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THE HUMAN VENTILATORY RESPONSE TO STRESS: RATE OR DEPTH?

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Abstract

Many stressors cause an increase in ventilation in humans. This is predominantly reported as an increase in minute ventilation (\dot{V}_E). But, the same \dot{V}_E can be achieved by a wide variety of changes in the depth (tidal volume, V_T) and number of breaths (respiratory frequency, f_R). This review investigates the impact of stressors including: cold, heat, hypoxia, pain and panic on the contributions of f_R and V_T to \dot{V}_E to see if they differ with different stressors. Where possible we also consider the potential mechanisms that underpin the responses identified, and propose mechanisms by which differences in f_R and V_T are mediated. Our aim being to consider if there is and overall differential control of f_R and V_T that applies in a wide range of conditions. We consider moderating factors, including exercise, sex, intensity and duration of stimuli. For the stressors reviewed, as the stress becomes extreme \dot{V}_E generally becomes increased more by f_R than V_T . We also present some tentative evidence that the pattern of f_R and V_T could provide some useful diagnostic information for a variety of clinical conditions. In the Physiological Society's year of "Making Sense of Stress", this review has wide-ranging implications that are not limited to one discipline, but are integrative and relevant for physiology, psychophysiology, neuroscience and pathophysiology.

INTRODUCTION

It is widely reported that “breathing” or minute ventilation (\dot{V}_E , L.min⁻¹) increases in response to a variety of external and internal stressors. In this context, “stress” is defined as adverse or demanding physiological, pathophysiological or psychological stimuli that perturb the respiratory system. What is much less frequently reported than \dot{V}_E , is *how* \dot{V}_E is increased, in terms of the relative contribution of tidal volume (V_T) and respiratory frequency (fR), and the mechanisms driving these contributions. The increase in \dot{V}_E can constitute *hyperpnoea* (increase in rate and depth of breathing commensurate with metabolic needs and arterial blood gas tensions), *hyperventilation* (increase in ventilation that is greater than that required by metabolic needs or arterial blood gas tensions) or *tachypnoea* (rapid [>20 brths.min⁻¹], shallow breathing). Which of these responses is evoked can, as we shall see, depend on the nature of the stressor.

How \dot{V}_E is increased is important because of the impact it can have on the more critical measure of alveolar ventilation (\dot{V}_A), or the air actually available for gas exchange within the lung; this has consequences for the physiological and biochemical status of the body. \dot{V}_A is not routinely reported, probably because it is more difficult to measure than \dot{V}_E , requiring the measurement or estimation of physiological dead space (V_{Dphys}). Multiplying this by fR ($[V_{Dphys}].fR$) gives “wasted ventilation” (\dot{V}_D) and so, $\dot{V}_A = \dot{V}_E - \dot{V}_D$.

V_{Dphys} is the sum of two separate components of lung volume, the first is the nose, pharynx and conduction airways which do not contribute in gas exchange. This component is often referred to as “anatomical” or “airway” dead space (V_{Danat}) (Murias *et al.* 2014) and is typically 2.2 mL.kg⁻¹ body weight, but is not fixed; varying with posture, breath holding and lung volume (Fowler, 1950; Nunn *et al.* 1959). Simplistically, V_{Danat} is generally assumed to be relatively constant at about 150 mL for a 70 kg an adult human. The second component of V_{Dphys} , called “alveolar V_D ”, consists of alveoli that are either well-ventilated but poorly perfused (e.g. apex of the lung in upright individuals) or well-perfused but poorly ventilated (e.g. as in small airway disease) (Murias *et al.* 2014). This can vary with body size and other more subtle factors.

It follows that if an increase in \dot{V}_E is achieved primarily via V_T , the effect of V_{Dphys} on \dot{V}_A is minimised (Sheel & Romer, 2012). In contrast, if an increase in \dot{V}_E is achieved primarily via fR , the effect of V_{Dphys} on \dot{V}_A is maximised (e.g. panting). An example is given in Table 1 using just V_{Danat} : showing that the same \dot{V}_E can result in a \dot{V}_A ranging between 0 and 6.0 L.min⁻¹.

Table 1. The effects of breathing frequency and tidal volume on alveolar ventilation. (Adapted from Braun, 1990).

Minute ventilation (\dot{V}_E , L.min ⁻¹)	Breathing frequency (fR , brths.min ⁻¹)	Tidal Volume (V_T , L)	Dead space* (\dot{V}_{Danat} , L.min ⁻¹)	Alveolar ventilation (\dot{V}_A , L.min ⁻¹)
7.5	50	0.15	7.5	0
7.5	30	0.25	4.5	3.0
7.5	20	0.375	3.0	4.5
7.5	10	0.75	1.5	6.0

*An anatomical dead space of 150 mL.brth⁻¹ is assumed.

As V_{Dphys} contributes to the work of breathing without contributing to \dot{V}_A , the work of breathing associated with any given \dot{V}_A is relatively increased when \dot{V}_E is achieved by fR rather than V_T . However, because increasing \dot{V}_E via fR has less of an effect on \dot{V}_A it also has less of an effect on alveolar and arterial PCO_2 and, therefore, blood gas homeostasis. The differing impact of \dot{V}_D on the work of breathing and blood gas homeostasis may, in itself, have implications for the respiratory pattern seen in response to differing stressors.

The Breathing Pattern

The breathing pattern is determined by four principle variables (for a review see Younes & Remmers, 1981): 1. Inspiratory-time profile 2. Inspiratory duration 3. Expiratory volume-time profile 4. Expiratory duration (Figure 1). Stressors can affect \dot{V}_E by altering one or more of these variables which, after addition of subtraction, then alter fR and/or V_T . Thus, fR may be increased by a reduction in both, or either, inspiratory and expiratory duration, or a reduction in one that exceeds the prolongation of the other.

INSERT FIGURE 1

Breathing patterns have primarily been examined in an attempt to gain an insight onto the output of the “respiratory centres” (Richter, 1982; Widdicombe & Widding, 1974). In this context, the ventilatory response has been characterised by the combination of V_T and fR ; it has been further separated into mean inspiratory flow (V_T /inspiratory time T_i) and the duty cycle (V_T /total cycle duration) (Clark & von Euler, 1972). Several authors (Pearson & Cunningham, 1973; Miller *et al.* 1974; Gardner, 1974; Bechbache *et al.* 1979) have pointed out that there are differing response times for changes in V_T , T_i and T_E . Cunningham (1974) suggests that the steady state relationships between these variables is not fully re-established for 20 minutes after ventilatory drive is altered, however most of the changes occur within 1-2 minutes.

The V_E measured represents the combination of a neural output and a mechanical response. The neural output and rhythm arise from excitatory inputs from a variety of sources. It may change during an inspiration (“Phasic”, e.g. with increasing lung volume [Hering-Bruer inflation reflex]) or may be impacted upon by a constant stimulus (“Tonic”, e.g. body temperature). The profile of neural output at the beginning of neural inspiration plays a role in determining V_T . In the present review we focus on short-term stress-induced changes in ventilation; this excludes consideration of sleep, which has an impact on the respiratory pattern, and has been reviewed elsewhere (Phillipson, 1978).

From the mechanical perspective, it is generally reported that for a given V_A there is a fR that minimises muscle *work* in relation to ventilation. However, Mead (1960) reported that in humans at rest and exercise the resulting fR is the one which is least costly in terms of *average force*. For a given response, V_T becomes smaller as the resistance or elasticity of the respiratory system increases. V_T is also affected by the lung volume and neural output at the onset of neural inspiration in relation to the absolute lung volume and consequent Functional Residual Capacity at the time (Younes & Remmers, 1981). At high lung volumes mechanical constraints can prevent V_T from increasing further, and when the rate of rise of neural output is high, a relatively short amount of time is allowed for lung volume to decrease; as a consequence mechanical inspiration can begin at a higher absolute volume, limiting V_T and driving

fR . As we shall see, such an inspiratory shift in end-expiratory lung volume following stimulation of respiratory neurons is a feature of the some environmental stressors and helps explain the respiratory response observed.

During sustained increases in ventilation in some pulmonary disease states and in situations where gas density is increased (e.g. hyperbaric environments), the relationship between fR and V_T can be altered to minimise the work of breathing (Dongelmans *et al.* 2011; West, 2012). This review primarily focuses on the initial dynamic response to stressors such as: cold, heat, hypoxia, pain and panic. Given that, from a mechanical perspective, an initial increase in \dot{V}_E via V_T is most efficient, when this response is not observed, factors other than respiratory mechanical efficiency must be taking precedence.

In order to avoid variations caused by respiratory mechanics, mouth occlusion pressure 100 ms after the onset of inspiration against a closed airway has been measured (P0.1). In this period the respiratory muscles should shorten solely in response to output from the respiratory centres in conscious humans (Whitelaw, Derenne & Millic-Emili, 1975; Whitelaw & Derenne, 1993). However, this approach does not avoid the reported impact of the use of respiratory instrumentation on breathing pattern. Mouthpieces and nose-clips have been reported to increase \dot{V}_E , V_T , T_I , T_E , mean inspiratory flow, mean expiratory flow, but decreases fR (Perez & Tobin, 1985).

Exercise

Exposure to environmental stressors often co-exists with exercise; this can mask the nature of the \dot{V}_E response to an environmental stress, which is over-ridden by the metabolic demands of exercise. Additionally, and with time, the heat production associated with exercise increases body temperature which can alter lung function (Tipton *et al.* 2017) and, independently, breathing pattern.

The involvement of central command (that is, the activity of motor and premotor areas of the brain relating to voluntary muscle contractions or “effort-induced modulation of autonomic function” [de Morree *et al.* 2012; Williamson *et al.* 2006]) in the rapid fR response to exercise is supported by the work of Bell & Duffin (2006) who reported an

immediate response of fR but not V_T on commencement and cessation of exercise, and with a change in the mode of exercise. Recent evidence suggests that fR is a valid marker of perceived exertion (RPE) during cycling exercise (Nicolò *et al.* 2014, 2016). RPE and fR also respond in a similar way to muscle fatigue (Marcora *et al.* 2008), muscle damage (Davies *et al.* 2009), hypoxia (Koglin & Kayser, 2013) and increases in body temperature (Hayashi *et al.* 2006), but appear disassociated from V_T (Noble *et al.* 1973; Nicolò *et al.* 2016). The close association between RPE and fR has led to the suggestion that they share a common regulatory mechanism involving central command (Nicolò *et al.*, 2016):

Central command, muscle afferent fibres and metabolic stimuli are major determinants of \dot{V}_E during exercise (Forster *et al.* 2012), but they act with different timings when exercise intensity changes, with metabolic stimuli having a slower time course than the faster inputs of central command and muscle afferents (Duffin, 2014). The fR and V_T responses to exercise are less well studied than the \dot{V}_E response, but there are some intriguing studies involving hypnosis and passive exercise that seem to indicate that fR and V_T are under separate control (Thornton *et al.* 2001; Bell & Duffin, 2006; Nicolò *et al.* 2016), with the suggestion that fR is less, and V_T more determined by metabolic factors. Ohashi *et al.* (2013) provided evidence from studies examining CO_2 homeostasis at rest that suggests that fR can be regulated by non-metabolic factors.

After the initial response to the onset of exercise, and at low work intensities, the ventilatory response is then primarily achieved by an increase in V_T . With increasing intensity (stress), fR is also increased (Sheel & Romer, 2012). During more strenuous exercise, once V_T reaches 50% to 60% of vital capacity, there is a plateau in V_T and further increases in \dot{V}_E are accomplished solely by increases in fR (Fujii *et al.* 2008b; Sheel & Romer, 2012). As mentioned, airway resistance, lung compliance and the work/force requirements of breathing can influence the response to a stressor. In exercise the initial increase in \dot{V}_E by V_T is efficient but is limited by lung compliance at higher V_T where increases in fR become preferable from a mechanical perspective.

The additional rise in \dot{V}_E caused by increases in fR is commonly referred to as the “tachypneic” breathing pattern of heavy exercise and is achieved via reductions in both inspiratory and expiratory time (Sheel & Romer, 2012). In general, the breathing

pattern and interaction of fR and V_T are highly variable between individual athletes during incremental exercise (Carey *et al.* 2008). The mode (running, cycling) and rate of exercise can also influence breathing pattern, with breathing becoming entrained to exercise rhythm in some individuals. Evidence is emerging that respiratory and locomotor rhythms during exercise; so-called “locomotor respiratory coupling” may be responsible (Lunt *et al.* 2011; Sheel & Romer, 2012).

Therefore, the determinants of the ventilatory response to exercise include: (i) a central medullary rhythm generator/integrator; (ii) neural inputs into this integrator from higher locomotor areas of the central nervous system (central command, central chemoreceptors, direct effect of temperature) and from the periphery (chemoreceptors, mechanoreceptor); and (iii) the regulation of the distribution of efferent motor output to the ventilatory muscles (Sheel & Romer, 2012). The interaction between these mechanisms remains largely unknown; evidence suggests that, in the absence of mechanical ventilatory constraints, there is differential regulation of V_T and fR during exercise. It would therefore seem important to consider the fR and V_T responses separately to fully understand the mechanisms underlying exercise hyperpnoea.

The initial response to various stressors includes an increase in the activity of the sympathetic nervous system. This is changed in a global fashion, leading to an increase in cardiovascular function and a release of adrenal catecholamines (Homma & Masaoka, 2008). Since the seminal work of Cannon (Cannon, 1929), the human ventilatory response to external and internal stressors has also been recognised as an important part of the body’s preparation during the “fight or flight” response, the prototypic human response to stress (Jansen *et al.* 1995; Taylor *et al.* 2000). Hyperventilation is often considered part of this response (Van Diest *et al.* 2001), but how this hyperventilation is brought about (fR and/or V_T) has not been thoroughly investigated. The pattern of fR and V_T may also have wider implications than just \dot{V}_A ; it is possible that the pattern itself is indicative of other physiological and pathophysiology pathways and states.

It is concluded that, in conscious humans, a variety of factors influence the pattern of breathing, these include: reflexes evoked by inflation, the level of chemoreflex

stimulation; the time variability of neural mechanisms; the level of consciousness; and the rhythm of body movements during exercise. It is concluded that *how* \dot{V}_E is increased matters. Whilst it is convenient to report only \dot{V}_E , it can be misleading if different stressors cause an increase in \dot{V}_E by different combinations of fR and V_T . Also, important information may be contained in the way \dot{V}_E is increased.

In the present review we examine the breathing pattern in terms of the fR and V_T across a range of stressors examining how that response differs depending on the nature of the stress. A review of this scope has not been undertaken previously. Our aim was to consider if there is an overall differential control of fR and V_T that applies in a wide range of conditions. In addition, if \dot{V}_E is increased by different combinations of fR and V_T the question then becomes, how? Therefore, where possible, we also consider the potential mechanisms that underpin the responses identified.

REVIEW METHODOLOGY

The following stressors were examined: sudden cold exposure and hypothermia, passive and active (involving exercise) hyperthermia, hypoxic exposure, induced pain and panic (triggered by rebreathing CO₂ or external sensory stimuli).

A literature search was undertaken using Medline, Pubmed, and Science Direct search engines to identify studies that reported both fR and V_T in humans following exposure to a stressful environment. Keywords and phrases used included: ['rate' OR 'frequency' OR 'ventilation'] AND ['volume' OR 'depth' OR 'ventilation'] AND ['cold water' OR 'cool water' OR 'hypothermia' OR 'heat' OR 'hot' OR 'hyperthermia' OR 'exercise' OR 'panic' OR 'anxiety' OR 'fear' OR 'pain' OR 'noxious' OR 'altitude' OR 'hypoxia']. The reference lists of relevant articles were searched and experts and colleagues working in the area were contacted regarding the existence of any additional studies suitable for inclusion. The searches were undertaken in August 2015 and no restrictions were made on study design, methodology or method of assessing fR and V_T . There was no blinding to study author, institution or journal at this stage. The methodologies of the reviewed studies were heterogeneous in terms of the: age and sex of participants; clothing and equipment used; and duration and intensity of the stressor.

We have focused on human studies but, in the absence of relevant human data, have included animal models to help determine underlying mechanisms. In terms of mechanistic pathways, as recently reviewed (Dempsey & Smith, 2014) there is no doubt that evidence from animals and animal models of human disease have helped our understanding of the peripheral and central chemoreceptors' input to ventilation, as well as their role in disease states such as heart failure, sleep apnoea and chronic obstructive pulmonary disease. Given this, it is argued that the organisation of peripheral receptors, their central reflex arcs and integration with the central respiratory pattern generator are likely to be similar between animals and humans. Indeed, Hess *et al.* (2013) have identified the pre-Botzinger complex and parafacial regions in the human brainstem and shown inspiratory and expiratory related activity with fMRI. Further evidence of correspondence comes with the role of Phox2b gene in the control of central chemoreception and respiration in humans (Weese-Mayer *et al.* 2003) and animals (Gaultier *et al.* 2004). However, we acknowledge that species differences exist, as with the relative strength of the pulmonary stretch receptors when activated by increases in ventilation brought about by stimulation of the carotid bodies; the dog displays tachycardia and the cat bradycardia; reflecting the predominance of lung inflation versus peripheral chemoreceptor reflexes, respectively. In comparison with humans, in some areas animal responses differ in terms of their magnitude (e.g. the ventilatory patterns to hyperthermia [Robertshaw, 2006]; vagal lung inflation reflexes [Guz *et al.* 1971]), in others they are similar (e.g. respiratory responses to cold water immersion [Datta & Tipton, 2006]).

Where possible, we extracted mean fR and V_T data before, during and after exposure to the various stressors. In some studies data were also extracted from a 'Control' group who were not exposed to the stress being examined. The percentage changes in both fR (x-axis) and V_T (y-axis) from baseline or control values were then calculated and plotted on a scatter graph. For clarity, the stressors are plotted separately and the associated legend and symbols briefly describe the individual data points.

The magnitude or intensity of a stress is likely to have an influence on the nature of the ventilatory response; this magnitude may change with factors such as absolute temperature or oxygen concentrations. It may also change with time due, for example, to increasing cooling, heating or hypoxia. It may also decrease with time such as with

the adaptation of peripheral thermal receptors following a sudden changes in skin temperature. As noted, the co-existence of exercise with environmental stress adds inputs to the breathing pattern compared to those when exposed at rest. We considered these influences (e.g. intensity and duration of stress and co-existent exercise) in our interpretation of the data.

RESULTS: VENTILATORY RESPONSES

Having reviewed the ventilatory response to exercise in the previous section, in the following sections fR and V_T data are examined in the following:

- Sudden or prolonged cold exposure (12 studies; 176 participants)
- Passive and Active hyperthermia (13 studies; 153 participants)
- Hypoxia (10 studies; 290 participants)
- Panic (8 studies; 470 participants)
- Pain (4 studies, 56 participants)

Cold Exposure

Rapid cooling of the skin by immersion in cold water produces the “cold shock” response (Tipton, 1989); this includes an inspiratory gasp, hyperventilation, tachycardia, peripheral vasoconstriction, hypertension, a marked reduction in cerebral blood flow velocity (Barwood *et al.* 2016; Croft *et al.* 2013; Mantoni *et al.* 2007) and increased circulating level of catecholamines (Barwood *et al.* 2014; Heymans *et al.* 1930; Tipton & Golden, 1987).

The cold shock response is evoked by the dynamic response of the peripheral cold thermoreceptors (Tipton, 1989). However, the precise afferent pathways responsible for the respiratory responses to cold-water immersion remain to be elucidated. It has been suggested that thermoafferents from the peripheral cold receptors directly stimulate respiratory networks (Goode *et al.* 1975; Keatinge & Evans, 1961), with the sensitivity of the central chemoreceptors remaining unchanged (Cooper *et al.* 1976). Part of the respiratory response to cold immersion may result from reflex stimulation of spinal networks including α -motorneurons innervating the intercostal muscles and diaphragm (Keatinge & Nadel, 1965). Keatinge & Nadel (1965) concluded that the

reflex respiratory responses to cold water in the cat are also mediated at midbrain level, with the cerebrum not being essential for the response.

Tipton & Harris (in Datta & Tipton, 2006) report that, following 60s upright immersion to the diaphragm of rats in 8° C water, *c-fos* protein immunohistochemistry identified activated neurones in the nucleus tractus solitarius, area postrema and dorsal motor nucleus; areas known to process cardiovascular and respiratory afferents. No expression was observed with immersion in water at 39° C. The areas generating respiratory rhythm (dorsolateral pons [Kölliker-Fuse nucleus], ventrolateral medulla between the facial nucleus and the lateral reticular nucleus) were not examined.

In naked individuals the cold shock response peaks in water between 15-10° C (Tipton *et al.* 1991). Below about 14° C there is increasing activation of cold nociceptors (Simone & Kajander, 1997). Studies have shown noxious cold stimuli (rat hind limb immersion in 4° C water) causes *c-fos* activation of neurons in Lamina I of the spinal dorsal horn (Todd *et al.* 2005), suggesting this ascending pathway is involved in transmitting the thermoreceptor volley following cold immersion to the pons (Hinckel & Schroder-Rosenstock, 1981). The pons has areas controlling eupnoea and apnoea (prolonged inspiration). It (Kölliker-Fuse [KF] nucleus) allows the frequency of breathing to change very quickly. The Hering-Breuer afferents project there and control inspiration off-switching; it is therefore a major regulator of respiratory phase switching (Abdala *et al.* 2016).

In vagotomized animals, eupnoea is transformed to gasping following removal of the pons or during severe hypoxia (Lumsden, 1924; Paton *et al.* 2006; Smith *et al.* 2007), and destruction of neurons in the rostral medulla with neurotoxins leads to the elimination of gasping but not eupnoea (Fung *et al.* 1994); this region was later shown to be in the pre-Bötzinger complex (Paton *et al.* 2006; St-John *et al.* 2009). This suggests that the neural mechanisms for gasping may be distinct from those necessary for the generation of eupnoea. That the first respiratory response to immersion in cold water is a gasp, suggests that the cold thermoreceptor volley elicited by cold immersion powerfully excites this area. However, there remains a possibility

that the initial “gasp” may be an augmented breath rather than a gasp, defined as the respiratory movement that occurs when the pons is removed or in extreme hypoxia.

The hyperventilation seen after the initial gasp of the cold shock response reflects a stress response accompanied by sympathetic overdrive (see Figure 2 Panel A). The speed of this response, as with the gasp response, suggests activation of an uncomplicated (direct) neural pathway, thought to be mediated through the tegmentum of the midbrain and the hypothalamus (Winters *et al.* 2000).

The cold shock response peaks during the first minute of immersion and then diminishes over the next minute as the peripheral thermoreceptors adapt. The respiratory response includes a three to four-fold increase in ventilation (Martin & Cooper, 1978). Several studies (Eglin & Tipton, 2005; Mantoni *et al.* 2007; Tipton *et al.* 1991) have reported increases in fR of >200% of baseline values, while corresponding V_T values did not typically exceed 100% (Figure 2 Panel A). This is particularly apparent if the respiratory data are recorded at a higher sampling frequency or breath by breath (Mekjavic *et al.* 1987; Datta & Tipton, 2006). For example, analysis of fR and V_T at 10 s periods during the first 20-30 s of immersion in cold water shows that the increase in \dot{V}_E is primarily determined by an increase in fR , with V_T not increasing until fR begins to fall back towards pre-immersion levels (Tipton *et al.* 1991). Thus, analysis of the components of \dot{V}_E after the first minute of immersion shows an increasing contribution of V_T to \dot{V}_E (Barwood *et al.* 2014; Hayward & Eckerson, 1984). This relationship between fR and V_T is similar to that seen between heart rate and stroke volume at high heart rates. On immersion in cold water, the relative increase above resting levels is greater for heart rate than stroke volume (Tipton, 1989). This suggests that in such stressful situations the rate, rather than depth, of the cardiac and respiratory pumps is primarily activated. Indeed, it has been concluded that fR is a better analogue of respiratory drive on initial immersion in cold water than V_T (Tipton *et al.* 1991).

Prompted by the initial gasp response, part of the cold shock response is an inspiratory shift in end-expiratory lung volume (Tipton, 1989). As mentioned, different patterns of fR and V_T are influenced by the starting lung volume (Figure 1) and rate of rise of neural output. The higher the lung volume and the faster the rate of rise of neural

output the smaller the V_T and the higher the fR (Younes & Remmers, 1981). Thus, the inspiratory shift in end-expiratory lung volume resulting from the cold shock gasp response pre-sets the respiratory system for a frequency driven response with high fR and small V_T .

After the first two minutes of immersion, and with the attenuation of the cold shock response, the respiratory responses become driven by thermoregulatory demands as represented by shivering, an involuntary form of skeletal muscle exercise (see Figure 2 Panel B). Thus, the ventilatory stimulus alters from rapid skin cooling (“thermal – dynamic”) to “thermally-evoked metabolic”. With this change comes a consequent diminution of the contribution of fR to \dot{V}_E and an increasing contribution of V_T . Hayward & Eckerson (1984) report an average 434 % increase in ventilation rate on immersion in cold water (0° C), but no differences in the responses of lightly clothed males and females. However, from 10-30 mins of exposure to cold water the \dot{V}_E in males was, on average, 20% greater than that of females, with \dot{V}_E at this time being primarily driven by the metabolic demands of shivering, and the increase in \dot{V}_E being predominantly caused by increased V_T (Hayward & Eckerson, 1984). Similarly, during 120 min exposure to 10° C cold air, the increased \dot{V}_E in men resulted from a greater V_T (Wagner & Horvath, 1985). The increases in \dot{V}_E during cold air exposures at 10 and 15 ° C in women were solely due to increases in V_T ; however in men the increases in \dot{V}_E resulted from increases in V_T at 15 ° C and both V_T and fR at 10 ° C (Wagner & Horvath, 1985).

INSERT FIGURE 2

Frank *et al.* (1997) induced mild deep body hypothermia in humans by intravenous infusion of 30 or 40 mL.kg⁻¹ of cold saline (4 ° C) on two separate days. V_T increased by between 60% and 170% on completion of the cold infusion, fR was unchanged. Similarly, when data for a two hour cold air exposure at either 10, 15 or 20 ° C were averaged, Wagner & Horvath (1985) found that although \dot{V}_E increased, probably as a result of shivering, only V_T increased; there was no change, or a slight reduction, in fR .

The surface area exposed and insulation of any clothing worn during cold exposure may also be relevant and help to describe some of the findings presented in Figure 2.

Simonova & Kozyreva (1994) have previously demonstrated that during forearm cooling the increase in \dot{V}_E was caused by an increase in fR ; but when the hand and face were cooled the increase in \dot{V}_E was caused by an increase in V_T . Whilst there are differences between the responses evoked by face compared to forearm cooling (cold pressor cp. diving response), it is more difficult to explain why hand and forearm cooling should produce such a difference in the ventilatory response. It is possible that the density of peripheral thermoreceptors located around the face is partially responsible for these observations. However, research in this area is sparse.

These findings, and the data presented in Figure 1, demonstrate a clear variation in the way \dot{V}_E is increased on cold exposure depending on the nature (duration, location and rate [intensity] of cooling) of that exposure. Sudden cooling of the skin on immersion, sufficient to evoke the dynamic response of the cutaneous cold receptors, results in an increase in \dot{V}_E primarily as a consequence of an increase in fR (Figure 2 Panel A). Longer exposures to cold and associated deep body cooling results in a similar response to that seen with exercise; an increase in \dot{V}_E due to a combination of increases in V_T and fR (Figure 2 Panel B). This is not unreasonable given that shivering is a form of skeletal muscle exercise with similar metabolic and chemical consequences and, therefore, requirements for \dot{V}_A .

Hyperthermia and exercise in the heat

Over 100 years ago Haldane (1905) established that hyperthermia is a potent stimulus for increasing \dot{V}_E . It is now well established that hyperthermia causes hyperventilation, an increase in V_A leading to hypocapnia and cerebral hypo-perfusion in resting and exercising humans which can reduce cerebral blood flow by as much as 20%; potentially decreasing oxygenation and brain convective cooling (Fujii *et al.* 2015; Gaudio & Abramson, 1968; Haldane, 1905; Hayashi, 2015; Nielsen & Nybo, 2003; Tsuji *et al.* 2016). Thus, a clear difference from the thermal panting of animals is that hyperthermia-induced hyperventilation in humans can cause a reduction in the arterial carbon dioxide tension (P_aCO_2) that is proportional to the increase in \dot{V}_E . However, the precise physiological mechanisms responsible for this hyperthermia-induced hyperventilation in humans are poorly understood. Potential causative factors include an increase in: deep body temperature (White, 2006); temperature of the hypothalamus (Boden *et al.* 2000); peripheral chemoreceptor sensitivity, possibly

specific to O₂ (Fujii *et al.* 2008a). Although hyperthermia increases peripheral chemoreceptor ventilatory O₂ drive in resting humans, the relative contribution of this drive to hyperthermia-induced hyperventilation is small (~20%), and appears to be unaffected by increasing deep body temperature (Fujii *et al.* 2008a).

INSERT FIGURE 3

The variability seen in the data in Figure 3 is due to the usual sources (sex, age, body composition, aerobic fitness) observed across most stressors. Two of the more important sources include the magnitude of the increases in deep body temperature and the co-existence of exercise.

Several studies have reported that hyperthermia-induced increases in \dot{V}_E at rest (passive) result from increased fR with little or no change in V_T (Chu *et al.* 2007; Curtis *et al.* 2007; Fan *et al.* 2008; Petersen & Vejby-Christensen, 1977; Vejby-Christensen, 1973a; Vejby-Christensen, 1973b). However, others have reported that hyperthermia can result in increases in fR and V_T (Cabanac & White, 1995; Fung *et al.* 1994; White, 2006). The latter findings are more consistent with the data presented in Figure 3, and with the reported relationship in humans between hyperthermia-induced hyperventilation and reduction in P_aCO_2 noted above. These discrepancies could be due to the different methodologies and degree of hyperthermia. For example, in the studies of Cabanac & White (1995), passive heating of humans to an oesophageal temperature (T_{es}) of 38.5 °C was required for hyperthermic-induced hyperventilation. Petersen & Vejby-Christensen (1977) reported a deep body temperature threshold near 38° C for the onset of a relative hyperventilation. Tsuji *et al.* (2012) have reported a threshold at an oesophageal temperature of about 38.2 °C. Passive heating that raised T_{es} by ~1.5° C was not reported to influence V_T (Curtis *et al.* 2007). Above these temperature, \dot{V}_E gradually increased with increasing T_{es} (Fujii *et al.* 2008a).

Hey *et al.* (1966) reported that during quiet breathing and in hyperpnoea there is a linear relation between \dot{V}_E and V_T , up to a V_T equal to about half of the vital capacity. Further increases in \dot{V}_E occur without further change in V_T . The authors report that this relationship is essentially unaltered by wide variations in $PACO_2$ and PaO_2 , by

metabolic acidemia, some drugs which affect respiration, and by moderate muscular exercise. When, however, the body temperature is raised fR is relatively increased.

During *exercise* in the heat, the identification of the thermal component of the increase in \dot{V}_E is complicated by the added demand of metabolism (Figure 3 Panel B). There is a strong association between body temperature and tachypnea during exercise, this may operate, in part, by increasing central command (Hayashi *et al.* 2006). Hayashi (2015) postulates that during exercise, output from central command and input from muscle mechanoreceptors and metaboreceptors via group III and IV muscle afferents modulate \dot{V}_E , and that these factors could contribute to hyperthermia-induced hyperventilation. Certainly, changes in deep body temperature cannot explain the fast response of fR to exercise and to variations in power output; these occur too fast to be explained by the invariably slow rise in body temperature.

Temporal changes in ventilation during exercise in the heat are likely to be directly associated with: i) temperature *per se* ii) the type and intensity of exercise, which may produce metabolites influencing ventilation (Chu *et al.* 2007), or iii) an interaction of both. Inspiratory duration has been reported to have an inverse relationship to body temperature, without directly affecting the off-switch to inspiration threshold (Bradley *et al.* 1974; Grunstein *et al.* 1973). Animal studies have implicated descending hypothalamic projections as well as cutaneous afferents in this response (Widdicombe, 1964). Tsuji *et al.* (2016) report that the oesophageal temperature-dependent increases in \dot{V}_E during light and moderate exercise occurs due to increases in fR and in spite of falling V_T . It is likely that alterations in cerebral blood flow during exercise impact upon the ventilatory drive, as reduced cerebral blood flow will activate thermoregulatory responses including hyperventilation; this will be further driven by CO_2 accumulation in the brain driving central chemoreceptors (Tsuji *et al.* 2016).

Six consecutive days of heat acclimation (37° C, 50% relative humidity) has been shown to have no effect on V_T or fR at rest or during an exercise-heat test (Fujii *et al.* 2012), and dehydration with maintained MAP has no effect on absolute V_T or fR , or the T_{es} -dependent slope changes of V_T or fR (Fujii *et al.* 2008b). Fujii *et al.* (2008a) have also demonstrated that \dot{V}_E is reduced by hyperoxia, induced by breathing 100% O_2 (an effect attributed to a dis-facilitation of carotid body chemoreceptors), and that

the absolute changes in \dot{V}_E gradually increase with increasing T_{es} . These findings suggest that the ventilatory drive from peripheral chemoreceptors increases with increases in deep body temperature in resting normoxic conditions. In both animal and human studies, hypoxic and hyperthermic stimuli have been shown to positively interact (Chu *et al.* 2007; Curtis *et al.* 2007; Eyzaguirre & Zapata, 1984; Natalino *et al.* 1977) in terms of their influence on resting or exercise ventilation. The direct influence of temperature on chemosensitive tissues may help explain this positive interaction between hypoxia and hyperthermia (Chu *et al.* 2007; Natalino *et al.* 1977; Petersen & Vejby-Christensen, 1977).

It is concluded that, in humans, increases in fR and V_T appear to be responsible for the higher \dot{V}_E during passive hyperthermia (denoted by the square symbols; Figure 3 Panel A). However, when deep body temperature is increased by approximately 1.5 – 2° C, or reaches 38.2-38.5 ° C, *i.e.* when the stress becomes more intense, fR appears to play an increasing role, perhaps as part of a vestigial panting response?

Hypoxia

Blood gases are controlled via central and peripheral respiratory chemoreceptor responses with different gains and delays. The slower acting central chemoreceptors are located throughout the brain stem (Nattie, 2009) and respond to increases in brain tissue $CO_2/[H^+]$. The faster responding peripheral chemoreceptors (carotid bodies) are located at the bifurcation of the common carotid arteries and respond to low arterial O_2 and high arterial CO_2 . The O_2 - CO_2 stimulus interaction is multiplicative and results in an augmented carotid body response in hypoxia and a blunted CO_2 response in hyperoxia (Lahiri *et al.* 1987), however over time the CO_2 response is restored in humans and other species (Dahan, 2007; Forster, 1971; Dempsey, 2014).

On ascent to high altitude, there is an immediate increase in \dot{V}_A , known as the hypoxic ventilatory response [HVR] (Schoene, 2001). This increase is mediated primarily by the carotid bodies (~90%) and partially by the aortic bodies (~10%) (Heymans *et al.* 1930; Timmers *et al.* 2003). Carotid and aortic bodies contain glomus (type I) cells, which release neurotransmitters in response to hypoxia, causing depolarization of nearby afferent nerve endings (Prabhakar, 2000; Timmers *et al.* 2003). In humans, glomic tissues other than the peripheral chemoreceptors, such as the glomus

trigeminale, the glomus jugulare, the glomus pulmonare, and the intrapulmonary neuroepithelial bodies, serve no discernible role in ventilatory responsiveness to hypoxia (Whipp, 1994). The carotid bodies therefore play a vital role in constraining the fall of arterial PO₂ in response to the challenge of hypoxaemia, and carotid chemoreceptor denervation leads to permanent abolition of normocapnic ventilatory responses to hypoxia, and reduced ventilatory responses to hypercapnia (Timmers *et al.* 2003).

Mekjavic *et al.* (1987) studied breathing during rest and incremental exercise in normoxic and hypoxic (FIO₂ = 0.12) environments. They reported that \dot{V}_E as well as mean inspiratory flow (V_T/TI) increased with exercise intensity and were augmented in the hypoxic environment. The ratio between TI and total breath durations increased with exercise intensity, but was unaffected by hypoxia. V_T and TI had linear, coinciding ranges in normoxic and hypoxic conditions up to V_T/TI values of about 2.5 L.s⁻¹. At higher values TI continued to decrease, whilst V_T tended to level off, an effect which was more evident in the hypoxic condition. The authors suggest that the hypoxic augmentation of exercise hyperpnea is primarily brought about by an enhancement of central inspiratory drive, with the timing component being largely unaffected by the hypoxic environment. At low to moderate levels of exercise hyperpnea inspiratory off-switch mechanisms are essentially unaffected by moderate hypoxia. This may explain why the relatively low metabolic demand of shivering thermogenesis is unaffected by normobaric hypoxia (Blatteis & Lutherer, 1976).

Given that hypoxia is a chemical stimulus requiring, in part, increased \dot{V}_A for its correction, an increase in \dot{V}_E via V_T on exposure to altitude can be regarded as an appropriate response. In support of this, Mateika *et al.* (2004) reported an increase in V_T with no change in fR during intermittent exposure to hypoxia.

INSERT FIGURE 4

The increased ventilatory drive during exposure to hypoxia, when in an awake state, appears to be primarily linked to an increase in V_T in humans (Figure 4). The hyperventilation induced by the HRV results in hypocapnia which “brakes” the ventilatory response.

It seems that, as with other stressors, the severity of the hypoxic stress appears to influence the pattern of the breathing response. During severe hypoxia a pronounced increase in fR and decrease in V_T has been reported, resulting in either a decrease (Gautier & Bonora, 1980) or increase (Miller & Tenney, 1975), in $PACO_2$ (for a review see Teppema *et al.* 2010). Persistent 5% hypoxia will arrest breathing (eupnoea) and trigger gasping - the latter being an intrinsic auto-resuscitative mechanism. If hypoxia persists then gasping stops in adults but not neonates (St-John, 1998). With regard to the effects of CNS hypoxia on ventilatory control, central respiratory depression has been reported (Schmidt *et al.* 1995). However, different respiratory-related neurons in the medulla or hypothalamus have been observed to both depolarize and hyperpolarize in response to physiological levels of hypoxia. The results obtained appear to be critically dependent on such methodological factors as state of consciousness, whether the carotid chemoreceptors are intact and the duration of hypoxia (Bisgard & Neubauer, 1994; Curran *et al.* 2000). However, when the response observed to hypoxia of any intensity or duration is an increase in ventilation, it must be concluded that the net effect is excitatory.

Bernardi *et al.* (2006) reported that successful high altitude climbers, who could reach the highest summits without oxygen, were characterised by a lower ventilatory sensitivity to hypoxia and a slower fR , compared to those who did not succeed or needed supplemental oxygen. These findings were supported by Puthon *et al.* (2015) who reported that fR was larger in control participants compared with elite high-altitude climbers, while V_T was larger in climbers compared with controls during maximal incremental cycling tests in both normoxic and hypoxic conditions.

Schoene *et al.* (1984) have previously demonstrated that the drop in arterial oxygen saturation that occurs with exercise at altitude is inversely related to HVR, and sojourners with high HVR may perform better at extreme altitude. From Figure 4 it is notable that those requiring supplemental oxygen during 15 days at 5,200 m (black triangle) increased \dot{V}_E by an increase in fR . Those not requiring supplemental oxygen (black square) increase \dot{V}_E by an equivalent increase in fR and V_T . Faulhaber *et al.* (2014) reported that individuals susceptible to acute mountain sickness (AMS) have a higher fR and smaller V_T at rest in acute hypoxia compared with those not susceptible

to AMS. Petersen & Vejby-Christensen (1977) concluded that those with a respiratory control system that is particularly sensitive to CO₂ and/or hypoxia, tend to increase \dot{V}_E by a relatively larger increase in fR compared to V_T . Why these differing responses are observed is a matter of conjecture, perhaps they represent the difference between an adaptive (chemically driven) response to altitude and a maladaptive (stress driven) response, underpinned by individual differences in the sensitivity of the chemoreceptors?

Whilst these somewhat disparate findings are difficult to interpret, they share one common theme, those who perform better at altitude or suffer less AMS, tend to increase their \dot{V}_E by V_T rather than fR and thus their \dot{V}_A should be better for a given amount of respiratory effort. As mentioned, the work of breathing and consequent heat production and oxygen demand by the respiratory muscles are higher per unit of \dot{V}_A if \dot{V}_E is increased by fR rather than V_T (more breaths required for the same \dot{V}_A if fR is major route for the increase in \dot{V}_E).

It is well established that hypoxic stimuli have an interactive effect on multiple superimposed stimuli including, but not limited to: exercise; CO₂; medication; narcotics; alcohol; and various disease states such as asthma and chronic obstructive pulmonary disease (Caruana-Montaldo *et al.* 2000). Similarly, different response are seen during exposure to hypoxia when sleeping (Berssenbrugge *et al.* 1983; Smith *et al.* 2007). Severe normobaric (NH) and hypobaric hypoxia (HH) also have different effects on ventilatory drive (Richard & Koehle, 2012). Savourey *et al.* (2003; 2007) observed a greater V_T in NH compared to HH, while fR tended to be lower for a given \dot{V}_E in NH as opposed to HH. fR was also significantly higher in HH than NH after 5 minutes, but reached similar values in both conditions at the end of the 40 minutes of exposure. Richard & Koehle (2012) also demonstrated that V_T was higher in NH than in HN at 5 min and 30 min, and greater than normobaric normoxia over an average of 5 hours; however, no differences between conditions were reported in fR .

Research examining the sex differences in the ventilatory response to hypoxia in healthy, awake humans has provided somewhat conflicting results (Aitken *et al.* 1986; Morelli *et al.* 2004; Tarbichi *et al.* 2003; Van Klaveren & Demedts, 1998). It is likely that variations in age, body morphology, menstrual cycle stage and inter-individual

variability may have contributed to these findings; however, studies in awake animals have also produced similar contradictory data (Morelli *et al.* 2004).

Panic and Pain

When conscious, in addition to the brainstem, many mid- and forebrain regions are also involved in breathing, including corticostriatal circuitry (Critchley *et al.* 2015). Humans can voluntarily override automatic respiratory pattern generation when playing wind instruments, speaking or swallowing, for example. Emotion and behaviour can also affect respiratory motor output through mechanisms that are not influenced by metabolic demands (Homma & Masaoka, 2008). Indeed, psychophysiological stress-induced respiratory reactions produce changes in ventilation which often precede changes in metabolic processes (Suess *et al.* 1980).

Unpleasant emotions such as panic or fear result in deviations from eupnoea that are distinct from those produced in response to metabolic requirements. Areas of the forebrain, limbic and cortical structures and hypothalamus have been implicated in systems that process information from the external environment and directly stimulate spinal respiratory motor neurones (Homma & Masaoka, 2008; Masaoka *et al.* 2005). Additionally, the sensation of pain (defined as an unpleasant sensory experience associated with actual or potential tissue damage) has been shown to affect the respiratory cycle through a mixture of behavioural response and a direct effect on medullary respiratory centres (Sarton *et al.* 1997; Ward, 2002).

Panic

Panic is defined as sudden uncontrollable or overwhelming fear or anxiety. Although centrally mediated, panic can be evoked by a wide range of real or apparent “threats”. The most consistent physiological change observed during laboratory-induced panic attacks is hyperventilation (Niccolai *et al.* 2009).

Authors have identified areas of the limbic system that have a central role in fear and panic responses (Homma & Masaoka, 2008). In particular, the temporal pole is associated with evaluation of an uncertain or dangerous environment, and the amygdala processes negative emotions such as anxiety and fear (Davis, 1992; Halgren *et al.* 1978; Reiman *et al.* 1989; Masaoka & Homma, 2004). The involvement

of the temporal lobe is consistent with patients with focal temporal lobe epileptic seizures who experience pre-ictal fear or anxiety (Masaoka & Homma, 2004). In human studies, electrical activity in the amygdala was increased during anticipatory anxiety and Pavlovian fear conditioning; the electrical activity was synchronous with the onset of inspiration and often occurred before the patient reported experiencing symptoms of panic or anxiety (Le Doux, 1998; Homma & Masaoka, 2008; Masaoka & Homma, 2004). Animal studies have identified an interruption of normal respiratory cycle and an increase in fR following electrical stimulation of the amygdala (Harper *et al.* 1984).

Carnevali *et al.* (2013) using rats selectively bred for high or low anxiety behaviour, have reported elevated fR responses, reduced sniffing and increased incidence of sighs in novel environments, anxiety-inducing restraint and acoustically stressful stimuli in high anxiety rats, with no habituation to repetitive stimuli. The authors conclude that these responses resemble those observed in anxious and panic patients, and that respiratory pattern may represent a promising method for assessing anxiety states in pre-clinical investigation. Human individual responses vary depending on learned emotional reactions; an increase in fR has been associated with individual trait anxiety scores (Masaoka & Homma, 2000); individuals with high anxiety scores have large increases in fR compared to those that are not anxious. Variation in individual response results from the interplay of factors such as memory, cognition and emotion (Masaoka & Homma, 2000; Tracey & Mantyh, 2007).

There may be a significant evolutionary reason for the relationship between emotion and respiration. The olfactory system is the only sensory modality that is not processed by the thalamus. Instead, information ascends directly to the limbic system (Masaoka *et al.* 2005). Direct stimulation of the olfactory limbic system can alter respiratory patterns in humans, with unpleasant odours increasing fR and reducing V_T (similar to panting). Perception of odour is dependent on aspiration (sniffing) and it is therefore possible that the relationship between the limbic system and respiration has a role in the detection of danger and evolutionary defence mechanisms (Homma & Masaoka, 2008).

Cunningham *et al.* (1972), Cunningham & Gardner (1977) and Gardner (1977) have remarked upon the possible shortening of resting expiratory time (T_E) due to anxiety in their subjects. Rigg *et al.* (1977) reported that \dot{V}_E and fR increased significantly on performance of mental arithmetic during both air breathing and rebreathing, whilst V_T was unchanged.

INSERT FIGURE 5 HERE

From Figure 5 it appears that the \dot{V}_E response to “panic” is primarily achieved by an increase in V_T . However, it is important to note that in the studies presented in Figure 5 panic was often (18 out of 22 studies) induced by carbon dioxide inhalation; this will evoke the respiratory response appropriate for hypercapnia (increase alveolar ventilation via an increase in V_T) rather than panic *per se*. With a progressive increase in hypercapnia V_T increases first, fR does not increase until hypercapnia reaches a significant level (Gelfand & Lambertsen, 1973; Duffin *et al.*, 2000). Hypercapnia in the intact animal augments V_T and expiratory flow rate. Hypercapnia and hypoxia cause a prominent decrease in spontaneous T_E (expiratory time), so that a larger V_T is expired in a shorter period (Rebuck *et al.* 1976), in part due to the recruitment of expiratory muscles (Gaitier *et al.* 1973). Inverse proportionalities have been observed between V_T and T_I and T_E during CO_2 inhalation for both the mean values at differing steady states (Cunningham *et al.* 1972) and breath-by-breath values during rebreathing (Clark & von Euler, 1972). During rapid changes in stimulation, these proportionalities may be altered due to differing response times for the changes in V_T , T_I and T_E . Hypercapnia independently inhibits the respiratory off-switch mechanism (increases its threshold) while increasing the rate of rise of inspiratory activity (von Euler & Trippenbach, 1976). Thus, whilst CO_2 exposure causes a robust fear response and panic symptom ratings in healthy volunteers and panic disorder patients (Leibold, 2016), it is not valid for looking at the ventilatory response to panic. Such studies are more appropriate for investigating the ventilatory response to hypercapnia.

The studies that induced panic by social anxiety (male touching the wrist of a female) or fear conditioning using unpleasant sensory stimuli, show a small increase in fR and a reduction in V_T with \dot{V}_E remaining unchanged (Wilhelm *et al.* 2001). An increase in fR is seen with anxiety produced by breathlessness and mechanical discomfort

(Gorman *et al.* 2000). Such an increase is apparent in patients that panic following respiratory challenge, as well as those exposed to other sensory stimuli and anticipatory anxiety. Cohorts that panic following audio-visual, olfactory, touch or electric shock conditioning do not exhibit an increase in V_T (Masaoka & Homma, 1977; Masaoka & Homma, 2001; Wilhelm *et al.* 2001).

It is concluded that the ventilatory pattern evoked by panic is confused by the method often used to evoke it (CO_2 inhalation – illustrated by the black circles in Figure 5) which preferentially increases V_T rather than fR . Those human studies which have not been confounded by hypercapnia (Rigg *et al.* 1977; Gorman *et al.* 2000; Masaoka & Homma, 2000; Wilhelm *et al.* 2001) and animal studies (Harper *et al.* 1984; Carnevali *et al.* 2013), have often reported an increase in fR in response to panic, particularly in individuals and animals with high baseline levels of anxiety.

Pain

“Pain” is a generic term that covers a range of types (e.g. somatic, visceral, neuropathic) and can be chronic or acute. Individual sensitivities to pain vary (e.g. there is a sex difference) as does the type of pain evoked by different situations and disease states (Tracey & Mantyh, 2007). Pain can be evoked by a variety of stimuli including temperature, mechanical and chemical stimuli, and the nerve fibres associated with the transmission of pain vary, including both small myelinated ($A\alpha$ - $A\delta$) and unmyelinated (C) fibres. It is perhaps unsurprising therefore that “pain” can produce a variety of responses depending on how, and in whom, it is evoked. In addition, there is a relative paucity of papers that provide details of the components of the ventilatory response to pain, those that do are presented in Figure 6.

The experience of pain calls for appraisal of the affected body area in a cognitive and emotional process. Transmission of nociceptive information occurs in several ways. The spinothalamic tract enables localisation and discrimination of pain by by-passing respiratory centres and communicating directly with the thalamus and sensory cortex (Tracey & Dickenson, 2012). Contrastingly, the spinothalamic tract transmits through the pons and medulla to the thalamus and higher centres that make up the “Pain Matrix” (Tracey & Mantyh, 2007). This matrix includes the amygdala and hippocampus, along with areas such as the anterior cingulate and prefrontal cortex

that are responsible for giving emotional significance to a sensory stimulus (von Leupoldt *et al.* 2009). Willer (1975) demonstrated that the anticipation of pain was enough to increase fR ; suggesting behavioural breathing control by higher centres may be responsible for changes in \dot{V}_E associated with acute pain.

Unfortunately the direct role of centres that make up the Pain Matrix is unclear and poorly defined due to the interplay of factors such as memory, cognition and emotion (Tracey & Mantyh, 2007). This interplay results in the “individualised” response to pain demonstrated in studies; higher perceived pain scores correlate with larger changes in respiratory parameters. Individualised responses are also evident in panic studies and may reflect learned emotional reactions to perceived threats in the external environment.

The spinomesencephalic tract communicates nociceptive information from the dorsal horn to the periaqueductal grey matter (PAG) and mediates the “fight or flight” response (Subramanian & Holstege, 2014; Tracey & Mantyh, 2007). Acute pain can induce a wide range of sympatho-adrenal responses that can *indirectly* increase \dot{V}_E (Christensen, 1991). Weissman *et al.* (1986) reported that the increase in \dot{V}_E , following the infusion of cortisol, epinephrine and glucagon to simulate plasma levels seen in patients following trauma, was due to increased V_T rather than fR .

A direct relationship between nociceptive afferents and respiratory networks explains the changes in \dot{V}_E with painful stimuli (Sarton *et al.* 1997). An increase in fR is often seen in surgical patients despite adequate anaesthesia (Rosenberg *et al.* 1980). Higher cortical centres, such as those involved in the Pain Matrix, are suppressed by anaesthetic agents (Eger *et al.* 1972). Patients under deep anaesthesia still exhibit a respiratory change following surgical stimulation in the absence of cardiovascular or somatic response (Borgbjerg *et al.* 1995; Eger *et al.* 1972). This finding suggests that nociceptive information can be transmitted directly to bulbar respiratory nuclei without involving higher centres. Waldrop *et al.* (1984) further support this suggestion by demonstrating increased phrenic nerve activity in decerebrate cats following noxious heating of the skin. The dorsolateral periaqueductal gray has a high density of opiate receptors and electrical stimulation of this area results in profound analgesia. Interestingly, stimulation of different areas of the PAG (ventrolateral) can also result in

changes in the respiratory pattern, such as slow, deep breathing, tachypnoea and breath holding (Subramanian & Holstege, 2014). Due to the close proximity of networks involved in pain transmission and those responsible for respiratory control in the medulla, pons and PAG, stimulation of nociceptive afferents may cause changes in respiratory function through action on any of these structures (Sarton *et al.* 1997; Subramanian & Holstege, 2014). For example, Bourke (1997) studying the administration of regional anaesthesia to four patients with trauma to the upper extremities and with an average pain score of 7.1/10; reports that relief of pain was associated with decreased \dot{V}_E in all four patients.

INSERT FIGURE 6 HERE

From Figure 6 it appears that the \dot{V}_E response to “pain” is generally achieved by a combination of an increase in V_T and fR . However, as noted above when discussing panic, it is important to note *how* the pain is induced. Pain that is produced by methods that alter the biochemical status of the body (ischaemia, hypoxia, hypercapnia) are as likely to evoke the respiratory response appropriate for these stressors, rather than pain *per se*. It is interesting to note that perioperative pain seems to be associated with an increase in fR and fall in V_T .

Duranti *et al.* (1991) identified a decrease in T_i and T_E during cutaneous electrical stimulation in humans, resulting in an increase in fR . V_T did not change, but increased with deep muscle electrical stimulation and ischaemic pain from a tourniquet, however, a larger increase in fR was seen, along with an increase in \dot{V}_E . The authors therefore inferred that the increase in \dot{V}_E seen during painful stimuli resulted from an increase in the drive to breathe, rather than a change in timing of components during the respiratory cycle. Sarton *et al.* (1997) confirmed this by describing an initial increase in fR and V_T after induction of pain (scored 4.5 to 5.5 on a 10 point scale) by transcutaneous electrical stimulation. During prolonged painful stimuli, the V_T returned to resting values whilst the fR remained elevated. Further testing whilst participants inhaled different CO_2 and O_2 gas mixes enabled authors to investigate whether pain induced a change in \dot{V}_E via the peripheral or central chemoreflexes. It was concluded that pain induced a “chemoreflex-independent tonic

ventilatory drive” (Sarton *et al.* 1997). It was unclear whether a stronger pain stimulus would have had more of an effect.

Pain seems to increase \dot{V}_E through variations in both fR and V_T (Duranti *et al.* 1991; Sarton *et al.* 1997; Ward, 2002). Higher cortical centres interact to produce a behavioural control of breathing that can be seen during anticipation of painful stimuli (Willer, 1975). In decerebrate unanaesthetised rats, mechanical nociceptive stimulation of a forelimb evoked abrupt increases in the rate of phrenic discharge with little effect on amplitude, whereas apnoea was evoked with the same stimulus applied to the cornea (Boscan & Paton, 2001); this illustrates the diversity of respiratory responses evoked by pain stimuli. However, as noted, anaesthetic agents that suppress higher centres do not prevent the increase in respiratory rate resulting from surgical stimulation (Rosenberg *et al.* 1980). It would therefore appear that the ventilatory response to pain is complex and results from interplay of factors including direct tissue damage, neural circuits in the midbrain and brainstem, along with emotional processing and memory. Further research is required to fully understand the mechanisms by which painful stimuli affect ventilation.

In conclusion, and as with panic, some of the methods used to evoke pain (e.g. hypercapnia, ischaemia, hyperoxia) directly influence \dot{V}_E and are therefore not valid to investigate the influence of pain on ventilation. When they are, V_T and fR appear to operate independently.

DISCUSSION

At rest, the relative contributions of fR and V_T to \dot{V}_E may be determined by energy optimisation of the neural mechanisms and respiratory muscles (to minimise the work of breathing), as well as summation of feed-forward and feedback drives. With the onset of a stressor, differences in the relative contributions of fR and V_T to \dot{V}_E may reflect the separate neural circuits sub-serving the different stressors. These neural circuits clearly differ depending on whether the stimulus is psychological, chemical or acute/chronic, moderate/intense. For example, with the stressors reviewed, as the stress becomes extreme, \dot{V}_E generally becomes increased more by fR than V_T .

The afferent neural pathways for pain and temperature are anatomically very close and extremes of heat and cold activate hot and cold nociceptors. Part of the ventilatory response to these stressors may arise due to direct stimulation at the spinal level of α -motorneurons innervating the intercostal muscles and diaphragm. Neuroanatomic studies corroborate the hypothesis that ascending neurons involved in transmitting the thermoreceptor volley following cold immersion are in the pons (Hinckel & Schroder-Rosenstock, 1981) very close to the neurons involved in respiratory phase switching. Evidence (Fung *et al.* 1994; Lumsden, 1924; Paton *et al.* 2006; St-John *et al.* 1984; St-John & Paton, 2004) suggests that the gasping and high f_R seen with cold shock and other thermal and psychological stressors may involve pathways that are distinct from those necessary for the generation of eupnoea. Pacemakers have only been found in the pre-Botzinger Complex of rat and mouse and they are only active during gasping; during eupnoea they are hyperpolarised (*i.e.* below the pacemaking membrane voltage threshold) and embedded in a synaptic network. The latter depends on reciprocal inhibitory synapses between sub populations of inspiratory and expiratory neurones of which there are at least six types (Paton *et al.* 2006; Smith *et al.* 2009; St-John *et al.* 2009).

Breathing results from a combination of complex and interacting mechanisms involving the central nervous system, peripheral afferent feedback and chemical drives (Figure 7). The relative contribution of these mechanisms are highly dynamic and state-dependent. The essential neural circuitry resides within the pons and medulla and has the capability to generate the eupneic pattern as well as co-ordinate cranial and motor activities (St-John, 1998; St-John & Paton, 2003; 2004); separation of these neural entities produces pathological changes in inspiratory and expiratory patterns (Abdala *et al.* 2009b; Smith *et al.* 2013). For example, sequential rostro-to-caudal pontine transection results in anpeusis (mid-pontine transection) and gasping (ponto-medullary transection) (Paton *et al.* 2006; Smith *et al.* 2007; St-John, 1998).

Impinging on the brainstem respiratory circuitry are afferent feedback signals, most notably from vagal pulmonary inflation (stretch) receptors and peripheral arterial chemoreceptors. The former provide, via the pons, graded timing signals to off-switch inspiration (von Euler, 1983), whereas the latter are activated by systemic hypoxia, hypercapnia and protons, and stimulate ventilation to ensure blood gas homeostasis.

Lung inflation is an important mechanism for increasing respiratory frequency at the expense of reducing tidal volume; denervation of the stretch receptors results in apneusis (St-John, 1998). Peripheral chemoreceptors also excite central chemoreceptors (Takakura *et al.* 2006), which reside on the ventral surface of the medulla oblongata in the retrofacial nucleus. In the latter nucleus, neurones respond to hypercapnia and their activity is a trigger for forced expiration manifested by abdominal muscle contraction (Abdala *et al.* 2009a; Feldman *et al.* 2013). Although absent at rest, forced expiration also occurs during: (i) exercise where it plays a major role in shortening expiratory time to allow frequency to increase, and (ii) during straining and the defensive reflexes of cough, sneeze and emesis, where expiratory effort provides propulsive force.

INSERT FIGURE 7 HERE

The ultimate determinant of the pattern of ventilatory response of a particular stimulant will reside within the site(s) of termination of the activated afferent fibres, and their onward connectivity patterns (Figure 7). There is a need for classical high resolution tract tracing to link specific afferent inputs to the respiratory network, as well as demonstration of the functional effects of activating those afferents on breathing, perhaps by adoption of optogenetics. Nevertheless, based on the known functional effects of various brain regions, it would be possible to make informed proposals as to how f_R and V_T are mediated by sensory afferent drives. Higher brain areas such as the insular cortex, amygdala and hypothalamus are known to produce changes in respiration associated with the conditioned, emotional responses that accompany affective behavioural responses (Pascoe & Kapp, 1985; Timms, 1981). These types of circuits undoubtedly co-ordinate “fight or flight” or ‘play dead’ responses capable of increasing and decreasing f_R and V_T (Applegate *et al.* 1983), and are mediated either via direct spinal connections to respiratory motor neurones that may bypass the brainstem respiratory network, or engage brainstem respiratory neuronal machinery.

Recent studies have demonstrated the importance of the pons, in particular the Kölliker Fuse (KF) nucleus, for both the normal eupneic breathing pattern and regulation of the timing of the phase transition of respiration. Indeed, based on the patterns of

respiration that can be evoked by modulating the pons and KF excitability (Chamberlin & Saper, 1994), we propose that the KF is one site for mediating changes in f_R and V_T . For example, activation of the KF slows respiration (Dutschmann & Herbert, 2006), its inhibition increases frequency (Abdala *et al.* 2016) whereas its opiate modulation depresses neural V_T (Levitt *et al.* 2015). These effects are most likely mediated by orchestration of the ventral respiratory column machinery, located in the ventrolateral medulla. This core oscillating network comprises multiple types of expiratory (in the Böttinger complex primarily) and inspiratory neurones (in the pre- Böttinger complex) that are inter-connected with inhibitory synapses and output to cranial and spinal motoneurones. In isolation from the pons, including the KF, the ventral respiratory column generates apneusis and gasping (Paton *et al.* 2006; Smith *et al.* 2007; St-John & Paton, 2004; St-John *et al.* 2009). Given the range of respiratory responses that can be elicited from the ventral respiratory column when connected to the pons it is a most likely site for directly mediating f_R and/or V_T changes.

Is there clinical relevance to understanding the pattern of breathing?

f_R and V_T are altered by a variety of diseases. For example tachypnea, particularly during exercise, is a prominent feature in various pulmonary, cardiovascular, chest wall and neuromuscular diseases. Congestive heart failure patients can respond to exercise with tachypneic hyperventilation, the severity of which is prognostic of morbidity and mortality (Dempsey & Smith, 2014; Johnson, 2000; Olson *et al.* 2008)

We also consider changes in reflex respiratory responses following stimulation of peripheral receptors to be revealing. An example of this is the substantial exaggeration of the hypoxic ventilatory response in human patients with systolic heart failure (Ponikowski *et al.* 2001). Indeed, these patients have sensitisation of their peripheral chemoreceptor reflex, but when this actually occurs in relation to the onset of heart failure is not known. Thus, future research to determine the relative onset of hypoxia ventilatory response sensitivity in patients with heart failure (i.e. coincident with, or after the onset) will be important to establishing the prognostic value of this respiratory change and its consequent value in initiating early and appropriate preventative therapy.

Respiratory pattern shifts have been reported in animal experiments of lung disease, with vagal mechanisms being implicated in simulated pulmonary embolism (Guz & Trenchard, 1971), acute chemical pneumonia (Trenchard & Guz, 1972) and experimental bronchial asthma (Gold *et al.* 1972). However, the relevance of these data for humans remains, as noted in the Introduction, is debatable due to species variations in vagal function (Guz *et al.* 1970).

In terms of human data, almost a century ago Professor J. B. S. Haldane described 'the effects of shallow breathing' in patients suffering from "Soldier's Heart" (Haldane *et al.* 1919): now known as Postural tachycardia syndrome (Mathias *et al.* 2011; Schondorf & Low, 1993). The condition was coined "Soldier's Heart" owing to its frequent occurrence among military personnel in the First World War. Although equivocal, it appears that the onset of the syndrome can be linked to infection, trauma, surgery or stress (Mathias *et al.* 2011). The condition was characterised by breathlessness on exertion, rapid pulse, fainting attacks, giddiness, exhaustion, lassitude, headache and irritability; with the symptoms exacerbated by common stimuli in daily life, including modest exertion, food ingestion and heat (Haldane *et al.* 1919; Mathias *et al.* 2011). The breathing of patients with the condition was described as 'remarkable' by Haldane in the initial studies after the Great War (Haldane *et al.* 1919). Their respiration was rapid 'from 20 to 60 or more per minute' and shallow, ranging from '250 to 350 c.c. or thereabouts' and their alveolar CO₂ was abnormally low (Haldane *et al.* 1919). Consequently, it was concluded that patients with Soldier's Heart were in the same state as a healthy individual at high altitudes. From this review we know this applies, in particular, those who tend to do badly at altitude (see "Hypoxia" above and Figure 4). It is certainly revealing that almost a century later, we still have a limited understanding of the regulation of ventilation during various psychological stresses.

From a clinical perspective, we have reported in this review that the relationship between fR and V_T may provide insights into those susceptible to AMS and perioperative pain. Indeed, a change in breathing pattern at rest whether fR , V_T and/or forced expiratory breathing can provide prognostic information and early clinical insight into disease onset, permitting early therapeutic intervention. Either the changes in breathing pattern at rest (e.g. inspiration to expiration duration ratio), or changes to the

established fR and V_T responses to stressors, could help with diagnosis and assist in stratification of medicine. An example is the emergence of forced expiration (stage II) that accompanies development of hypertension when rats are exposed to repeated bouts of intermittent hypoxia (Zoccal *et al.* 2008). Given that intermittent hypoxia is also associated with central and obstructive sleep apnoea, commonly associated with hypertension or heart failure, future research should test the hypothesis that a change in breathing pattern is indicative of the development of sleep apnoea and cardiovascular disease. Moreover, we speculate that there will be a correlation between breathing patterns and mortality and morbidity in cardiovascular disease.

Whilst we have mainly considered the relationship between fR and V_T , the effect of dead space ventilation also has clinical significance. Measuring the dead space fraction (V_D/V_T) has been shown to have prognostic value in patients with Acute Respiratory Distress Syndrome (ARDS). In this fraction, V_D refers to alveolar dead space resulting from alveoli that are ventilated but not perfused. The affected airways are unable to take part in gas exchange and cause arterial hypoxaemia due to right-to-left intrapulmonary shunting. Nuckton *et al.* (2002) found that for every increase of 0.05 in dead space fraction, risk of mortality from ARDS increased by 45%. Subsequent studies showed V_D/V_T is persistently elevated through acute, subacute and intermediate phases, and only decreases in those that survive ARDS (Kallet *et al.* 2004; Raurich *et al.* 2010). Positive End Expiratory Pressure (PEEP) decreases V_D/V_T by recruiting more of the lung, until the point that overexpansion injury occurs. Although bedside monitoring of dead space fraction is difficult, with various methods such as volumetric capnography, it could provide invaluable insight into the clinical responsiveness to treatment of ARDS, as well as identify the most severely affected individuals requiring therapeutic intervention.

CONCLUSIONS

We have examined the ventilatory response to a wide range of stressors with the aim of considering if there is an overall differential control of fR and V_T that applies in a wide range of conditions and if so, why. It appears that for the stressors reviewed (exercise, cooling, heating, hypoxia, pain and panic), as the stress becomes more intense \dot{V}_E generally becomes increased more by fR than V_T , regardless of whether this was the case at lower intensities of stress. We have suggested that, given the

range of respiratory responses that can be elicited from the ventral respiratory column when connected to the pons, it is a most likely site for directly mediating fR and/or V_T changes.

We were tempted to speculate that the ventilatory response evoked by a stress depends on the nature of that stress, with metabolic/chemical stimuli normally resulting in an increase in both fR and V_T , and non-metabolic/non-chemical intense stimuli (thermal, nociceptive, psychological) primarily resulting in an increase in fR . However, current understanding of the pathways involved, the complex integration, multiple mechanical and physiological determinants of the ventilatory response and experimental difficulty in evoking and isolating a standardised stressor, make this impossible to test definitively at this time.

We conclude that a careful analysis of the breathing pattern of a patient might be informative diagnostically; there are likely to be associations between breathing pattern and potential causes of a disease; these could inform effective treatment strategy. In the areas of AMS, disease-related hypoxic ventilatory responses and clinical psychology we have presented some tentative evidence to support the idea that the pattern of the fR and V_T response of an individual may provide information regarding their physiological and pathophysiological state. Much more investigation is required in this area to determine the utility of this approach.

Although comprehensive, the current review is not systematic in nature; the data it sought were often not reported or not the main purpose of the study reviewed. Indeed, with the reporting of fR and V_T typically neglected in the relevant scientific literature, it was difficult to draw together sufficient evidence to reach a conclusion. Furthermore, the data we have examined in some areas are confused by the complex nature of some of the methodologies adopted (competing stimuli, confounding factors), the duration and intensity of stimuli and individual variation.

The strength of this review is that its findings have implications for teaching, research methodology and future physiological and clinical research. The findings are not limited to one discipline, but are integrative and relevant for physiology, psychophysiology, neuroscience and pathophysiology. They highlight an important

consideration that has been overlooked in some research areas and applied situations. More research is required to gain further insight into the patterns of the ventilatory responses produced by stressors and what they reveal.

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FIGURE LEGENDS

Figure 1. The route by which V_T and f_R may be altered (from Younes & Remmers, 1981).

Figure 2. Increase in tidal volume and respiratory frequency in response to the cold shock response (cold exposure for ≤ 120 s) on Panel A and prolonged cooling (> 120 s) on Panel B. Data extracted from the following references: Barwood *et al.* (2013; 2014); Button *et al.* (2015); Eglin *et al.* (2015); Eglin & Tipton (2005); Frank *et al.* (1997); Hayashi *et al.* (2006); Mantoni *et al.* (2007; 2008); Tipton & Golden (1987); Tipton *et al.* (1991); Wagner & Horvath, (1985).

Figure 3. Increase in tidal volume and respiratory frequency in response to passive heating on Panel A and the combination of exercise and heat exposure on Panel B. Data extracted from the following references: Cabanac & White (1995); Curtis *et al.* 2007; Fan *et al.* (2008); Fujii *et al.* (2008a; 2008b; 2012); Hayashi *et al.* (2006; 2011); Nelson *et al.* (2011); Tsuji *et al.* (2012a; 2012b; 2015).

Figure 4. Increase in tidal volume and respiratory frequency in response to hypoxic exposure. Solid triangle represents individuals who required supplementary oxygen and the solid square represents those who did not require supplementary oxygen at altitude (5200m) (Bernardi *et al.* 2006). Data extracted from the following references: Bernardi *et al.* (2006); Berssenbrugge *et al.* (1983); Curtis *et al.* (2007); Easton & Anthonisen (1988); Faiss *et al.* (2013); Georgopoulos *et al.* (1989); Morelli *et al.* (2004); Puthon *et al.* (2015); Richard *et al.* (2014); Savourey *et al.* (2007).

Figure 5. Increase in tidal volume and respiratory frequency in response to “panic” induced by CO_2 inhalation (hypercarbia). Open diamonds represents anxiety

associated with anticipatory electric shock (Masaoka & Homma, 2001) and open squares represents social anxiety associated with being touched by an individual (Wilhelm *et al.* 2001). Data extracted from the following references: Bailey & Holt (2002); Gorman *et al.* (2000); Hoit *et al.* (2007); Masaoka & Homma (2001); Papp *et al.* (1997); Pine *et al.* (1998; 2000); Wilhelm *et al.* (2001).

Figure 6. Increase in tidal volume and respiratory frequency in response to painful stimuli. Open triangles represent pain experienced before an intercostobrachial nerve block in hand injuries (Bourke, 1997) and open squares represents post cholecystectomy operative pain (Joris *et al.* 1992). Data extracted from the following references: Bourke (1997); Duranti *et al.* (1991); Joris *et al.* (1992); Sarton *et al.* (1997).

Figure 7. The brainstem respiratory network.

The brainstem respiratory network is organized into compartments that extend from the pons to caudal areas of the medulla. These include in the pons the Kolliker–Fuse nucleus (KF) and the lateral parabrachial region (LPBr). In the medulla exists the ventral respiratory column (VRC) consisting of (rostral to caudal) the Bötzing complex (BötC), pre-Bötzing complex (Pre-BötC), the rostral and caudal ventral respiratory groups (r/c VRG). The VRC is located ventral to the nucleus ambiguus (NA), caudal to the facial nucleus (VII) and extends to the lateral reticular nucleus (LRt). Much interconnectivity between the Bötzing and pre-Bötzing complexes is reciprocally inhibitory whereas the projections from central chemoreceptive areas coexisting within the retrotrapezoid nucleus (RTN) and the para facial respiratory group (pFRG) are excitatory to the VRC. The KF plays a dominant role in cranial-spinal motor co-ordination and respiratory phase switching. Visceral afferents such as lung inflation and peripheral chemoreceptor inputs relay via the nucleus tractus solitarii in the dorsomedial medulla (not shown) and connect directly or indirectly (via the pons) to the VRC. The image on the left is a parasagittal section from a rat brainstem. Abbreviations: Pn, ventral pontine nucleus; LRt, lateral reticular nucleus; SO, superior olive. Scp, superior cerebellar peduncle; V, motor nucleus of the trigeminal nerve.