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The biological impact of living with chronic breathlessness – A role for the hypothalamic–pituitary–adrenal axis?

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ABSTRACT

Breathlessness is a common and distressing symptom in advanced cardiorespiratory disease, with recognised psychological, functional and social consequences. The biological impact of living with chronic breathlessness has not been explored. As breathlessness is often perceived as a threat to survival, we propose that episodic breathlessness engages the stress-response, as regulated by the hypothalamic–pituitary–adrenal (HPA) axis. Furthermore, we hypothesise that chronic breathlessness causes excessive stimulation of the HPA axis, resulting in dysfunctional regulation of the HPA axis and associated neuropsychological, metabolic and immunological sequelae. A number of observations provide indirect support for this hypothesis. Firstly, breathlessness and the HPA axis are both associated with anxiety. Secondly, similar cortico-limbic system structures govern both breathlessness perception and HPA axis regulation. Thirdly, breathlessness and HPA axis dysfunction are both independent predictors of survival. There is a need for direct observational evidence as well as experimental data to investigate this hypothesis which, if plausible, could lead to the identification of a new biomarker pathway to support breathlessness research.

Introduction

Breathing is a basic instinct essential to survival. It is not surprising, therefore, that the symptom of breathlessness is often perceived as a threat to survival and is commonly associated with a fear of dying [1]. The psychological, functional and social consequences of living with this chronic stressor, in the context of advanced cardiorespiratory disease, have been prolifically described in the literature, with evidence, across a range of diagnoses, indicating that it causes significant psychological distress, physical disability and social isolation [2–4]. The biological impact of living with chronic breathlessness has not been explored, however. Due to the survival threat associated with breathlessness, one would intuitively expect the sensation of breathlessness to engage the physiological stress-response system and that the biological consequences of breathlessness might be effectuated through this system. On the basis of this presumption, an understanding of stress biology might provide clues about the biological impact of breathlessness.

The biological consequences of living with chronic stress are being increasingly elucidated in the psychoneuroendocrinological literature. The ability to measure the function of the hypothalamic–pituitary–adrenal (HPA) axis, an important regulator of the stress-response, has been a key advance in the understanding of this area. It is now recognised that the prolonged or repeated exposure to stressful triggers may actually result in a dysregulated or dysfunctional HPA axis [5]. This state is characterised by a disrupted circadian pattern of cortisol secretion, with loss of normal rhythm and responsiveness [6,7]. This pattern of HPA axis dysfunction is believed to result in a range of metabolic, immunological and neuropsychological consequences [8] and has been found to be associated with important health outcomes including psychiatric morbidity [9], increased cardiovascular mortality [10] and reduced survival in cancer patients [11,12].

As breathlessness is a chronic stressor, we hypothesise that living with breathlessness causes a dysregulated HPA axis and that this, by extension, may result in important adverse biological and clinical outcomes, independent of the underlying disorder inducing the breathlessness. While a relationship between breathlessness and HPA axis function might seem intuitive, there is no evidence

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in the literature to indicate that a direct relationship between the two actually exists. There is much to suggest that such a relationship might exist, however, given the many intersections between the neuroscience of the respiratory system and that of the stress-system, as extensively reviewed by Abelsen et al. [13].

In the absence of evidence of a direct relationship, we have explored the literature for associations that might be suggestive of the co-existence of HPA axis dysfunction and breathlessness. We have identified three factors which appear to be associated with both breathlessness and HPA axis dysfunction, providing a link between the two. Firstly, we have identified that anxiety is associated with both breathlessness and HPA axis dysregulation. Secondly, related to this, we have noted that the areas of the cortico-limbic system involved in breathlessness processing are similar to the areas involved in regulating the HPA axis. Finally, we have observed that both breathlessness and HPA dysregulation are independent predictors of survival.

For each factor linking breathlessness and the HPA axis, we present the evidence, first in relation to breathlessness and then in relation to the HPA axis. We then postulate various mechanisms by which the mutual association of interest might causally link breathlessness and HPA axis dysregulation. We wish to highlight from the outset that we are not attempting to prove causality through the presentation of these indirect associations and are simply evaluating the scientific plausibility of our hypothesis, as well as generating related hypotheses about potential causal mechanisms involved. We hope that this exploration will ultimately facilitate the design of an experimental study to test our hypothesis.

Anxiety is associated with both breathlessness and HPA axis dysregulation

Association between breathlessness and anxiety

Anxiety appears to be a prominent part of the experience of breathlessness, regardless of the underlying disease. Qualitative studies report anxiety, panic and fear as significant features of the breathlessness experience in COPD and lung cancer [3,4], as well as in heart failure and motor neurone disease [4]. Anxiety disorders are also highly prevalent in respiratory disease. In COPD, generalised anxiety disorder has a prevalence ranging from 10% to 15.8% [14–17] compared with a lifetime rate of 5.1% in the general public [18], and panic disorder has a prevalence of 8–32% [17,19,20] compared with a lifetime prevalence rate of 1.5% in the general population [17,21]. Within COPD, breathlessness level has been shown to be positively correlated with anxiety level, independent of demographics and disease severity [22], suggesting that the high prevalence of anxiety seen in COPD may, in part, be explained by breathlessness. Interestingly, respiratory disorders also appear to be more prevalent in patients suffering from anxiety disorders. The life-time prevalence rate of respiratory disorder has been shown to be as high as 47% in patients with panic disorder compared to 13% in obsessive compulsive disorder [17,23]. In addition, intrinsically irregular breathing patterns have been demonstrated in patients suffering from panic disorder [24].

Theoretical knowledge of breathlessness genesis and evidence of anxiety-related changes in breathlessness perception support the possibility of a causal relationship between breathlessness and anxiety, the temporal nature of which appears to be complex. Theoretically, breathlessness perception is understood to have both sensory and affective dimensions [25], which may be measured using separate subjective scales in experimental studies [26] and which may be distinguished clinically by different breathlessness descriptors [27]. Accordingly, anxiety may be understood as an emotional response to the affective dimension of the sensation. There is also evidence to suggest that breathlessness occurs in response to anxiety. Qualitative studies of breathlessness experience suggest that breathlessness triggers anxiety and anxiety triggers breathlessness, resulting in a self-perpetuating cycle [28]. In addition, an induced negative affective state, such as anxiety, has been shown to increase the affective component of breathlessness perception in COPD patients [29]. Furthermore, distraction techniques, which are often used in anxiety management, have been shown to reduce the affective component of breathlessness perception both in healthy volunteers experiencing induced breathlessness [30] and in exercising COPD patients [31]. Thus, the theory and the evidence suggest that a bidirectional relationship between breathlessness and anxiety is likely.

Association between HPA axis dysregulation and anxiety

As well as being associated with breathlessness, anxiety has also been shown to be associated with HPA axis dysregulation. Cross-sectional large-scale population studies have demonstrated that the normal distinct pattern of cortisol secretion is absent in those suffering from anxiety disorder [32,33], though the pattern of disruption has been inconsistent across studies. Hek et al. [33] demonstrated that the cortisol awakening response, which is calculated by measuring the cortisol rise after 30 min of awakening, was significantly reduced in 145 community-based patients with a variety of chronic anxiety disorders (>65 years) compared to 1643 normal controls. By contrast, Vreeburg et al. [32] demonstrated that the one-hour cortisol awakening level was significantly higher in a group of 774 patients with a current diagnosis of anxiety disorder in comparison with 342 normal controls. Both of these large studies suggest that anxiety is associated with HPA dysregulation but the reported pattern of dysregulation appears to conflict. The determinants of the pattern of HPA dysregulation observed in association with anxiety disorder are not known but factors which may be implicated include subdiagnosis, population and chronicity. In relation to chronicity, for example, it is postulated that a recent diagnosis of anxiety disorder may be associated with a hyperactive HPA axis which, over time, becomes hypoactive [33]. Further studies are necessary in order to better interpret these findings.

The evidence of an association between anxiety disorder and HPA axis dysregulation is strengthened by recent longitudinal data in which 837 patients with anxiety disorder (42.8%), depression (22.2%) or both (35%) were followed over 2 years [34]. In this study, a lower cortisol awakening response at baseline was independently associated with a significantly more unfavourable course of disease after 2 years of follow-up [34], suggesting that HPA axis dyregulation may be implicated in anxiety disorder progression. This finding suggests that the association between anxiety and HPA axis dysregulation is worthy of further investigation.

Could breathlessness cause HPA axis dysregulation through its association with anxiety?

Clearly, it is not possibly to prove a causal association between breathlessness and HPA axis dysregulation outside of an experimental study. However, the intimate, bidirectional relationship between breathlessness and anxiety suggests that they might operate together along a causal chain of common effects, one potential effect being HPA axis dysregulation. As anxiety is a product of the limbic system, it is likely that any impact which breathlessness might have on HPA axis function, through its relationship with anxiety, is effected by modulation of the cortico-limbic control of the HPA axis. The potential role for the cortico-limbic sys-