REVIEW

Dyspnea and emotional states in health and disease

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Summary
Anxiety and depression can increase the intensity of dyspnea out of proportion to the impairment in cardiorespiratory function and may contribute to the degree of disability associated with dyspnea. The effect of anxiety/depression on the sensory and affective components of reported dyspnea in patients with respiratory disorders might be of particular importance in improving the accuracy of the diagnostic process. However, the exact cause-relationship between dyspnea and anxiety/depression are unclear. A multidimensional model of dyspnea subsuming sensory components (i.e. intensity and quality) and affective components has recently been proposed. Affective responses drive patients to seek treatment which can cause them to alter their lifestyle to avoid dyspnea. Brain imaging techniques help identify distinct cortical structures involved in processing the discrete components of dyspnea.

Contents

Introduction ................................................................. 650
Effects of emotional states on dyspnea perception .................................................. 650
Chronic obstructive pulmonary disease (COPD) ..................................................... 650
Asthma ................................................................. 650

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Introduction

The influence of emotional states on symptom perception in respiratory disease is a topic of growing interest to researchers and clinicians. Patients with chronic lung disease who suffer from dyspnea often exhibit anxiety or depressive symptoms. These emotional states have been shown to predict poorer quality of life and functional status and likely contribute to the degree of disability associated with dyspnea and increased use of medical services. Emotional states may shape the quality and intensity of dyspnea at a given level of respiratory activity and partly explain why the relationship between dyspnea and the degree of impairment in lung function is not strong. Although anxiety and depression may lead to worsening of dyspnea, the exact cause relationships and direction of causality between dyspnea and anxiety/depression are unclear.

Surprisingly, despite frequent discrepancies between respiratory patients’ self-reported dyspnea and the extent of underlying pathophysiology, few studies have investigated the effect of psychopathology on ratings of perceived dyspnea by applying psychophysical methods, that is, the quantitative study of the relationship between dyspnea and the evoked conscious sensory response. A critical appraisal of symptoms can only come with application of psychophysical techniques applied within the framework of respiratory and sensory physiology. As with pain, dyspnea should be measured adequately. A consensus statement of the American Thoracic Society (ATS) has recently proposed that “instruments or section of instruments pertaining to dyspnea should be classified as addressing domains of sensory-perceptual experience, affective distress, or symptom/disease impact or burden”. Sensory-perceptual measures include ratings of intensity (real-time dyspnea measures), and sensory quality. Affective distress can pertain to either a perception of immediate unpleasantness or to a cognitive-evaluative response to or judgment about the possible consequence of what is perceived. Impact measures, although very important, do not directly assess “what breathing feels like”.

This review focuses on the following: (i) The effect of anxiety/depression on perceived dyspnea in health and disease, (ii) Differentiation between sensory and affective components in patients with respiratory disorders, and (iii) Brain processing of the discrete components of dyspnea.

Effects of emotional states on dyspnea perception

Chronic obstructive pulmonary disease (COPD)

The greatest attention has been focused on the psychological parameters of COPD. A systematic review of 64 studies focusing on patients with severe disease, indicated that the level of anxiety and depression in COPD patients was comparable to or higher than the levels detected in cancer, AIDS, renal and cardiac patients. The question arises as to whether anxiety and depression can intensify dyspnea out of proportion to the level of impairment evidenced by the cardiorespiratory function. Dahlen et al. investigated whether psychological factors assessed by the hospital anxiety and depression (HAD) scale were correlated to the risk of relapse in patients with acute exacerbation of asthma and COPD. In their series patients with probable anxiety and/or depression had the same dyspnea score as patients without anxiety or depression. Also, the risk of treatment failure was significantly related to HAD, but not to dyspnea. More recently, it has been shown that the degree of chronic emotional dyspnea assessed by a graded scale does not differ between non-depressed and depressed COPD patients with similar levels of airway obstruction but a greater level of anxiety in the latter group. Other studies have shown a significant association between anxiety/depression (HAD scale) and increase in intensity of dyspnea at rest and after 6 min walking test in patients with mild to moderate COPD. A pulmonary rehabilitation program (PRP) reduced both dyspnea and anxiety/depression but this association remained stable over the course of PRP even when improvements in the outcomes were achieved during PRP. In addition the negative association between anxiety/depression and dyspnea is not thought to provide proof of causality between these variables. Further studies are needed to determine a specific cause-effect relationship.

A recent study has shown that the presence of panic attacks (i.e. acute intense anxiety associated with physical symptoms and cognitive fears) or panic disorders in individuals with COPD may be associated with a heightened perception of dyspnea. Livermore et al., compared the perceptual response to a resistive load in COPD patients with panic attack (PA) or panic disorders (PD) and healthy subjects. The dyspnea rating increased linearly for all groups with increasing the resistive load. Patients with PA or PD rated their level of dyspnea significantly higher than did other subjects. In addition, the higher the levels of depression between the groups, the greater the rating of dyspnea as the magnitude of resistive load increased. So the diagnosis of panic attack/disorder should be carefully considered in patients with respiratory obstructive disorders.

Asthma

Janson et al. have documented correlations between depression/anxiety (HAD scale) and the report of asthma-related symptoms, such as attacks of breathlessness during rest and activity, and waking with either attacks of breathlessness or chest tightness. On the other hand, Chetta et al.
were not able to find any relationship between personality profile by applying the Minnesota Multiphasic Personality In-
ventory (MPI) questionnaire, and perceived dyspnea on a Borg scale at 20% FEV<sub>1</sub> (forced expiratory volume in 1 s) fall during
a bronchial provocation test. By contrast, significantly higher
levels of perceived breathlessness have been reported during
induced bronchoconstriction in asthmatics with comorbid
panic disorders. 23 In patients with near-fatal asthma psycho-
logical disturbances might affect asthma control. In a study by
Boulet et al., 24 patients with near-fatal asthma exhibited more
psychological problems than the non-asthmatic group. How-
ever, an increase in Borg was associated with a concurrent
decrease in peak expiratory flow (PEF %pred) similarly in the
two groups. Also, perception of dyspnea on a Borg scale at 20% fall in FEV<sub>1</sub> during methacholine-induced bronchoconstriction
was similar in near-fatal and non-near-fatal asthma groups (3
vs 2.5, Borg units, respectively).

Although the ventilatory response to inspiratory loads is
governed primarily by respiratory system mechanics and re-
flexes, behavioral or cognitive factors may play a role in this
response as well. Lavietes et al. 25 hypothesised that patients
with a specific psychological trait will associate a greater
degree of dyspnea during loaded breathing task than other-
wise healthy control subjects. They recruited subjects with
Chronic Fatigue Syndrome (CFS), and normal healthy sub-
jects. The choice of CFS was motivated by the fact that
somatisation was thought to explain in part the symptom of
CFS. Subjects were divided into two groups. The "responder"
group reported Borg scores higher than those of the second
"non-responder" group at all times during resistive breathing
protocol. Responders presented higher depression scores
(Center for Epidemiologic Study depression scale) than did
non-responders. Of note a greater percentage of patients
(42%) with psychological problems were in the "responder"
group than in the "non-responder" group (17%). On the other
hand, no differences on depression scale were found in
control subjects, regardless of load response. Thus the
diagnosis of panic attack/disorder should be carefully con-
sidered in patients with severe respiratory obstructive
disorders.

**Affective components of dyspnea and brain processing**

Any assessment of dyspnea should try to measure the in-
tensity and quality of the sensation of respiratory dis-
comfort and the emotional and behavioral response to the
breathing discomfort. 13 Pivotal studies 26–28 have provided
compelling evidence that sensory intensity and the un-
pleasantness of pain are discrete dimensions since they can
be independently manipulated in laboratory and clinical
situations. They even appear to be separated by separate
neural pathways, a lateral thalamic system that projects to
the primary sensory cortex and subserves sensory aspects,
and a medial thalamic system that projects to the limbic
cortex and subserves affective aspects. 28 Further develop-
ment regarding the affective dimensions of pain has been
divided into an initial stage A1 of immediate un-
pleasantness or discomfort, and later stage A2 of cogni-
tively mediated emotional reactions such as depression,
anxiety, fear, etc., that may lead to behavioral outcomes. 28

Recently, brain image techniques have been used to iden-
tify distinct cortical structures and pathways that have
been shown to be more involved in either sensory or affec-
tive aspects of pain. 27,29 It has been postulated (but not
definitely proven) that these structures might also process
the discrete components of dyspnea. 30,31 In this regard
Davenport and Reep 32 have described the two major
pathways suggested to process respiratory sensation to the
sensory cortex. The first pathway arises predominantly
from respiratory muscle afferents, is relayed to the brain-
stem medulla, and projects to the ventroposterior thalamus
area, from where thalamocortical projections ascend to the
primary and secondary somatosensory cortex. The second
pathway includes mainly vagal afferents from the lungs and
airways which are relayed in the brainstem medulla.

First evidence has suggested similar multidimensionality
in the perception of both pain and dyspnea. 29–31 Von Leu-
poldt and Dahme 34 have recently shown in healthy subjects
breathing against increased inspiratory loads that with
increasing intensity of dyspnea the perceived unpleasantness
increased stronger than the perceived intensity, indicating
that the sensory and the affective dimensions of dyspnea can
be differentiated similarly to the perception of pain.

These findings help clarify and explain old and recent
data. Boulet et al. 35 were able to show that perception of
airflow obstruction and breathlessness following meth-
acholine challenge testing were correlated with each other.
Mean perception scores were higher for asthmatics than
controls but anxiety levels during methacholine was low in
both groups and did not correlate with dyspnea. However,
it must be noted that perception of airway obstruction was
defined as a sensation of a change in breathing pattern
while dyspnea was defined as an unpleasant sensation
associated with bronchoconstriction. We argue against this
contention as unpleasantness is likely to define the affec-
tive component while intensity of dyspnea (Borg scale)
defines one of the two aspects of the sensory component.

More recently de Peuter et al. 36 have calculated the
linear slope between a 20% fall in FEV<sub>1</sub>, and the increase in
the symptom scores of intensity and affectivity during
a histamine bronchial provocation test in patients with
asthma. Sensitivity appears to be positively related to trait
anxiety, state anxiety, daily asthma symptoms and cata-
strophic thinking during an asthma exacerbation in daily
life. These relationships were overall stronger for affective
than for sensory symptom slopes. By applying stepwise
multiple regression analysis, the state of anxiety was the
best predictor of the affective symptom slopes, whereas
catastrophic thinking during an asthma exacerbation was
the best predictor for the sensory symptom slopes. In
contrast, the relation between state anxiety and sensory
symptoms was not significant. These results have clinical
implications. A high sensitivity seems favorable because it
allows the early detection of deteriorating lung function
and quick medication relief. A moderate degree of asthma-
specific anxiety is adaptive because it may be associated
with enhanced perception of bronchoconstriction. In con-
trast, absence of anxiety may lead to indifference and
neglect of symptoms. 37
A differentiation between the sensory and affective components of reported dyspnea in patients with comorbid depression might be of particular importance and improve the accuracy of the diagnostic process, symptom perception, and therapeutic interventions. This has been pointed out in previous studies demonstrating that high negative affectivity reduces the accuracy of global rating of dyspnea perception. This might lead to an increased use of health care resources to find relief from the overly negatively perceived symptom. Put et al. found that asthmatics with high negative affectivity had overall more intense dyspnea than patients scoring low affectivity; in addition negative affectivity modulated the effects of suggestions on dyspnea. In this regard, Davenport et al. used respiratory-related evoked potential (RREP) methodology in a group of asthmatic children with a story of life-threatening asthma. They found an absence of P1 component after respiratory occlusion (i.e. the dyspneic sensory signal was not activating the somatosensory cortex). These data suggest the presence of an asthma-specific deficit in the latter cortical processing of respiratory load information. Nonetheless, it might be interesting in this regard to examine whether patients with blunted perception of dyspnea have a specific deficit in the affective rather than the sensory aspects of their perceptual processing.

A multidimensional model of dyspnea subsuming sensory components (i.e. intensity and quality) and affective components has recently been proposed. Affective responses are a major stimulus for learning strategies to avoid biologically threatening sensations; they also drive patients to seek treatment and can cause them to alter their lifestyle to avoid dyspnea. An exaggerated perception of dyspnea, which may lead to excessive use of medical resources, may be an over-response in the affective dimension. In this connection, it has been hypothesised that the affective dimension of dyspnea (unpleasantness, emotional response) does not strictly depend on the intensity of dyspnea. Banzett and co-workers tested the hypothesis that the ratio of immediate unpleasantness (A1) to sensory intensity (SI) would vary, depending on the type of dyspnea. Three different stimuli were applied to healthy subjects. The first (maximal hyperpnea against inspiratory resistance) evoked work and effort sensations with relatively low unpleasantness (mean A1/SI = 0.64). The second stimulus (hypercapnia with restricted ventilation), titrated to produce dyspnea ratings similar to those obtained by applying the first stimulus; it evoked air hunger and produced significantly greater unpleasantness (mean A1/SI = 0.95). The third stimulus (further increase of the second stimulus, maximal hypopnea) was even higher until air hunger was intolerable, evoking the highest intensity and unpleasantness ratings and ratio (A1/SI = 1.09). The data show that: 1. unpleasantness of dyspnea can vary independently from perceived intensity, this is consistent with the prevailing model of pain, 2. multiple dimensions of dyspnea exist and can be measured. Determining whether a change in dyspnea reflects a change in the primary sensation or an affective response may inform us about the role of the psychological state of the patient in ratings respiratory discomfort and help guide therapies so as to reduce the A1/SI ratio and subsequent discomfort.

Additional studies from von Leupoldt et al. in healthy subjects breathing against inspiratory load during attention and distraction indicate that while subjects attend their breathing only intensity score on VAS influences Borg scale ratings. In contrast, only the VAS unpleasantness scores influences Borg scale rating when subjects are distracted. Directing the patient’s attention away from respiratory sensation decreases unpleasantness but not intensity, even if the difference in A1/SI is quite small.

Carriere-Kohman et al. have shown no correlation between patients’ state of anxiety and their anxiety associated with dyspnea during treadmill testing. Also, exercise training decreased dyspnea and related anxiety. These data indicate that the decrease in anxiety is specific for dyspnea and not related to a decrease in overall anxiety. The same group demonstrated that in COPD patients the relationship between affective and sensory dimensions can be changed within individual subjects. The authors pointed out that a supervised exercise training program reduced dyspnea-related anxiety more than the intensity of breathing effort. This also suggests that the affective state can limit a patient’s exercise tolerance during pulmonary rehabilitation, by reducing its beneficial effect.

Negative affective states, when compared with positive affective states, increase the perception of dyspnea during cycling exercise in patients with COPD. The affective unpleasantness of dyspnea during exercise is predictive of a greater symptom burden in patients’ everyday life and a greater reduction in their health-related quality of life. In other words, those patients experiencing their dyspnea as very unpleasant showed greater symptom burden in their everyday life. No such effect was found for sensory intensity of dyspnea.

Limbic structures have been identified as brain structures involved in the perception of pain. Banzett et al. and Evans et al. speculated that limbic structures were also involved in the perception of dyspnea. They found activation of mid/anterior insula during severe air hunger. In a functional imaging study (PET) Peiffer et al. were able to identify an area in the right posterior cingulated cortex during loaded breathing-induced dyspnea which they hypothesised to be associated with affective cognitive factors. Several regions in the posterior cingulated gyrus have indeed been previously been shown to be activated by various predominantly unpleasant sensory affective functions such as pain, emotion, anxiety, and related symptoms. Von Leupoldt et al. investigated the cortical area associated with the processing of affective unpleasantness of dyspnea by magnetic resonance imaging (fMRI) in healthy subjects. Dyspnea was induced by inspiratory resistive breathing with concomitant positive and negative emotional stimulation. The BOLD (blood oxygen level-dependent contrast) technique showed that negative emotional situations were associated with similar levels of intensity but higher unpleasantness of dyspnea when compared with concomitant positive emotional stimulation. Higher unpleasantness was associated with neural activation of limbic system (anterior insula and amygdala). The data suggest that unpleasantness but not intensity is processed in the human anterior insula and amygdala, and that different pathways might process affective and sensory dimensions of perceived dyspnea. The same group has recently shown that lesions of the right anterior insula cortex are associated with reduced sensitivity for the perception of dyspnea and pain, especially...
for their perceived unpleasantness. This study supports the theoretical assumption of a dual cortical processing of respiratory signals of dyspnea.

Von Leupoldt et al.52 have also shed light on the underlying brain mechanisms of perceived dyspnea in patients with asthma. Using function fMRI, they compared neural responses to experimentally-induced dyspnea by resistive load breathing and brain activation with neural responses evoked by heat pain induced by contact thermode in patients with asthma and healthy controls. Patients and controls rated the sensory intensity of both sensations similarly, while the affective unpleasantness of dyspnea and pain was reduced only in asthmatic patients. The perceptual differences were mirrored by a decrease in insula cortex activity, but with an increase in periaqueductal gray activity in asthmatic patients during both increased dyspnea and pain.52 These results suggest a down-regulation of affect-related insula cortex activity by periaqueductal gray activity during both sensations in patients with asthma. Moreover, a longer duration of asthma was correlated with a greater decrease in insula cortex response during increasing dyspnea. According to these authors this might represent a brain habituation mechanism that reduces the affective unpleasantness of dyspnea in patients with mild to moderate asthma. It is worth noting that reduced brain activation during dyspnea might constitute an important risk factor in asthma. In a more recent study of the same group53 a negative relationship was found between increased volume of periaqueductal gray and reduced reports of affective unpleasantness. These alterations are likely to contribute to the blunted perception of dyspnea, at least in patients with mild to moderate asthma. In turn, increased periaqueductal gray activity might lead to increased inhibition of dyspnic sensory afferent to the insular cortex with reduced insular activity without structural change in this area. It is not understood, however, how the insula gives rise to perceptions of breathlessness. Given the complexity of the sensation, activation of the insular cortex during dyspnea probably occurs in concert with a larger neural network functioning with the insula to mediate dyspnea perception.29,31,48,54

Neural circuitry underlying stress and emotion can regulate inflammation,55,56 and peripheral inflammatory mediators can influence mood and cognitive function.57 The body of evidence establishes bi-directional causal links between inflammation and psychological state.58 Asthma, like many inflammatory disorders, is affected by psychological stress suggesting that reciprocal modulation may occur between peripheral factors regulating inflammation and the central neural circuitry underlying emotion and stress reactivity.59 The neural circuitry involved remains, however, elusive and conjectural. Rosenkrantz et al.59 used the late phase component of an allergic reaction as a model to identify brain regions activated by emotional and physiological cues. Using fMRI, they showed that activity of the anterior cingulated cortex (ACC) and insula to asthma-relevant emotional stimuli is associated with markers of inflammation and airway obstruction in asthmatic subjects exposed to antigen. In particular, greater signal changes in the ACC and insula in response to antigen asthma-relevant stimuli are associated with larger increase in eosinophils and are correlated negatively with FEV1. According to Rosenkrantz et al.54,59 these results suggest a neural basis for emotion-induced modulation of airway disease in asthmatic patients. More recently the same group measured neural signal (fMRI) in response to asthma emotional cues, following allergen exposure in asthmatics with a dual response to allergen challenge, asthmatics with only an immediate response and healthy controls. Insula was activated by asthma-relevant cues (emotional stimuli) compared to general negative cues during the late phase of dual response in asthmatics.60 Like in the previous study59 the degree of this differential activation predicted changes in airway inflammation and the decrease in lung function. These findings suggest that changes in neural activity are likely to reflect both afferent and efferent processes. If the late phase response to allergen depends, at least in part, on neural responsivity to disease-relevant information, then reducing this responsivity should decrease the magnitude of the latter phase response. Thus far, whether functional brain imaging of the interaction between emotion and inflammation reflects an asthma neurophenotype remains to be defined.

Conclusions

Anxiety/Depression are likely contributors to the degree of disability associated with dyspnea in patients with chronic respiratory disease. However, a reciprocal interaction between the perception of Anxiety/Depression and dyspnea should be taken into account. A differentiation between the sensory and affective components of the reported dyspnea in these patients might be of particular importance and improve the accuracy of the symptom perception. Neuroimaging studies have shed light on the brain networks involved in the perception of sensory and affective components of dyspnea. Whether this can contribute to the development of more effective therapeutic strategies for dyspnic patients remains to be elucidated.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In doing so, we confirm that we have followed the regulations of our institutions concerning intellectual property. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submission of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.
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