Thorax Online First, published on April 21, 2009 as 10.1136/thx.2008.104869

# QUALITATIVE ASPECTS OF BREATHLESSNESS IN HEALTH AND DISEASE

Jaclyn Smith[1], Paul Albert[2], Enrica Bertella[3], James Lester[2], Sandy Jack[2], Peter Calverley[2]

[1]Respiratory Research Group, University of Manchester, University Hospital of South Manchester, Manchester, UK

[2]School of Infection and Immunity, University of Liverpool, University Hospital Aintree, Liverpool, UK

[3]Cattedra di Malattie dell'apparato respiratprio, University of Brescia, Spedali Civili di Brescia, Italy

Correspondence and requests for reprints:

Dr Jaclyn A. Smith

University of Manchester, ERC Building, Second floor

Wythenshawe Hospital, Manchester M23 9LT, UK

Telephone: +44 161 291 5879

Fax: +44 161 291 5730

Email: jacky.smith@manchester.ac.uk

**Key words:** Dypsnoea, Principal Components Analysis

**Word Count:** 3516

**ABSTRACT (**word count 250)

**Introduction:** Patients with respiratory disease use many different expressions to describe the sensation they experience as breathlessness. Although previous analyses have identified multiple dimensions of breathlessness, there is little agreement about their number and nature. This study has applied a novel approach, Principal Component Analysis (PCA), to understanding descriptions of breathlessness in health and disease and extracting representative components.

**Methods:** 202 patients (asthma n=60, chronic obstructive pulmonary disease n=65, interstitial lung disease n=41 and idiopathic hyperventilation n=36) and 30 healthy volunteers were studied. All subjects performed spirometry and gave binary responses to 45 descriptions recalling their experience of breathlessness at the end of exercise; patients repeated this for resting breathlessness. PCA identified response patterns in the questionnaire data and extracted discriminatory components. Components scores were calculated for each individual using the regression method.

**Results**: PCA identified six distinct components of breathlessness on exercise, explaining 62.8% of the variance: (1) air hunger, (2) affective, (3) nociceptive, (4) regulation, (5) attention and (6) miscellaneous qualities. Rest components explaining 63.1% of variance were (1) affective, (2) air hunger, (3) nociceptive, (4) wheeze, (5) regulation and (6) miscellaneous. Components identified on exercise differed significantly between disease groups and controls and related to FVC percent predicted.

**Discussion:** Our analysis suggests that air hunger is the dominant sensation during exercise whilst affective distress characterised resting breathlessness in patients with a range of respiratory disorders including idiopathic hyperventilation where lung mechanics are normal. This suggests that common mechanisms operate in qualitative aspects of breathlessness.

## INTRODUCTION

Breathlessness is one of the most frequent and distressing symptoms experienced by patients with lung disease and is usually defined as an uncomfortable awareness of breathing [1]. Healthy subjects also experience breathlessness during exercise and this may be characterised as physiologically appropriate breathlessness. The clinical assessment of breathlessness usually focuses on the degree or intensity of the symptom and much scientific effort has been dedicated to understanding the factors that determine the severity of breathlessness [2-4]. Less attention has been paid to the quality of the sensation and whether this differs between conditions, although some believe this is the case[5 6].

Patients with a respiratory disease use a wide variety of terms to describe the sensations experienced when they become breathless. These sensations cannot be assessed objectively[7] and instead representative verbal descriptors have been identified[8]. Although previous analyses in health [9 10] and disease[5 8 11-13] have identified clusters of these descriptors (using cluster analysis), there is little consistency in their number and nature and moreover, they are not sufficiently robust to aid in differential diagnosis.

An alternative approach to cluster analysis is to use principal component analysis (PCA) which uncovers the latent structure (dimensions) of a set of variables, in this case breathlessness descriptors, by identifying important sources of variation. PCA has the advantage that it does not assume that distinct groups of descriptions exist; a variable can appear in two separate components and components can be allowed to correlate with each other. Differences in the interpretation of descriptions by subjects can therefore be accommodated whilst also avoiding the constraint of generating a hierarchic classification. This has been shown to be a useful technique for identifying patterns of respiratory symptoms in children[14] but only one study has applied PCA to breathlessness, analysing a mixture of symptoms and qualitative descriptors in an attempt to identify subjects with medically unexplained breathlessness[15].

We have applied PCA to the responses of healthy volunteers and discrete patient groups, to descriptions of breathlessness. We chose our patient groups to represent a range of mechanical abnormalities, both fixed and variable, that are applied to the respiratory system and our principal focus was on the recall of the sensation of breathlessness perceived at the end of exercise. We hypothesised that the quality of breathlessness would differ between healthy volunteers and patients with respiratory disease and would also differ between breathlessness recalled at end-exercise and that experienced at rest, although this analysis was confined to patients with disease, where this might occur. Finally, we have explored the relationship between the components of breathlessness and spirometry as an objective measurement of altered lung mechanics.

## METHODS

### *Patients*

Consecutive patients attending the out-patient clinic and the respiratory function laboratory of University Hospital Aintree were recruited. Healthy control subjects of a similar age were identified from hospital staff and relatives of our patients. The study was approved by the local research ethics committee and written consent was obtained from all participants.

Diagnoses were confirmed by review of the medical records and subjects categorised as chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease (IHV) and idiopathic hyperventilation (IHV) when they unequivocally met the established diagnostic criteria for these disorders[16-18], (see on-line supplement for details). Patients with more than one condition causing breathlessness were excluded.

All patients performed spirometry using a wedge bellows spirometer (Vitalograph-R, Vitalograph Ltd, Buckinghamshire. UK); control subjects were tested using an ultrasonic portable spirometer (Easy One, NDD medical Technologies Zurich, Switzerland). The best of three manoeuvres has been reported, measured to ATS/ERS standards [19].

### *Questionnaire*

A questionnaire comprising 45 short phrases describing breathlessness and previously shown to be valid and reliable[8], was completed by each subject twice. Patients were asked to think about how they felt when breathless at rest, and respond to all items (yes or no). Subjects were then asked to think about how they felt when breathless on exercise and respond to the same set of items; healthy subjects completed only the exercise section. Unless they requested assistance, subjects were left alone and given as much time as they needed to complete the questionnaires.

### *Data analysis*

All statistical analyses were performed using SPSS 13.0 (SPSS Inc, Chicago, Ill). Principal Components Analysis (PCA) was used to identify response patterns in the questionnaire data both at rest and on exercise[20]. PCA is an exploratory technique for investigating patterns within a set of variables; in the current analysis, responses to a series of descriptions of breathlessness. The large numbers of responses can be reduced to a much smaller number of representative components, based on the covariance among responses. If subsets of symptoms are correlated, this suggests they are measuring aspects of a common underlying process; several components may suggest a series of underlying processes. The steps involved in each analysis were as follows.

1. Item selection: Redundant questions were removed, i.e. question responses with partial correlation coefficients >0.4 to other question responses. To maximise the informative content of the analysis, items that correlated with several other variables were removed first.

2. Component extraction: PCA was used to generate the components and we selected the numbers of components for analysis based on the Eigenvalues and scree plots.

3. Rotation: Component rotation is used to improve the interpretability of the results. An oblique rotation was chosen (Promax), assuming that that components of breathlessness were unlikely to be entirely independent of one another. The loading of the items onto each

component is a measure of the relationship between that item and the component; the greater the loading, the purer a measure of that component the item is. Only items with the conventional loading of 0.4 and above were interpreted.

4. Component Scores: For each subject included in the analysis, it is possible to calculate scores for the individual components. These scores are derived from the subjects' responses to the items comprising each component and their loadings. Scores were calculated using the regression method; for each component the scores are standardised; each has a mean value of 0 and a standard deviation of 1. The scores indicate the relative importance of that qualitative component of breathlessness for each individual, not the intensity of breathlessness.

Additionally we applied agglomerative hierarchical cluster analysis (using the squared Euclidean distance as the dissimilarity measure) to the data set in order to compare the components with the clusters formed. This allowed comparison of our result to those previously generated using this questionnaire [8].

There are no available criteria against which the solution in a PCA can be tested. However the solution can be assessed for face validity of the components and by examining the relationships between the component scores generated and other available variables. Therefore we examined whether diagnostic grouping and also spirometric abnormality significantly predicted component scores using multivariate analysis of variance (MANOVA). If the predictor terms were significantly related to the components scores (according to Pillai's test) then individual associations between predictors and components were examined using specific tests. As patients with different conditions will inevitably have differences in spirometry, the relationships between components scores and spirometry were adjusted for differences due to diagnosis.

## RESULTS

310 patients and 35 normal subjects were approached to fill in the questionnaire, 234 patients and 35 normal subjects agreed to take part in the study. 32 patients and 5 healthy volunteers were excluded, leaving 202 patients and 30 normal subjects for analysis. The main reasons for exclusion were: inconsistency in answering the repeat questions (greater than one item answered differently) and failure to give a response to more than 5 questions. Patient characteristics, diagnoses and spirometry are shown in table 1.

**Table 1** Subjects' characteristics

| **Diagnosis** | **Gender** | **Mean Age** | **$FEV_1$% predicted** | **FVC% predicted** | **$FEV_1$/FVC ratio** |
|---|---|---|---|---|---|
| Asthma (n=60) | 19M/41F | 48.2 (±15.4) | 80.6% (±26.6) | 93.3% (±26.7) | 71.6% (±12.1) |
| COPD (n=65) | 32M/33F | 67.9 (±9.2) | 42.0%* (30.5-56.5) | 78.3% (±21.3) | 40.2%* (33.0-55.5) |
| Interstitial Lung Disease (n=41) | 24M/17F | 68.7 (±9.9) | 72.0% (±18.9) | 73.2% (±20.2) | 78.1% (±8.4) |
| Idiopathic Hyperventilation (n=36) | 8M/28F | 53.7 (±15.2) | 93.0%* (88.0-104.5) | 99.3% (±14.4) | 79.1% (±7.6) |
| Healthy Controls (n=30) | 11M/19F | 53.8 (±12.7) | 106.5% (±16.0%) | 113.3% (±17.2%) | 77.2% (±6.3) |

Data are means and standard deviations except for *median and interquartile range

### *Component extraction*

Exercise: For this analysis data were pooled for the control and patient groups. 35 items were included in the PCA (Kaiser-Meyer-Olkin measure of sampling adequacy 0.95, Bartlett's Test of sphericity <0.001); item selection is summarised in the online supplement (Online

Table E1). Six components with Eigenvalues >1 were identified (Online Figure E1), explaining 62.8% of the variance in the data. The main break in the scree plot was after one component as the first component explained the majority of the variance however the inclusion of the additional five components added a further 20% to the variance explained. The questionnaire items loading >0.4 onto each component are shown in Table 2, along with the proportion of variance explained by each component. We named each component based on the theme represented by the most strongly loading items. For the descriptions of breathlessness on exercise, the dominant component was air hunger; items referring to a need for more air. The other independent components explaining smaller percentages of the total variance were (in order of magnitude): affective; items suggesting emotional distress, nociceptive; descriptions of unpleasant sensations, regulation; perceptions of inappropriately regulated breathing, attention; subjective awareness of breathing and miscellaneous descriptions including sighing, air not tasting right and breath stopping. Several descriptions featured in more than one component e.g. air hunger loaded onto the air hunger and affective components.

Rest: Only data for the patients was used for this analysis. 34 items were included in the PCA (Kaiser-Meyer-Olkin measure of sampling adequacy 0.92, Bartlett's Test of sphericity <0.001); item selection is summarised in online supplement (online Table E2). Again, six components with Eigenvalues >1 were identified (Figure E2), explaining 63.1% of the variance in the descriptions. The questionnaire items loadings are shown in Table E3. The items in the components were either identical to or synonymous with to those for exercise; (1) affective, (2) air hunger, (3) nociceptive, (4) wheeze, (5) regulation and (6) miscellaneous descriptions. An additional component representing wheeze emerged but the attention component was not present. At rest the dominant component was the affective one.

To assess whether the absence of controls from the analysis had produced this change in the components and the variance explained, the PCA was repeated on the exercise data without the healthy volunteers. This confirmed the air hunger component still explained most of the variance (see online Table E4) and the nociceptive items split into two components.

**Table 2** Pattern Matrix: item loadings on exercise for patients and controls, six component solution with Promax rotation. The magnitude of the component loadings represent how good each item is as an indicator of the component.

| **COMPONENTS (% variance)**<br>Items | **Component Loadings** | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** |
| **(1) AIR HUNGER COMPONENT (42.6%)** | | | | | | |
| cannot breathe deeply enough | 0.86 | | | | | |
| need to take a deeper breath | 0.83 | | | | | |
| breathing too shallow | 0.77 | | | | | |
| not satisfied by my breathing | 0.67 | | | | | |
| can't get enough air into my chest | 0.67 | | | | | |
| cannot breathe enough | 0.67 | | | | | |
| | | | | | | |
| **(2) AFFECTIVE COMPONENT (5.8%)** | | | | | | |
| desperate for breath | | 0.89 | | | | |
| suffocating | | 0.86 | | | | |
| gasping for breath | | 0.74 | | | | |
| hunger for more air | 0.52 | 0.68 | | | | |
| fighting for breath | | 0.65 | | | | |
| | | | | | | |
| **(3) NOCICEPTIVE COMPONENT (4.6%)** | | | | | | |
| chest aches | | | 0.82 | | | |
| chest feels tight | | | 0.77 | | | |
| raw sensation in chest | | | 0.74 | | | |
| wheezy | | | 0.65 | | | |
| raw sensation in throat | | | 0.50 | | | |
| winded in my chest | | | 0.41 | | | |
| | | | | | | |
| **(4) REGULATION COMPONENT (3.7%)** | | | | | | |
| breathing is too deep | | | | 0.88 | | |
| breathing is too fast | | | | 0.68 | | |
| breathing is too heavy | | | | 0.63 | | |
| breathing feels unpleasant | | | | 0.50 | | |
| can't control my breathing | | | | 0.41 | | |
| | | | | | | |
| **(5) ATTENTION COMPONENT (3.1%)** | | | | | | |
| puffed | | | | | 0.71 | |
| aware of my breathing | | | | | 0.66 | |
| need breath | 0.47 | | | | 0.53 | |
| short of breath | | | | | 0.52 | |
| out of breath | | | | | 0.49 | |
| | | | | | | |
| **(6) MISCELLANEOUS COMPONENT (3.0%)** | | | | | | |
| want to sigh | | | | | 0.42 | 0.61 |
| air does not taste right | | 0.48 | | | | 0.59 |
| my breath stops | | 0.47 | | | | 0.55 |
| | | | | | | |

All items shown load over 0.40 onto PCA components.

### *Agglomerative Hierarchical Cluster Analysis*

The exercise pooled control and patient data were analysed using all 45 descriptions. This generated a complex dendrogram. Using the criteria as previously applied by Elliot et al [8] (squared Euclidean distance of 12.5), 17 clusters of descriptions were produced (Figure E3 and Table E5). At a Euclidean distance of 17.5 the cluster analysis gave 6 clusters. However these did not seem to represent coherent themes - for example the items in the air hunger and affective components appeared in a single cluster.

### *Breathlessness Component Scores in Health and Disease*

Using the scores generated by the regression method, we were able to examine the validity of the components by assessing their ability to discriminate between control subjects and those with respiratory disease. Gender and age had no significant effect on any component score, but for the regulation component there was a trend towards a significant gender difference at rest (p=0.06) and on exercise (p=0.09).

*Exercise component scores*

Diagnostic category significantly influenced the component score for all six exercise components (air hunger p<0.001, affective p<0.001, and nociceptive p<0.001, regulation p<0.001, attention p=0.001 and miscellaneous p=0.008). Post-hoc analyses (Bonferroni correction for multiple comparisons) suggested compared to controls, the value of the component scores was greater for the air hunger component (p<0.001, for all diagnoses), the regulation component (p<0.001, for all diagnoses) and the nociceptive component (p<0.001, for all diagnoses), see Figure 1. There were also significantly different scores compared to controls for the affective component in asthma, COPD and ILD (p=0.005, p<0.001 and p<0.001 respectively) but not IHV (p=0.125); a similar pattern occurred for the attentive component (COPD p<0.001, ILD p=0.001 and borderline significance for IHV p=0.06 and asthma p=0.082). In contrast, the miscellaneous component was significantly higher in IHV than asthma or ILD (p=0.03 and p=0.007, respectively).

*Rest component scores*

The only significant difference between the diagnostic groups at rest was for the affective component (p=0.04). Post hoc analysis suggested a higher score in COPD subjects than in asthma (p=0.04), Figure E4.

***Breathlessness Component Scores and Spirometry***

MANOVA models (exertion and rest) were generated with component scores as the dependant variables and spirometry as predictors; $FEV_1$/FVC ratio was used to indicate airflow obstruction and FVC percent predicted as a marker of volume change. All models were adjusted for age, gender and diagnosis.

In the multivariate model for exercise, FVC percent predicted independently predicted all the breathlessness component scores, except for the miscellaneous component (air hunger ($p<0.001$), affective ($p<0.001$), nociceptive (p=0.001), regulation ($p<0.001$) and attention (p=0.02). Post hoc analyses suggested FVC percent predicted was significantly related to air hunger, affective and nociceptive components, independent of diagnosis (see table 3). $FEV_1$/FVC ratio was not significant in the model (p=0.37).

At rest $FEV_1$/FVC ratio and FVC percent predicted did not significantly influence the components scores when the model was adjusted for age, gender and diagnosis.

**Table 3** Post-hoc analyses for variables significantly predicting breathlessness components on exercise in MANOVA. Diagnosis reflects the independent impact of a specific diagnostic category.

| **Components** | **Independent variables** | **p** |
|---|---|---|
| Exercise Air Hunger | FVC (% predicted) | 0.02 |
| | Diagnosis | <0.001 |
| Exercise Affective | FVC (% predicted) | 0.004 |
| Exercise Nociceptive | FVC (% predicted) | 0.02 |
| | Diagnosis | 0.001 |
| Exercise Regulation | Diagnosis | <0.001 |
| Exercise Attentive | Diagnosis | <0.001 |
| Exercise Miscellaneous | - | - |

## DISCUSSION

Although breathlessness is a cardinal symptom in respiratory disease relatively little attention has been paid to its qualitative aspects. This reflects the difficulty in developing consistent themes from the range of attributes associated with this symptom. The replication of cluster analysis results in different patient groups has seldom been shown, while the resulting dendrograms are difficult to interpret. This is the first study to demonstrate that PCA can be successfully applied as an alternative to this approach and can identify different components of breathlessness experienced both at rest and end-exercise. The variation in the description of breathlessness at end-exercise was dominated by a single component relating to air hunger whereas at rest descriptions with emotional connotations (affective component) were the most important discriminators. Much smaller contributions were made by other components representing nociceptive sensations, attributes related to how breathing is regulated, wheeziness and the attention paid to the act of breathing. In general, the association of these variables and the diagnosis was closer on exercise than in the resting data. Gender and age had no significant effect on any component score, suggesting the differences seen in perceived intensity of exertional breathlessness in older women[21] are not associated with differences in quality of breathlessness.

To aid comparison with published data we used the same list of descriptions of breathlessness reported by Elliot et al [8]. Like them, we obtained a relatively complex dendrogram with a large number of clusters. This implies that breathlessness is a complicated sensation with a large number of dimensions, but we were not able to replicate the clusters formed and these differed significantly from the components indicated by the PCA. In contrast, PCA produced a smaller number of components with good face validity. When a simpler structure was derived from the cluster analysis (6 clusters) it was apparent that the items in the air hunger and affective components from the PCA formed a single cluster, i.e. were not discriminated by this technique. Furthermore, the remaining clusters lacked consistent themes.

Although the terms used to describe each cluster and each component are arbitrary and can be debated, the patients clearly identified qualities of unsatisfied inspiration within the grouping ‘air hunger’ as the dominant perception of breathlessness on exercise. By contrast, terms related to emotional distress, ‘affective’ attributes were the ones most characteristic of breathlessness perceived at rest reflecting the frightening nature of this sensation, previously identified by patients, for instance those with COPD [22].

The validity of the PCA was confirmed by our analysis of the derived component scores. We found that exercise components clearly distinguished between breathlessness in health and disease but there were few significant differences between the different conditions for both rest and exercise. However, there was a difference in the affective component scores between asthma and COPD, which could reflect the reported prevalence of depression in COPD which is itself associated with chronic breathlessness [23 24].

The dominance of air hunger as the major quality of breathlessness on exercise, irrespective of the differences in the mechanical behaviour of the lungs and those reporting it, is initially surprising. This may reflect a common mechanism generating this sensation on exercise. Air hunger is equally induced by both hypercapnia and hypoxia in health[25] but is also experienced by ventilated quadriplegic subjects[26], supporting a model in which air hunger is mediated, at least in part via the chemoreceptors and is independent of respiratory muscle contraction; studies in paralysed un-sedated volunteers confirming the later[27]. However the adequacy of pulmonary inflation is also important in both inducing and relieving air hunger[28], suggesting the sensation results from a balance between chemo and mechanoreceptor inputs[29]. In disease the factors modulating this interaction are complex. We speculate that mechanical limitation at end-exercise is a possible unifying explanation for the dominance of air hunger across our disease groups. Patients with significant airflow obstruction who report breathlessness show dynamic hyperinflation of their end-expiratory lung volume during exercise[30]. Moreover the degree of breathlessness increases significantly as the end-inspiratory lung volume approaches the inspiratory reserve volume [29 31]. A similar situation may apply in interstitial lung disease where the absolute inspiratory reserve volume is reduced[32]. Although patients with IHV do not have any mechanical limitation to breathing at rest they do show respiratory rather than cardiovascular limitation on exercise and the large tidal volume breathing they adopt at end-exercise is likely to encroach on the inspiratory reserve volume and generate a dissimilar sensation of unsatisfied inspiration[33]. This interpretation is in keeping with our limited physiological data which showed that FVC rather than $FEV_1$ was related to the sensation of breathlessness irrespective of the diagnosis. Thus a common mechanism may explain why seemingly different diseases at rest produce qualitatively similar sensations.

Our study investigated respiratory diseases as a cause of breathlessness and omitted other conditions, such as congestive heart failure where a mixture of cardiac and pulmonary abnormalities contribute directly or indirectly to dyspnoea. Our patient groups represent a spectrum of respiratory disease, all causing breathlessness but characterised by different mechanical abnormalities, the asthma and COPD groups representing variable and fixed airflow obstruction and the ILD group, a purer form of elastic respiratory loading. Previous reports have not always included healthy controls within the same study as patients[5 8 11], and have not studied subjects with IHV. The IHV subjects acted as a 'positive control' group i.e. subjects with symptoms of breathlessness but with normal spirometry, diffusion capacity and resting lung volumes. Patients with IHV are often felt to have psychological problems underlying their breathlessness but our data indicate that the sensation experienced is the same as in patients with structural lung disease. The association of air hunger as the dominant exercise related symptom was not different to that where breathlessness was due to organic factors, nor was there any stronger attribution of breathlessness to factors associated with the affective or emotional components we identified, something which might be expected if psychological factors played a dominant role in this condition.

Our study has some limitations. We used a questionnaire developed by others to try and reduce variability between our datasets. However, the descriptions within this questionnaire are not strongly representative of the work or effort of breathing, an attribute previously described as being strongly related to breathlessness[34]. However, our main interest was to identify the qualitative dimensions of breathlessness rather than dimensions inextricably related to the intensity of respiratory drive, such as work and effort. It also would have been interesting to objectively establish the exercise capacity of all the participants but PCA requires a large number of subjects making this impractical, not withstanding the difficulties in identifying a suitable standardised test for all the disease groups studied. The range of spirometric abnormalities in the selected patient groups should be sufficient to encompass a wide range of exercise performance. Finally, we related breathlessness to a specific point during exercise, namely, maximum exercise performance and it is possible that mechanisms operating earlier in exercise may be associated with a different quality of respiratory sensation. However, given the number of individuals questioned identifying a specific point to consider made it easier for them to focus on the wide range of attributes they were asked to classify.

Our data suggest that the qualitative experience of breathlessness involves a variety of unpleasant sensations which are shared by a range of respiratory conditions irrespective of their aetiology. Whether the same is true for other conditions where breathlessness limit exercise remains to be determined. We have not identified significant differences in the qualitative attributes of breathlessness which are disease related and so the present clinical practice of quantifying the intensity of the sensation relative to the task which produces it appears to capture the important attributes of breathlessness.

**COMPETING INTERESTS:** None

**FUNDING:** British Lung Foundation

## REFERENCES


1. Burki NK. Dyspnea. *Lung* 1987;165(5):269-77.

2. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;85(6):751-8.

3. Killian KJ. Assessment of dyspnoea. *Eur Respir J* 1988;1(3):195-7.

4. Cockcroft A, Adams L, Guz A. Assessment of breathlessness. *Q J Med* 1989;72(268):669-76.

5. Simon PM, Schwartzstein RM, Weiss JW, Fencl V, Teghtsoonian M, Weinberger SE. Distinguishable types of dyspnea in patients with shortness of breath. *Am Rev Respir Dis* 1990;142(5):1009-14.

6. Scano G, Stendardi L, Grazzini M. Understanding dyspnoea by its language. *Eur Respir J* 2005;25(2):380-5.

7. Schwartzstein RM, Cristiano LM. Qualities of Respiratory Sensation. In: Adams L, Guz A, editors. *Respiratory Sensation*: Informa Health Care, 1996:125-150.

8. Elliott MW, Adams L, Cockcroft A, MacRae KD, Murphy K, Guz A. The language of breathlessness. Use of verbal descriptors by patients with cardiopulmonary disease. *Am Rev Respir Dis* 1991;144(4):826-32.

9. Simon PM, Schwartzstein RM, Weiss JW, Lahive K, Fencl V, Teghtsoonian M, et al. Distinguishable sensations of breathlessness induced in normal volunteers. *Am Rev Respir Dis* 1989;140(4):1021-7.

10. Harver A, Mahler DA, Schwartzstein RM, Baird JC. Descriptors of breathlessness in healthy individuals: distinct and separable constructs. *Chest* 2000;118(3):679-90.

11. Wilcock A, Crosby V, Hughes A, Fielding K, Corcoran R, Tattersfield AE. Descriptors of breathlessness in patients with cancer and other cardiorespiratory diseases. *J Pain Symptom Manage* 2002;23(3):182-9.

12. von Leupoldt A, Balewski S, Petersen S, Taube K, Schubert-Heukeshoven S, Magnussen H, et al. Verbal descriptors of dyspnea in patients with COPD at different intensity levels of dyspnea. *Chest* 2007;132(1):141-7.

13. Moy ML, Lantin ML, Harver A, Schwartzstein RM. Language of dyspnea in assessment of patients with acute asthma treated with nebulized albuterol. *Am J Respir Crit Care Med* 1998;158(3):749-53.

14. Smith JA, Drake R, Simpson A, Woodcock A, Pickles A, Custovic A. Dimensions of respiratory symptoms in preschool children: population-based birth cohort study. *Am J Respir Crit Care Med* 2008;177(12):1358-63.

15. Han J, Zhu Y, Li S, Zhang J, Cheng X, Van den Bergh O, et al. The language of medically unexplained dyspnea. *Chest* 2008;133(4):961-8.

16. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000;161(2 Pt 1):646-64.

17. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23(6):932-46.

18. GINA. Global Strategy for Asthma Management and Prevention, 2002 (updated 2005).

19. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38.

20. Tabachnick BG, Fidell LS. Principal Components and Factor Analysis. *Using Multivariate Statistics*. 5th ed. Boston: Allyn & Bacon, 2007:607-675.

21. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *J Appl Physiol* 2008;104(6):1583-93.

22. Rennard S, Decramer M, Calverley PM, Pride NB, Soriano JB, Vermeire PA, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J* 2002;20(4):799-805.

23. Laurin C, Lavoie KL, Bacon SL, Dupuis G, Lacoste G, Cartier A, et al. Sex differences in the prevalence of psychiatric disorders and psychological distress in patients with COPD. *Chest* 2007;132(1):148-55.

24. Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly outpatients with chronic obstructive pulmonary disease: prevalence, and validation of the BASDEC screening questionnaire. *Int J Geriatr Psychiatry* 2000;15(12):1090-6.

25. Moosavi SH, Golestanian E, Binks AP, Lansing RW, Brown R, Banzett RB. Hypoxic and hypercapnic drives to breathe generate equivalent levels of air hunger in humans. *J Appl Physiol* 2003;94(1):141-54.

26. Banzett RB, Lansing RW, Reid MB, Adams L, Brown R. 'Air hunger' arising from increased PCO2 in mechanically ventilated quadriplegics. *Respir Physiol* 1989;76(1):53-67.

27. Banzett RB, Lansing RW, Brown R, Topulos GP, Yager D, Steele SM, et al. 'Air hunger' from increased PCO2 persists after complete neuromuscular block in humans. *Respir Physiol* 1990;81(1):1-17.

28. Manning HL, Shea SA, Schwartzstein RM, Lansing RW, Brown R, Banzett RB. Reduced tidal volume increases 'air hunger' at fixed PCO2 in ventilated quadriplegics. *Respir Physiol* 1992;90(1):19-30.

29. O'Donnell DE, Banzett RB, Carrieri-Kohlman V, Casaburi R, Davenport PW, Gandevia SC, et al. Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. *Proc Am Thorac Soc* 2007;4(2):145-68.

30. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158(5 Pt 1):1557-65.

31. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004;24(1):86-94.

32. O'Donnell DE, Chau LK, Webb KA. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. *J Appl Physiol* 1998;84(6):2000-9.

33. Jack S, Rossiter HB, Pearson MG, Ward SA, Warburton CJ, Whipp BJ. Ventilatory responses to inhaled carbon dioxide, hypoxia, and exercise in idiopathic hyperventilation. *Am J Respir Crit Care Med* 2004;170(2):118-25.

34. O'Donnell DE, Bertley JC, Chau LK, Webb KA. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997;155(1):109-15.

**FIGURES LEGENDS**

Figure 1 Comparison of diagnostic groups for each component score on exercise, mean and 95% confidence intervals shown; Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD), Idiopathic Hyperventilation (IHV).

**ON-LINE DATA SUPPLEMENT**

# QUALITATIVE ASPECTS OF BREATHLESSNESS IN HEALTH AND DISEASE

Jaclyn Smith[1], Paul Albert[2], Enrica Bertella[3], James Lester[2], Sandy Jack[2], Peter Calverley[2]

[1]Respiratory Research Group, University of Manchester, University Hospital of South Manchester, Manchester, UK

[2]School of Infection and Immunity, University of Liverpool, University Hospital Aintree, Liverpool, UK

[3]Cattedra di Malattie dell'apparato respiratprio, University of Brescia, Spedali Civili di Brescia, Italy

## METHODS

Patient Characterisation

All patients attended the respiratory outpatient department of University Hospital Aintree, with the clinical diagnosis made by a Respiratory Physician. Asthma patients were diagnosed by history, spirometry and, where appropriate, histamine challenge and atopic testing; all patients were on step 2 or above on the GINA (Global Initiative for Asthma) Guidelines. COPD patients were diagnosed by spirometry and were at stages II-III of the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Guidelines. Pulmonary Fibrosis patients were diagnosed by pulmonary function tests with evidence of fibrosis on high resolution computerised tomography scan.

Idiopathic Hyperventilation: The IHV patients had symptoms suggestive of hyperventilation (unexplained breathlessness, dizziness, chest tightness), but normal pulmonary function (volume divisions, forced expiratory flows, diffusing capacity, airway reactivity), cardiac function (resting and exercise 12-lead ECG, ST segment depression $< 1$ mm) and endocrine function (blood glucose; thyroid, renal and liver function) and were recruited from respiratory clinics at University Hospital Aintree. The resting arterial PCO2 (PaCO2) IHV inclusion criterion was 30mmHg and also partially or fully compensated respiratory alkalosis. Patients had a normal response to moderate intensity exercise, normal central chemoresponsiveness and attenuated peripheral chemoreceptor sensitivity.

## RESULTS

**Table E1.** Items included and excluded from analysis for exercise PCA

| | **Included items** | **Excluded items** |
|---|---|---|
| 1 | out of breath | breathless |
| 2 | short of breath | difficult to breath |
| 3 | puffed | can't get enough air into my chest |
| 4 | aware of my breathing | breathing not sufficient |
| 5 | need s breath | want to take in more air |
| 6 | breathing takes too much effort | chest feels tired |
| 7 | breath does not go in enough | smothering |
| 8 | cannot breathe deeply enough | breathing bad air |
| 9 | cannot breathe enough | cannot breathe fast enough |
| 10 | need to take a deeper breath | cannot breathe out fast enough |
| 11 | breathing uncomfortable | |
| 12 | breathing too shallow | |
| 13 | not satisfied by my breathing | |
| 14 | fighting for breath | |
| 15 | desperate for breath | |
| 16 | gasping for breath | |
| 17 | hunger for more air | |
| 18 | wheezy | |
| 19 | breathing feels tiring | |
| 20 | breathing feels unpleasant | |
| 21 | chest feels tight | |
| 22 | chest aches | |
| 23 | suffocating | |
| 24 | my breath stops | |
| 25 | air does not taste right | |
| 26 | breathing is too deep | |
| 27 | raw sensation in chest | |
| 28 | raw sensation in throat | |
| 29 | cannot breathe in fast enough | |
| 30 | can't control my breathing | |
| 31 | breath does not go out enough | |
| 32 | breathing is too heavy | |
| 33 | breathing is too fast | |
| 34 | winded in my chest | |
| 35 | want to sigh | |

**Table E2.** Items included and excluded from analysis for rest PCA

| | Included items | Excluded items |
|---|---|---|
| 1 | out of breath | puffed |
| 2 | short of breath | breathless |
| 3 | aware of my breathing | difficult to breath |
| 4 | need s breath | want to take in more air |
| 5 | breathing takes too much effort | gasping for breath |
| 6 | can't get enough air into my chest | breathing feels tiring |
| 7 | breathing not sufficient | smothering |
| 8 | breath does not go in enough | breathing bad air |
| 9 | cannot breathe deeply enough | cannot breathe fast enough |
| 10 | cannot breathe enough | can't control my breathing |
| 11 | need to take a deeper breath | cannot breathe out fast enough |
| 12 | breathing uncomfortable | |
| 13 | breathing too shallow | |
| 14 | not satisfied by my breathing | |
| 15 | fighting for breath | |
| 16 | desperate for breath | |
| 17 | hunger for more air | |
| 18 | wheezy | |
| 19 | chest feels tired | |
| 20 | breathing feels unpleasant | |
| 21 | chest feels tight | |
| 22 | chest aches | |
| 23 | suffocating | |
| 24 | my breath stops | |
| 25 | air does not taste right | |
| 26 | breathing is too deep | |
| 27 | raw sensation in chest | |
| 28 | raw sensation in throat | |
| 29 | cannot breathe in fast enough | |
| 30 | breath does not go out enough | |
| 31 | breathing is too heavy | |
| 32 | breathing is too fast | |
| 33 | winded in my chest | |
| 34 | want to sigh | |

**Table E3.** Pattern Matrix: item loadings at rest for patients only, 6 component solution, Promax rotation. The magnitude of the component loadings represent how good each item is as an indicator of the component.

| **COMPONENTS (% variance)** Items | **Component Loadings** | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** |
| **(1) AFFECTIVE COMPONENT (41.5%)** | | | | | | |
| desperate for breath | 0.99 | | | | | |
| fighting for breath | 0.93 | | | | | |
| hunger for more air | 0.90 | | | | | |
| gasping for breath | 0.90 | | | | | |
| suffocating | 0.63 | | | | | |
| cannot breathe in fast enough | 0.57 | | | | | |
| my breath stops | 0.56 | | | | | |
| breathing takes too much effort | 0.53 | | | | | |
| | | | | | | |
| **(2) AIR HUNGER COMPONENT (6.2%)** | | | | | | |
| breath does not go in enough | | 0.82 | | | | |
| cannot breathe deeply enough | | 0.80 | | | | |
| breathing too shallow | | 0.76 | | | | |
| aware of my breathing | -0.44 | 0.70 | | | | |
| breathing not sufficient | | 0.69 | | | | |
| need to take a deeper breath | | 0.68 | | | | |
| cannot breathe enough | 0.46 | 0.65 | | | | |
| not satisfied by my breathing | | 0.64 | | | | |
| need s breath | | 0.60 | | | | |
| can't get enough air into my chest | 0.42 | 0.46 | | | | |
| | | | | | | |
| **(3) NOCICEPTIVE COMPONENT (5.4%)** | | | | | | |
| raw sensation in chest | | | 0.74 | | | |
| raw sensation in throat | | | 0.66 | | | |
| air does not taste right | | | 0.45 | | | |
| chest aches | | | 0.41 | | | |
| | | | | | | |
| **(4) WHEEZE COMPONENT (3.7%)** | | | | | | |
| chest feels tight | | | | 0.81 | | |
| wheezy | | | | 0.80 | | |
| chest feels tired | | | | 0.55 | | |
| | | | | | | |
| **(5) REGULATION COMPONENT (3.2%)** | | | | | | |
| breathing is too deep | | | | | 0.91 | |
| breathing is too heavy | | | | | 0.68 | |
| breathing is too fast | | | | | 0.41 | |
| | | | | | | |
| **(6) MISCELLANEOUS COMPONENT (3.0%)** | | | | | | |
| want to sigh | | | | | | 0.76 |
| out of breath | | | | | | 0.59 |
| breathless | | | | | | 0.54 |
| breath does not go out enough | | | | | | 0.53 |
| short of breath | | | | | | 0.50 |

All items shown load over 0.40 onto PCA components.

**Table E4.** Item loadings on exercise for patients only, 6 component solution, Promax rotation

| **COMPONENTS (% variance)** Items | **Component Loadings** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| **(1) AIR HUNGER COMPONENT (39.8%)** | | | | | | | |
| cannot breathe deeply enough | 0.95 | | | | | | |
| breath does not go in enough | 0.94 | | | | | | |
| breathing not sufficient | 0.91 | | | | | | |
| can't get enough air into my chest | 0.77 | | | | | | |
| need to take a deeper breath | 0.67 | | | | | | |
| breathing too shallow | 0.67 | | | | | | |
| not satisfied by my breathing | 0.54 | | | | | | |
| | | | | | | | |
| **(2) AFFECTIVE COMPONENT (6.5%)** | | | | | | | |
| desperate for breath | | 0.89 | | | | | |
| suffocating | | 0.88 | | | | | |
| gasping for breath | | 0.76 | | | | | |
| fighting for breath | | 0.70 | | | | | |
| hunger for more air | | 0.66 | | | | | |
| breathing bad air | | 0.61 | | | | | 0.45 |
| my breath stops | | 0.52 | | | | | |
| difficult to breath | | 0.44 | | | | | |
| | | | | | | | |
| **(3) NOCICEPTIVE COMPONENT 1 (4.9%)** | | | | | | | |
| chest feels tight | | | 0.79 | | | | |
| chest aches | | | 0.75 | | | | |
| raw sensation in chest | | | 0.69 | | | | |
| wheezy | | | 0.64 | | | -0.45 | |
| winded in my chest | | | 0.43 | | | | |
| | | | | | | | |
| **(4) ATTENTION COMPONENT (4.2%)** | | | | | | | |
| aware of my breathing | | | | 0.75 | | | |
| breathless | | | | 0.70 | | | |
| out of breath | | | | 0.61 | | | |
| need s breath | | | | 0.61 | | | |
| puffed | | | | 0.51 | | 0.46 | |
| | | | | | | | |
| **(5) REGULATION COMPONENT (3.2%)** | | | | | | | |
| breathing is too deep | | | | | 0.83 | | |
| breathing is too heavy | | | | | 0.56 | | |
| breathing is too fast | | | | | 0.55 | .40 | |
| cannot breathe out fast enough | | | | | 0.51 | | |
| | | | | | | | |
| **(6) NOCICEPTIVE COMPONENT 2 (3.2%)** | | | | | | | |
| breathing feels unpleasant | | | | | | 0.66 | |
| raw sensation in throat | | | | | | 0.60 | |
| breathing uncomfortable | | | | | | 0.56 | |
| | | | | | | | |
| **(7) SIGH COMPONENT (2.8%)** | | | | | | | |
| want to sigh | | | | 0.50 | | | 0.72 |

All items shown load over 0.40 onto a single PCA component.

**Table E5** Comparison of Elliot cluster analysis and current cluster analysis; clusters at squared Euclidean distance of 12.5.

| | **Items for Current Analysis** | | **Items Elliott Analysis 1991** |
|---|---|---|---|
| Cluster 1 | I feel that I am breathing bad air | Cluster 1 | I feel out of breath |
| | I feel that air does not taste right | | I feel short of breath |
| | I feel I am suffocating | | I feel puffed |
| | I feel I am smothering | | I feel breathless |
| | I feel that my breath stops | | I am aware of my breathing |
| | | | I feel a need to breathe |
| Cluster 2 | Breathing too deep | | My breathing takes too much effort |
| | | | It is difficult to breathe |
| Cluster 3 | Can't breathe out enough | | I can't get enough air into my chest |
| | Can't breath out fast enough | | My breathing is not sufficient |
| | | | My breath does not go in enough |
| Cluster 4 | Chest feels raw | | I feel I cannot breathe deeply |
| Cluster 5 | Throat feels raw | | I feel I cannot breathe enough |
| | | | I want to take in more air |
| Cluster 6 | I feel short of breath | | I feel a need to take a deeper breath |
| | I feel breathless | | My breathing feels uncomfortable |
| | I feel out of breath | | My breathing is too shallow |
| | I feel a need to breathe | | I do not feel satified by my |
| | | | |
| Cluster 7 | I feel puffed | Cluster 2 | I feel I am fighting for breath |
| | I am aware of my breathing | | I feel desperate for breath |
| | | | I feel I am gasping for breath |
| Cluster 8 | I feel I cannot breathe enough | | I feel a hunger for more air |
| | My breathing is not sufficient | | |
| | My breath does not go in enough | Cluster 3 | I feel wheezy |
| | Can't breathe in enough | | |
| | Need to take in more air | Cluster 4 | My breathing feels tiring |
| | Need a deeper breath | | My chest feels tired |
| | I feel I cannot breathe deply enough | | My breathing feels unpleasant |
| | Not satisfied | | |
| | Too shallow | Cluster 5 | My chest feels tight |
| | | | |
| Cluster 9 | My breathing takes too much effort | Cluster 6 | My chest aches |
| | It is difficult to breathe | | |
| | Breathing feels tiring | Cluster 7 | I feel I am suffocating |
| | | | I feel I am smothering |
| Cluster 10 | Breathing not fast enough | | I feel that my breath stops |
| | I cannot breathe fast enough | | |
| | | Cluster 8 | I feel that I am breathing bad air |
| Cluster 11 | My breathing is too heavy | | I feel that air does not taste right |
| | My breathing is too fast | | My breathing is too deep |
| | | | I feel a raw sensation in my chest |
| Cluster 12 | I feel desperate for breath | | I feel a raw sensation in my throat |
| | I feel I am gasping for breath | | |
| | I feel I am fighting for breath | Cluster 9 | I cannot breathe fast enough |
| | I feel a hunger for more air | | I cannot breathe in fast enough |
| | | | I feel I can't control my breathing |
| Cluster 13 | Breathing uncomfortable | | My breath does not go out enough |
| | Breathing feels uncomfortable | | I cannot breathe out fast enough |
| | I feel I can't control my breathing | | My breathing is too heavy |
| | | | |
| Cluster 14 | My chest feels tired | Cluster 10 | My breathing is too fast |
| | My chest ache | | |
| | I feel winded in my chest | Cluster 11 | I feel winded in my chest |
| | | | |
| Cluster 15 | My chest feels tight | Cluster 12 | I feel I want to sigh |
| | | | |
| Cluster 16 | I feel wheezy | | |
| Cluster 17 | I feel I want to sigh | | |

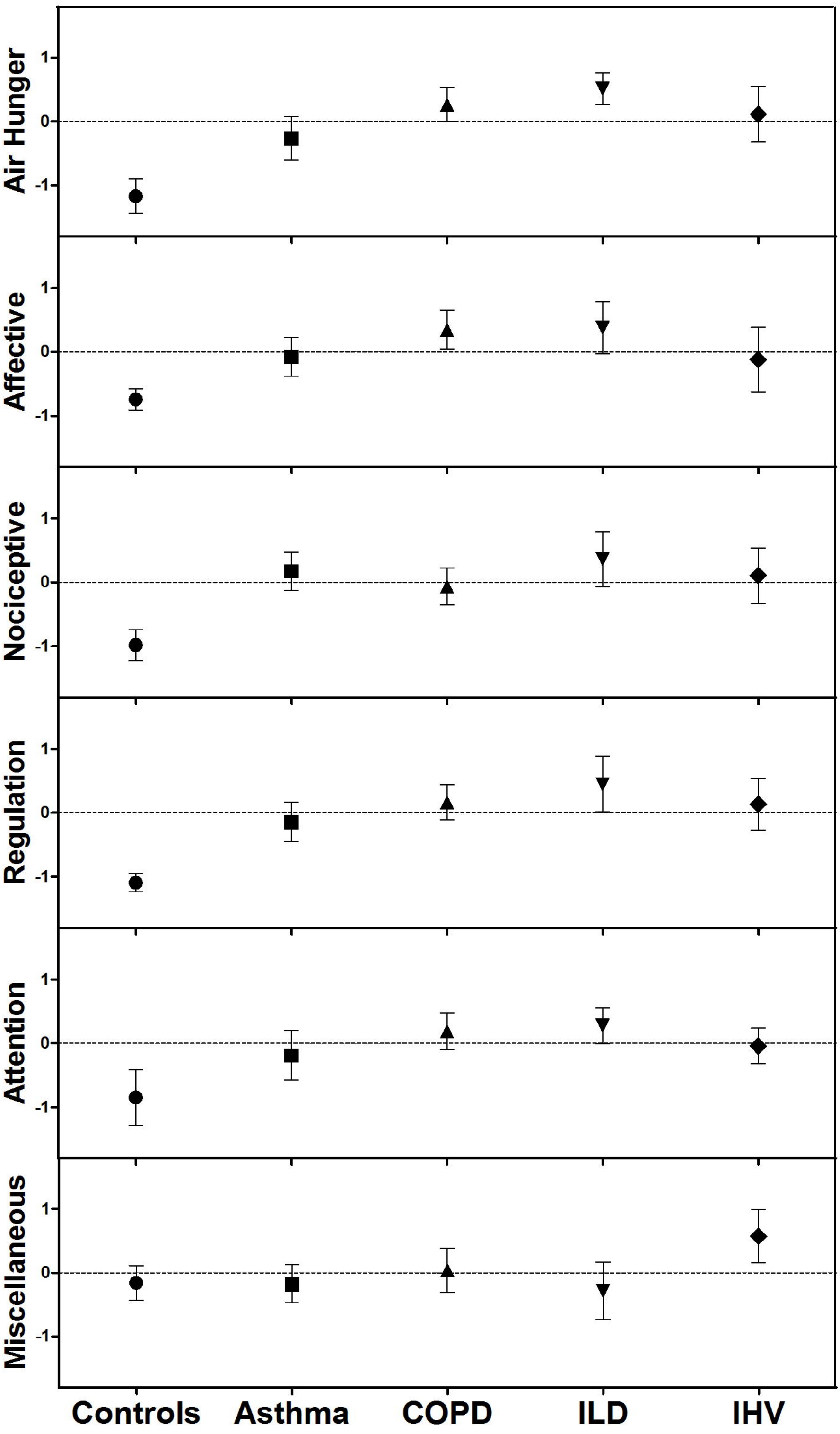
## FIGURE LEGENDS

Figure E1 Scree Plot showing Eigenvalues for descriptor components on exercise, reference line at Eigenvalue of 1.0. There is a break in the scree plot after the first component, but six components have Eigenvalues >1.0.

Figure E2 Scree Plot showing Eigenvalues for descriptor components at rest, reference line at Eigenvalue of 1.0. There is a break in the scree plot after the first component, but six components have Eigenvalues >1.0.

Figure E3 Comparison of diagnostic groups for each component score at rest, patient groups only.

Figure E4 Dendrogram of agglomerative hierarchical cluster analysis. Dashed lines show number of clusters formed at a squared Euclidean distance of 12.5 (17) and dashed and dotted line at 17.5 (6).



Air Hunger
Affective
Nociceptive
Regulation
Attention
Miscellaneous
1
0
-1
Controls
Asthma
COPD
ILD
IHV