernaerts *et al.* 2010; Hoareau *et al.* 2012). In humans, severe mechanical constraints on respiratory muscles can limit tidal volume, leading to air hunger independent of increased chemical drive to breathe due to impaired gas exchange (O'Donnell *et al.* 2009).

The effects of airway obstruction on inspiratory effort are magnified by any stimulus that increases voluntary or automatic drive to breathe, e.g. exertion, hyperthermia and stress. Because of the dramatic increase in respiratory effort during exertion, many brachycephalic dogs are exercise-intolerant, and even mild exercise can result in fainting and cyanosis in severely affected animals (Riecks *et al.* 2007). In fact, there is new evidence that severely affected dogs, particularly bulldogs, experience chronic hypercapnia and hypoxaemia, even at rest (Hoareau *et al.* 2012). It is likely that these dogs are hypoventilating relative to respiratory demand, especially during exertion, partly because they are unable to overcome extreme airflow resistance, coupled with chronic respiratory muscle fatigue (Hoareau *et al.* 2012).

Therefore, brachycephalia predisposes animals to experience severe and unpleasant respiratory effort, and, if tidal volume is limited in the face of increased automatic drive, they would also experience air hunger. Such experiences will develop at much lower exercise intensities than in healthy animals, or even at rest in severe cases. Likewise, increased respiratory effort and early onset air hunger are reported to occur during exertion by humans with chronic interstitial and obstructive pulmonary diseases (O'Donnell *et al.* 2009).

Conclusions

Breathlessness is a negative affective experience relating to respiration. Breathlessness is multi-dimensional and comprises at least three qualitatively distinct sensations: air hunger, respiratory effort and chest tightness. Air hunger is reported to be the most unpleasant sensation and probably has the greatest potential to compromise animal welfare. While these qualities have different neurophysiological bases, each occurs in a variety of conditions and situations, and in reality, multiple qualities are experienced simultaneously or in succession. The many possible combinations of factors that increase ventilatory drive and impair respiratory function, leading to breathlessness, indicate a significant potential for it to compromise the welfare of mammals. Matters of particular concern considered above include drowning/asphyxia, brachycephalic obstructive airway syndrome and killing of animals with impaired respiratory function using gases causing hypercapnia or hypoxia. However, wider ranging evaluations are merited, and species differences should be explored. Accordingly, using as a basis the understanding provided here, we encourage animal welfare scientists, veterinarians, laboratory scientists, regulatory bodies and others involved in evaluations of animal welfare to consider whether or not breathlessness contributes to any compromise they may observe or wish to avoid or mitigate.

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References

Adams L, Lane R, Shea SA, Cockcroft A, Guz A. Breathlessness during different forms of ventilatory stimulation: a study of mechanisms in normal subjects and respiratory patients. *Clinical Science* 69, 663–72, 1985

Anonymous. EC (European Community) Directive 93/119/EC on the protection of animals at the time of slaughter or killing. *European Community Official Journal* 340, 21–34, 1993

Anonymous. *The humane killing of animals under Schedule 1 to the Animals (Scientific Procedures) Act 1986 Code of Practice*. United Kingdom Home Office, Norwich, UK, 1997

Anonymous. *Canadian Council on Animal Care Guidelines on: Euthanasia of animals used in science*. Ottawa, Ontario, Canada, 2010

Anonymous. *American Veterinary Medical Association Guidelines for the Euthanasia of Animals*. Schaumberg, Illinois, 2013

Bannasch D, Young A, Myers J, Truve K, Dickinson P, Gregg J, Davis R, Bongcam-Rudloff E, Webster MT, Lindblad-Toh K, *et al.* Localization of canine brachycephaly using an across breed mapping approach. *PLoS One* 5, e9632, 2010

Banzett RB, Lancaster J, Brown R, Topulos GP, Yager D, Steele SM, Londofio B, Loring SH, Reid MB, Adams L, *et al.* 'Air hunger' from increased PCO_2 persists after complete neuromuscular block in humans. *Respiration Physiology* 81, 1–18, 1990

Banzett RB, Mulnier HE, Murphy K, Rosen SD, Wise RJS, Adams L. Breathlessness in humans activates insular cortex. *Neuroreport* 11, 2117–20, 2000

Banzett RB, Pedersen SH, Schwartzstein RM, Lansing RW. The affective dimension of laboratory dyspnea: Air hunger is more unpleasant than work/effort. *American Journal of Respiratory and Critical Care Medicine* 177, 1384–90, 2008

Bernaerts F, Talavera J, Leemans J, Hamaide A, Claeys S, Kirschvink N, Clercx C. Description of original endoscopic findings and respiratory functional assessment using barometric whole-body plethysmography in dogs suffering from brachycephalic airway obstruction syndrome. *The Veterinary Journal* 183, 95–102, 2010

Bianchi AL, Denavit-Saubie M, Champagnat J. Central control of breathing in mammals: Neuronal circuitry, membrane properties, and neurotransmitters. *Physiological Reviews* 75, 1–45, 1995

Biondo AW, De Morais HA. Chloride: A quick reference. *Veterinary Clinics: Small Animal Practice* 38, 459–65, 2008

***Bruss M**. Lipids and ketones. In: Kaneko J, Harvey JW, Bruss ML (eds). *Clinical Biochemistry of Domestic Animals*. Pp 81–115. Academic Press, Boston, USA, 2008

Buchanan GF, Richerson GB. Role of chemoreceptors in mediating dyspnea. *Respiratory Physiology and Neurobiology* 167, 9–19, 2009

Corfield DR, Murphy K, Guz A. Does the motor cortical control of the diaphragm 'bypass' the brain stem respiratory centres in man?. *Respiration Physiology* 114, 109–17, 1998

Dalmau A, Rodriguez P, Llonch P, Velarde A. Stunning pigs with different gas mixtures: aversion in pigs. *Animal Welfare* 19, 325–33, 2010

Davenport PW, Vovk A. Cortical and subcortical central neural pathways in respiratory sensations. *Respiratory Physiology and Neurobiology* 167, 72–86, 2009

***De Morais HA, Dibartola SP**. Acid-base disorders. In: Bonagura JD (eds). *Kirk's Current Veterinary Therapy 14*. Pp 54–61. Saunders Elsevier, St. Louis, USA, 2009

Denton DA, McKinley MJ, Farrell M, Egan GF. The role of primordial emotions in the evolutionary origin of consciousness. *Consciousness and Cognition* 18, 500–14, 2009

el-Manshawi A, Killian KJ, Summers E, Jones NL. Breathlessness during exercise with and without resistive loading. *Journal of Applied Physiology* 61, 896–905, 1986

Evans KC. Cortico-limbic circuitry and the airways: Insights from functional neuroimaging of respiratory afferents and efferents. *Biological Psychology* 84, 13–25, 2010

Evans KC, Banzett RB, Adams L, McKay L, Frackowiak RS, Corfield DR. BOLD fMRI identified limbic, paralimbic, and cerebellar activation during air hunger. *Journal of Neurophysiology* 88, 1500–11, 2002

Fasanella FJ, Shively JM, Wardlaw JL, Givaruangsawat S. Brachycephalic airway obstructive syndrome in dogs: 90 cases (1991–2008). *Journal of the American Veterinary Medical Association* 237, 1048–51, 2010

Foster DM, Smith GW. Pathophysiology of diarrhea in calves. *Veterinary Clinics of North America: Food Animal Practice* 25, 13–36, 2009

Gandevia SC. Roles for perceived voluntary motor commands in motor control. *Trends in Neurosciences* 10, 81–5, 1987

Gilbert FF, Gofton N. Terminal dives in mink, muskrat and beaver. *Physiology and Behavior* 28, 835–40, 1982

***Hawkins P, Playle L, Golledge HDR, Leach M, Banzett RB, Coenen AML, Cooper JJ, Danneman P, Flecknell PA, Kirkden RD,** *et al. CO_2 consensus report*. University of Newcastle on Tyne, UK, 2006

Hoareau GL, Jourdan G, Mellema M, Verwaerde P. Evaluation of arterial blood gases and arterial blood pressures in brachycephalic dogs. *Journal of Veterinary Internal Medicine* 26, 897–904, 2012

Iossa G, Soulsbury CD, Harris S. Mammal trapping: a review of animal welfare standards of killing and restraining traps. *Animal Welfare* 16, 335–52, 2007

Jensen D, Ofir D, O'Donnell DE. Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans. *Respiratory Physiology and Neurobiology* 167, 87–100, 2009

Johnson MS, Martin M. Investigation of dyspnoea in dogs. *In Practice* 30, 558–66, 2008

Kumar GK, Prabhakar NR. Peripheral chemoreceptors: Function and plasticity of the carotid body. *Comprehensive Physiology* 2, 141–219, 2012

Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: Review and hypotheses. *Respiratory Physiology and Neurobiology* 167, 53–60, 2009

Leduc D, Cappello M, Gevenois PA, De Troyer A. Mechanics of the canine diaphragm in ascites: a CT study. *Journal of Applied Physiology* 104, 423–8, 2008

von Leupoldt A, Sommer T, Kegat S, Baumann HJ, Klose H, Dahme B, Buchel C. The unpleasantness of perceived dyspnea is processed in the anterior insula and amygdala. *American Journal of Respiratory and Critical Care Medicine* 177, 1026–32, 2008

Lindinger MI, Heigenhauser GJF. Effects of gas exchange on acid-base balance. *Comprehensive Physiology* 2, 2203–54, 2012

Ludders JW, Schmidt RH, Dein FJ, Klein PN. Drowning is not euthanasia. *Wildlife Society Bulletin* 27, 666–70, 1999

Manens J, Bolognin M, Bernaerts F, Diez M, Kirschvink N, Clercx C. Effects of obesity on lung function and airway reactivity in healthy dogs. *The Veterinary Journal* 193, 217–21, 2012

Manning HL, Mahler DA. Pathophysiology of dyspnea. *Monaldi Archives for Chest Disease* 56, 325–30, 2001

Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. *The New England Journal of Medicine* 333, 1547–53, 1995

Manning HL, Shea SA, Schwartzstein RM, Lansing RW, Brown R, Banzett RB. Reduced tidal volume increases 'air hunger' at fixed PCO_2 in ventilated quadriplegics. *Respiration Physiology* 90, 19–30, 1992

Mellema MS. The neurophysiology of dyspnea. *Journal of Veterinary Emergency and Critical Care* 18, 561–71, 2008

Nehashi S, Nishino T, Ide T. Inhaled furosemide inhibits behavioral response to airway occlusion in anesthetized cats. *Anesthesiology* 95, 1234–7, 2001

Niel L, Weary DM. Rats avoid exposure to carbon dioxide and argon. *Applied Animal Behaviour Science* 107, 100–9, 2007

O'Donnell DE, Hong HH, Webb KA. Respiratory sensation during chest wall restriction and dead space loading in exercising men. *Journal of Applied Physiology* 88, 1859–69, 2000

O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. *Respiratory Physiology and Neurobiology* 167, 116–32, 2009

Packer RMA, Hendricks A, Burn CC. Do dog owners perceive the clinical signs related to conformation inherited disorders as 'normal' for the breed? A potential constraint to improving canine welfare. *Animal Welfare* 21, 81–93, 2012

Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, Calverley PM, Gift AG, Harver A, Lareau S, *et al.* An official American thoracic society statement: Update on the mechanisms, assessment, and management of dyspnea. *American Journal of Respiratory and Critical Care Medicine* 185, 435–52, 2012

Peiffer C. Dsypnea and emotion: what can we learn from functional brain imaging?. *American Journal of Respiratory and Critical Care Medicine* 177, 937–9, 2008

Peiffer C, Poline J-B, Thivard L, Aubier M, Samson Y. Neural substrates for the perception of acutely induced dyspnea. *American Journal of Respiratory and Critical Care Medicine* 163, 951–7, 2001

Prabhakar NR, Peng Y-J. Peripheral chemoreceptors in health and disease. *Journal of Applied Physiology* 96, 359–66, 2004

Reinero CR. Advances in the understanding of pathogenesis, and diagnostics and therapeutics for feline allergic asthma. *The Veterinary Record* 190, 28–33, 2011

Riecks TW, Birchard SJ, Stephens JA. Surgical correction of brachycephalic syndrome in dogs: 62 cases (1991–2004). *Journal of the American Veterinary Medical Association* 230, 1324–8, 2007

Schenck PA, Chew DJ. Hypocalcemia: A quick reference. *Veterinary Clinics: Small Animal Practice* 38, 455–8, 2008

Schlueter C, Budras KD, Ludewig E, Mayrhofer E, Koenig HE, Walter A, Oechtering GU. Brachycephalic feline noses. CT and anatomical study of the relationship between head conformation and the nasolacrimal drainage system. *Journal of Feline Medicine and Surgery* 11, 891–900, 2009

***Schwartzstein RM, Adams L**. Dyspnea. In: Mason RJ, Broaddus VC, Martin TR, King TE, Schraufnagel DE, Murray JF, Nadel JA (eds). *Murray and Nadel's Textbook of Respiratory Medicine*. Pp 613–27. Saunders Elsevier, Philadelphia, USA, 2010

Schwartzstein RM, Simon PM, Weiss JW, Fencl V, Weinberger SE. Breathlessness induced by dissociation between ventilation and chemical drive. *American Review of Respiratory Disease* 139, 1231–7, 1989

***Sherwood L, Klandorf H, Yancey P**. *Animal Physiology: From Genes to Organisms*. 1st Edtn. Brooks/Cole, Belmont, California, 2005

Tomczak SE, Guenette JA, Reid WD, McKenzie DC, Sheel AW. Diaphragm fatigue after submaximal exercise with chest wall restriction. *Medicine and Science in Sports and Exercise* 43, 416–24, 2011

Undem BJ, Nassenstein C. Airway nerves and dyspnea associated with inflammatory airway disease. *Respiratory Physiology and Neurobiology* 167, 36–44, 2009

Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain* 68, 157–67, 1996

Widdicombe J. Lung afferent activity: Implications for respiratory sensation. *Respiratory Physiology and Neurobiology* 167, 2–8, 2009

Zhang W, Davenport PW. Activation of thalamic ventroposteriorlateral neurons by phrenic nerve afferents in cats and rats. *Journal of Applied Physiology* 94, 220–6, 2003

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