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Breathlessness and inflammation: potential relationships and implications

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Abstract

Purpose of Review: Breathlessness and chronic inflammation both span a wide range of disease contexts and hold prognostic significance. The possibility of a causal relationship between the two has been hypothesised. The aims of this article are 1) to review the intersections between breathlessness and inflammation in the literature, 2) to describe potential mechanisms connecting the two phenomena, and 3) to discuss the potential clinical implications of a causal relationship.

Recent findings: There is a very limited literature exploring the relationship between systemic inflammation and breathlessness in COPD, heart failure and cancer. One large study in cancer patients is suggestive of a weak association between self-reported breathlessness and inflammation. Studies exploring the relationship between inflammation and MRC (Medical Research Council) Dyspnoea grade in COPD patients have produced inconsistent findings. Though a causal relationship has not yet been proven, there is evidence to support the existence of potential mechanisms mediating a relationship. This evidence points to a role for the skeletal muscle and stress hormone systems.

Summary: There is much progress to be made in this area. Interventional studies, evaluating the impact of anti-inflammatory interventions on breathlessness, are needed to help determine whether a causal relationship exists. If proven, this relationship might have important implications for both the treatment and impact of breathlessness.

Keywords: ‘breathlessness’, ‘inflammation’, ‘stress’, ‘skeletal muscle’

Breathlessness and Inflammation: potential relationships and implications

Introduction

Chronic breathlessness is a distressing symptom, of growing significance, which affects millions of people throughout the world (1). Its genesis is multifactorial, resulting from the interaction of physiological, psychological, social and environmental factors (2). Though it is highly prevalent in cardiorespiratory disease, such as COPD and heart failure (3), the experience of breathlessness extends far beyond this context. It is a prominent symptom in panic disorder (4), in the frail elderly (5), and in the last weeks of life (6). Severity of breathlessness has been shown to predict mortality independent of underlying lung function in both COPD (7) and pulmonary fibrosis (8). It also predicts 10-year mortality in older adults independent of age, gender and underlying disease (9). These facts suggest that the symptom of breathlessness has an origin and impact beyond that of the lungs. Indeed, there is growing recognition of breathlessness as a disorder of the brain, where input from multiple peripheral systems, including the cardiorespiratory system, is centrally co-ordinated (10).

Chronic inflammation is a process that has the potential to explain the presence of breathlessness across a range of contexts, as well the independent relationship between breathlessness and prognosis. The term 'inflammation' may be defined as '*a complex biological response of vascular tissues to harmful stimuli*' (11). It results in the release of a heterogeneous group of polypeptides or glycoproteins, termed 'cytokines', which influence cell growth, differentiation and activation, and which facilitate communication between both cells and tissues (12). In the clinical setting, this

response is characterised by raised levels of plasma biomarkers including cytokines [e.g. interleukin (IL)-6 and tumour necrosis factor (TNF)-α], cytokine antagonists, acute-phase proteins [e.g. C-reactive protein (CRP)], and immune cells [e.g. neutrophils and natural killer (NK) cells] (13).

In the short-term, the inflammatory response is protective and beneficial. In the long-term, however, chronic activation of this state may result in significant tissue damage. Accordingly, chronic systemic inflammation has been associated with a wide range of diseases including COPD (13-18), heart failure (19-20), metabolic syndrome (21), and autoimmune disorders such as multiple sclerosis and systemic lupus erythematosus (SLE) (22). It has also been linked to the development of psychiatric disorders such as depression and bipolar disorder (23). Furthermore, there is evidence associating it with a range of cancer symptoms including pain (24), anorexia-cachexia syndrome (25-26), depression (27-28) and fatigue (29). Indeed, it has been proposed that chronic inflammation may underlie the commonly observed clustering of these symptoms within individual cancer patients, a theory supported by the animal model of cytokine-induced sickness behaviour (30-32).

To date, the relationship between breathlessness and inflammation has not been explicitly investigated. There are some clues in the literature that might suggest a relationship, however. The aim of this article is to review the intersections between breathlessness and inflammation in the literature and to describe postulated mechanisms which may connect the two phenomena.

Evidence linking breathlessness and inflammation

Chronic inflammation has been studied extensively in the context of COPD, heart failure and cancer. Though the relationship between breathlessness and chronic inflammation has not been of primary interest within such studies, the measurement of breathlessness-related constructs within some of these studies provides insight into this relationship.

A small number of studies have investigated inflammation in relation to disability due to breathlessness, as measured using the MRC (Medical Research Council) Dyspnoea grading system, in patients with COPD. Whilst Pinto-Plata et al. (15) (n=88) did not identify a significant association between MRC Dyspnoea grade and CRP, Garrod et al. (33) (n=43) demonstrated that those with an MRC Dyspnoea grade of 5 had significantly higher inflammatory markers (CRP and IL-6) than those with an MRC Dyspnoea grade of 1-2. More recently, in a large cohort study of 1775 COPD patients (ECLIPSE), the subgroup with persistent inflammation at one year of follow-up (16%) were observed to have a higher mean MRC Dyspnoea grade at baseline (34). This variable was not found to be an independent predictor of inflammation in a logistic regression model, however.

There has been very limited study of systemic inflammation in relation to the sensory or perceptual experience of breathlessness. The findings from one large European study, which included 1446 patients with advanced cancer, suggest that inflammation may be as relevant to breathlessness as it is to the other self-reported cancer symptoms (31). In this cross-sectional analysis, a wide range of symptoms were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- Core Questionnaire (EORTC QLQ- C30), and CRP levels were found to correlate significantly with breathlessness, as well as pain, fatigue, anorexia, and cognitive dysfunction. Interestingly, the correlation with CRP was low for all symptoms, with the correlation between CRP and breathlessness ($r=0.150$) being similar to that for CRP and pain ($r=0.154$). It is noteworthy that these low correlations were considered to be clinically significant by the authors due to the multiple factors affecting both inflammation and symptoms in this patient sample.

Systemic inflammation has also been explored in relation to the New York Heart Association (NYHA) grading system in patients with heart failure and in relation to exercise tolerance in COPD. In a cross-sectional study involving 66 patients with heart failure, Nozaki et al. (20) identified that soluble TNF-α receptor levels increased significantly as NYHA grade increased. Furthermore, Dixon et al. (35)

demonstrated a significant positive association between NYHA grade and levels of both TNF-β and IL-10 in a sample of 30 heart failure patients. In COPD, exercise tolerance has been found to be significantly associated with markers of inflammation in a number of cross-sectional studies. Yende et al. (36) (n=187) found that IL-6 levels predicted exercise tolerance, independent of quadriceps strength. Pinto-Plata et al. (15) (n=88) identified a significant inverse association between 6-minute walk distance and CRP level, independent of age and lung function. Similarly, Broekhuizen et al. (37) (n=102) demonstrated that exercise capacity and 6-minute walk distance were significantly lower in those with a raised CRP in comparison to those with a normal CRP, despite a similar mean FEV1 (forced expiratory volume in 1 second) for both groups.

Finally, there is some evidence in the literature to suggest a relationship between systemic inflammation and quality of life in COPD, a construct to which breathlessness contributes. Broekhuizein et al. (37) (n=102) found that patients with a raised CRP had a significantly higher score on the symptom domain of the St. George's Respiratory Questionnaire (SGRQ). Similarly, Garrod et al. (33) (n=43) demonstrated a moderate positive correlation between CRP level and total SGRQ score ($r=0.43$, $p<0.01$). This relationship has recently been confirmed in a large longitudinal study (ECLIPSE), where SGRQ was found to be an independent predictor of systemic inflammation at one-year follow-up (34).

Potential mechanisms linking breathlessness and inflammation

Whilst some of the evidence outlined above points to a possible association between breathlessness and inflammation, none of the evidence is sufficient to prove a causal relationship. There is evidence in the literature of mechanisms which might causally link breathlessness to inflammation, however. Two possible mechanisms appear to link breathlessness and inflammation in a bidirectional manner, suggesting particular relevance. These mechanisms arise through the effects of breathlessness and inflammation on 1) the skeletal muscle system, and 2) the stress hormone system (see Figure 1).

The skeletal muscle system

One hypothesis linking breathlessness and systemic inflammation is that systemic inflammation contributes to breathlessness through its effects on skeletal muscle. This hypothesis is illustrated in Figure 1.

Lower limb muscle dysfunction is characterised by muscle atrophy, a shift from type I to type II fibres, mitochondrial dysfunction, reduced oxidative capacity, and muscle weakness (38). There is growing evidence in the literature supporting the independent contribution of this condition to the genesis of breathlessness. Quadriceps muscle strength has been shown to be inversely associated with exertional breathlessness both in patients with cardiorespiratory disease (39) and in older adults (5). In addition, physiological studies in COPD patients suggest that lower limb muscle dysfunction results in early development of lactic acidosis during exercise, with a consequent increase in neural respiratory drive, and thus breathlessness (40-41). There is also evidence that ventilatory drive is increased as a result of direct feedback to the central nervous system (CNS) from grade III/IV sensory afferents in lower limb muscle as they respond to the local release of anaerobic metabolites during exercise (42).

Systemic inflammation is known to contribute to muscle wasting in a range of conditions including sepsis, cancer, and COPD (43-45). Several cytokines, particularly TNF-α, are known to upregulate expression of nuclear factor kappa B (NF-κB) in muscle tissue, a key transcription factor which regulates the ubiquitin-proteasome pathway, a major effector of proteolysis (44). In animal studies, IL-6 has been shown to induce proteolysis pathways (46) and to inhibit the secretion and activity of insulin-like growth factor-1 (IGF-1) (47). Furthermore, anti-IL-6 receptor antibodies have been shown to reverse muscle wasting in IL-6 transgenic mice (46).

In the context of breathlessness, systemic inflammation may arise in response to the underlying

disease or in response to breathlessness-induced inactivity. Inactivity is considered to be a major contributor to skeletal muscle dysfunction in the context of breathlessness, as evidenced by longitudinal studies in COPD patients (38, 48). Though disuse of muscle is itself a direct activator of the ubiquitin-proteasome pathway (44), inactivity might also cause muscle wasting by activating the systemic inflammatory response. In support of this hypothesis, several population cohort studies have shown evidence of an inverse relationship between levels of CRP and physical activity (49-50). Furthermore, a number of interventional studies, conducted in diverse health populations, have shown a reduction in inflammatory markers after exercise-training, suggesting a causal relationship between physical activity and inflammation, which is currently not fully understood (49).

Thus, breathlessness may contribute to systemic inflammation through inactivity, and systemic inflammation (either due to inactivity or the underlying disease) may, in turn, contribute to breathlessness through its effects on muscle catabolism.

The stress hormone system

A second hypothesis linking breathlessness and inflammation is that breathlessness causes systemic inflammation through the effects of breathlessness-related stress on the hypothalamic-pituitary-adrenal (HPA) axis (51). This hypothesis is illustrated in Figure 1.

The relationship between breathlessness and emotion is well-established in the literature. Qualitative studies of the experience of breathlessness suggest a bidirectional relationship between breathlessness and anxiety, where anxiety is both a response to and a trigger for breathlessness (52). The perception of breathlessness is known to have both sensory and affective dimensions (53-54), and negative affective states have been shown in laboratory studies to modulate the affective dimension (55). Furthermore, functional imaging studies have shown that breathlessness is processed in the insular cortex, the amygdala and the anterior cingulate cortex (56-57), areas of the

brain involved in emotion and behaviour regulation in response to stressful physical and psychological stimuli (51, 58) (see Figure 2). These observations all suggest that the stress hormone system may be engaged by the experience of breathlessness.

The hypothalamic-pituitary-adrenal (HPA) axis is a key component of the stress hormone system. This axis regulates the production of glucocorticoids, such as cortisol, in response to stress and circadian signals, through a negative feedback loop (see Figure 2). In the context of repeated or prolonged exposure to stressful triggers (as might occur in chronic breathlessness), this regulatory system becomes dysregulated, which may manifest as loss of diurnal variation in cortisol secretion, hypercortisolism or hypocortisolism (59-60).

There is ample evidence in the literature of close interaction between the HPA axis and the systemic inflammatory response, with inflammation being both a cause and a consequence of HPA axis dysregulation. Cytokines, such as IL-1, IL6, TNF-α, and INF (interferon)-α, have been shown to activate the HPA axis and downregulate glucocorticoid receptors in several studies (23), resulting in decreased negative feedback and excessive stimulation of the HPA axis in chronic inflammatory states. Importantly, this cytokine-induced HPA activity has been shown to be requisite for cytokine-induced muscle-atrophy (61). Dysfunctional HPA axis activity itself has been shown to result in increased levels of systemic inflammation (62). This may happen in the context of hypocortisolism, due to loss of cortisol-induced anti-inflammatory effects, or in the context of hypercortisolism, due to glucocorticoid resistance (62). Consistent with this, HPA axis dysregulation has been identified in association with several auto-immune, inflammatory and metabolic disorders (62).

Thus, breathlessness-induced stress may result in HPA axis dysregulation, resulting in systemic inflammation, which, in turn, may contribute to breathlessness through effects on the skeletal muscle system.

Future research and clinical implications

The hypotheses presented in this article suggest that systemic inflammation may contribute to and be a consequence of chronic breathlessness. It is now necessary to test these hypotheses and prove this relationship.

A major barrier to knowledge of this relationship to date has been the lack of measurement of breathlessness, alongside markers of inflammation, in clinical studies. Though many studies have explored the relationship between inflammation and breathlessness-related constructs, no studies have undertaken detailed assessments of breathlessness alongside markers of inflammation, taking into account both the sensory and affective dimensions of breathlessness, as well as its impact on function. Inadequate measurement of breathlessness is likely to result in false-negative findings in association studies.

With robust measures of breathlessness on board, it would be useful to conduct a longitudinal study to assess the temporal relationship between breathlessness, inflammation, psychological stress, HPA axis dysfunction and muscle wasting. This would facilitate the design and interpretation of later interventional studies conducted to test the specific mechanistic hypotheses. An obvious interventional study would be the investigation of the effect of an anti-inflammatory intervention on breathlessness, as well as its effects on skeletal muscle and HPA axis function. This design would allow both the causal relationship and its mediators to be examined.

Clinically, a proven relationship might have significant implications for the treatment and impact of breathlessness. If systemic inflammation were proven to contribute to the genesis of breathlessness, this would open the door to a wide range of potential anti-inflammatory therapies in the treatment of breathlessness. Possible candidate agents might include cytokine inhibitors, NSAIDs, eicosapentanoic fatty acid supplements, and exercise. Randomised controlled trial evaluation of

each of these agents would be necessary, with breathlessness as the primary endpoint and skeletal muscle function, inflammation and HPA axis function as intermediate or biomarker endpoints. Interventions which target the hypothesised mediators of the breathlessness-inflammation relationship might, alternatively, be more effective than targeting inflammation directly, as these agents would have a direct effect on both breathlessness and inflammation, as well as an indirect effect on breathlessness through inflammation. Such agents include exercise (targeting skeletal muscle) and psychological therapies (targeting stress and the HPA axis).

Should systemic inflammation be found to be a consequence of breathlessness, this might explain the currently unexplained association between breathlessness severity and mortality across a range of diagnoses including COPD (7), pulmonary fibrosis (8), cancer (63) and the elderly (9). It might also explain the survival benefit associated with breathlessness management in a recent RCT evaluation of a multi-disciplinary breathlessness service (64). Given the effects of systemic inflammation on mood and skeletal muscle, breathlessness-induced systemic inflammation might also contribute to the depression and disability commonly seen in association with breathlessness. Thus, treatment of breathlessness or associated systemic inflammation might confer benefits beyond relief of the symptom itself.

Conclusion

The relationship between systemic inflammation and breathlessness is virtually unexplored in the literature. This relationship is certainly worthy of investigation given the observed associations between inflammatory markers and breathlessness-related constructs in the literature, the availability of plausible mechanistic hypotheses linking the two phenomena, and the potential clinical implications that a proven causal relationship might confer. Whilst it is exciting to contemplate these possible links, there is much work to done in this field, and it is now necessary to move from theoretical postulation to investigation.

Key points

- The relationship between systemic inflammation and chronic breathlessness has been explored, as a secondary objective, in a small number of studies
- Some studies have reported a significant association between markers of inflammation and constructs relating to breathlessness, including self-reported breathlessness intensity, disability due to breathlessness, quality of life, and exercise-tolerance. Causal inferences cannot be made from these studies, however.
- A causal relationship between breathlessness and systemic inflammation, if proven, might be mediated through the effects of both phenomena on skeletal muscle function and stress hormone regulation.
- The relationship between breathlessness and inflammation needs significant further investigation, which will necessitate the conduct of interventional studies.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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Figure 1: Hypothesised relationship between breathlessness and systemic inflammation.

A bidirectional relationship exists between 1) breathlessness and skeletal muscle dysfunction, and 2) breathlessness and stress. Systemic inflammation has a bidirectional relationship with both skeletal muscle dysfunction and stress and may indirectly influence breathlessness through these relationships. Abbreviations: HPA, hypothalamic-pituitary-adrenal axis.

Figure 2. Schematic diagram of the HPA axis, showing its regulation by the amydala, midbrain, prefrontal cortex and hippocampus, and illustrating the negative feedback regulation of cortisol via glucocorticoid receptors. Activation and inhibition are indicated by the symbols '+ve' and '-ve', respectively. Abbreviations: VN, paraventricular nucleus; CRH, corticotrophin releasing hormone; GR, glucoreceptor; MR, mineralocorticoid receptor.

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This randomised controlled trial evaluated an integrated palliative and respiratory care service for patients with advanced disease suffering from refractory breathlessness ('breathlessness support service'), comparing it to a 'waiting list' control. The group receiving the breathlessness support service had significantly better mastery of breathlessness at 6 weeks. As well as this, non-cancer patients receiving the breathlessness service had a significantly better survival rate at 6 months compared to the control group.