Dyspnea 2009

Program

San Diego
May 15th–16th
University of California
Dyspnea 2009

Program & Abstracts
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# PROGRAM

## May 16th

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<td>Analgesia-inducing properties of dyspnea: a comparison of &quot;air hunger&quot; with &quot;sense of excessive inspiratory effort. C. Morelot-Panzini</td>
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Bradley Undem, Ph.D. (John Hopkins University):

‘Afferent information relevant to dyspnea’, May 15th, 9.30am

Brad was trained in pharmacology at the University of Wisconsin and has been at Hopkins since then. Starting with an interest in asthma immunology, he developed an interest in immune-nerve interactions. His more recent work has combined novel and traditional approaches to study the classification and physiology of unmylenated pulmonary afferents.

Donald McCrimmon, Ph.D. (North West University)

‘Brainstem respiratory control and its relation to dyspnea’, May 15th, 10.45am

Don trained in physiology at the University of Wisconsin and went on to postdoc in one of the leading labs in brainstem neurophysiology. He has published several review articles on respiratory control, as well as original research on respiratory rhythm generation and brainstem neurochemistry and even a neural connection between pain and breathing.

Richard Gracely, Ph.D. (University of North Carolina):

‘What we know about pain that can help us understand dyspnea’, May 16th, 9.30am

Rick was trained in experimental psychology at Brown University, and has had a long and distinguished career in pain science as an NIH intramural researcher and as a professor at U. Michigan and UNC. His central interest has been the psychophysical measurement of pain. His interests include functional brain imaging, effects of analgesics, and fibromyalgia. His contributions to the understanding of dyspnea are not new: a few of us were fortunate to attend a lecture he gave on pain perception at an NIH workshop on respiratory sensation in 1984!

Irene Tracey, D.Phil. (Oxford University):

‘Visceral pain and the analogy to dyspnea’, May 16th, 10.45

Irene was trained at Oxford in the use of magnetic resonance to study muscle and brain biochemistry, and went on to develop an interest in functional magnetic resonance imaging while at the MGH NMR Center in Boston. From there she became interested in pain, and has done studies on both somatic and visceral pain. Through a graduate student, she has recently become interested in dyspnea and its relation to pain.
ABSTRACTS OF ORAL PRESENTATIONS
(in order of presentation)
Dyspnea-12 provides an overall score that is comparable to established measures of breathlessness in cardiopulmonary disease

Janelle Yorke¹, Paul W Jones², Caroline Shuldham³, Shakeeb H Moosavi⁴

¹ Faculty of Health and Social Care, University of Salford, ² Respiratory Medicine, St George’s Hospital Medical School, ³ Nursing and Clinical Governance, Royal Brompton and Harefield Trust, ⁴ National Heart and Lung Institute, Respiratory Medicine Group, Imperial College London, UK.

Multiple Dimensions of Dyspnea. May 15th, 1.30pm

Abstract:

Background: We previously described the Dyspnea-12, an instrument for the quantification of dyspnea based on the language used by patients. The Dyspnea-12 is unidimensional, but physical and emotional (affective) domains can be identified. How the Dyspnea-12 compares with established measures of dyspnea, and how well it reflects the different aspects of dyspnea is not yet known.

Aim: 1) To compare the total Dyspnea-12 score (D12-TOTAL) with modified Borg scale ratings of breathlessness intensity (BORG-INT) and breathlessness distress (BORG-DIS), and MRC dyspnea scale ratings in patients with cardiopulmonary disease. 2) To test how well BORG-INT and BORG-DIS ratings predict D12-TOTAL scores. 3) To test how well BORG-INT and BORG-DIS ratings predict Dyspnea-12 physical and affective domain scores (D12-AFF, D12-PHY).

Methods: Patients with COPD (n=123), interstitial lung disease (n=129), chronic heart failure (n=106) completed an 81-item dyspnea descriptor list from which the Dyspnea-12 is derived, rated their breathlessness on separate Borg intensity and Borg distress scales and completed the MRC dyspnea scale. The average D12-TOTAL, the average BORG-INT and the average BORG-DIS were computed for each level on the MRC dyspnea scale in the entire cohort (n=358). Pearson’s correlations examined how each measure of dyspnea changed with increasing levels on the MRC dyspnea scale. Stepwise multiple regression analysis was performed on the entire group (n=358) with D12-TOTAL entered as the dependent variable, and Borg-DIS and Borg-INT entered as predictor variables. A further stepwise multiple regression analysis was performed with the same predictor variables but with D12-AFF as the dependent variable.

Results: D12-TOTAL correlated significantly with MRC grade (Pearson’s r=0.382, P<0.001). Average D12-TOTAL scores, Borg-DIS ratings, and Borg-INT ratings increased linearly with similar gradients of between 8-10% of full-scale per increment in MRC grade, and all three measures only reached approximately 50% of full-scale at MRC grade 5 (Figure). Borg-DIS and Borg-INT ratings both significantly predicted D12-TOTAL (stepwise multiple regression, P<0.001), and Borg-DIS ratings had more impact than Borg-INT ratings (Beta=0.483 and 0.194 respectively). With D12-AFF as the dependent variable, only Borg-AFF ratings entered the regression model contributing significantly to predicting D12-AFF scores (P<0.001).

Conclusions: The overall measure of dyspnea obtained using the Dyspnea-12 instrument is comparable to other more established measures of dyspnea. As well as providing an overall measure of dyspnea, the Dyspnea-12 score reflects the different aspects of dyspnea and is particularly responsive in the affective domain of dyspnea.
Title: Validating a 3-factor measurement model of dyspnea sensory quality

Authors:

M Parshall, PhD, RN¹; A Carle, PhD²; R Taylor, MD, FACC³; J Powers, MSN, C-ACNP⁴;
U Ice, MSN, RN¹

University of New Mexico College of Nursing¹ and School of Medicine³, Albuquerque, NM
Department of Psychology, University of North Florida,² Jacksonville, FL; Raymond G. Murphy VA
Medical Center⁴, Albuquerque, NM

Presentation session and time:

Multiple Dimensions of Dyspnea. May 15th, 1.45pm

Abstract:

Purpose: To test a 3-factor measurement model of dyspnea, based on multiple sensory quality
descriptor ratings identified in a study of emergency department visits for COPD (Parshall Res Nurs
Health 2002; 25:331-344). The model consisted of 3 factors and 7 descriptors: SMOTHERING
(smothering, suffocating, air hunger); EFFORT (work, effort); TIGHTNESS (tight, constricted). This
model validation study was conducted with adults hospitalized for new onset or exacerbated heart
failure (N = 119).

Methods: Patients enrolled after admission (median hospital day 1) and completed dyspnea descriptor
ratings for the day of enrollment (Study Day 1) and a recall rating for the day of admission (Study Day
0) using 0-10 numerical ratings. Confirmatory factor analysis (CFA) was used to test the 3-factor, 7-
descriptor model for Study Days 1 and 0. Models were estimated with a mean and variance adjusted
maximum likelihood chi-square estimator suitable for small samples that do not satisfy an assumption
of multivariate normality. Models were evaluated by goodness of fit tests and multiple fit indices
according to prespecified criteria. Using the same CFA estimation method and evaluation criteria, the
model was also back-tested against the original COPD study data to assess comparability across
diagnoses.

Results: Each of the 7 descriptors was endorsed by over 60% of the sample on Study Day 0
supporting their content validity in this population. Item means ranged from 5.1 to 6.7 for Study Day 0
and 1.1 to 2.5 for Study Day 1. For each descriptor, the Study Day 0 score was significantly greater
than the Study Day 1 score (Wilcoxon signed rank test, |z| > 6.5, p < .0001 for all comparisons). Zero-
order correlations among the descriptors ranged from .52 to .84 for Study Day 0 and .58 to .79 for
Study Day 1. The 3 factor, 7-descriptor model demonstrated good fit to the data and met or exceeded
criteria for all fit indices for Study Day 0 and Day 1. Cronbach’s alpha for the 7 descriptor ratings was
.94 for both Study Day 0 and Study Day 1 and was ≥ .88 for each factor on both study days.
Comparable fit and reliability statistics were found using the original COPD study data.

Conclusions: The 3-factor, 7-descriptor measurement model of dyspnea sensory quality is sufficiently
similar across time points and diagnoses that the same questionnaire could be used for patients with
heart failure or COPD in acute care settings. Given the heterogeneity of both diagnoses, it may not be
necessary to use diagnosis-specific questionnaires to assess dyspnea intensity and sensory quality.
Support: National Institute of Nursing Research-1 R15 NR008883-01A1

An earlier version of this abstract, based on a preliminary analysis, was presented at the 2008 ERS
International Congress.
Title: DAILY CHANGE IN DYSPNEA SENSORY QUALITY IN RELATION TO BREATHING DISTRESS IN HOSPITALIZED ADULTS

Authors: M Parshall, PhD, RN¹; R Taylor, MD, FACC²; J Powers, MSN, C-ACNP²; U Ice, MSN, RN¹

University of New Mexico College of Nursing¹ and School of Medicine², and Raymond G. Murphy VA Medical Center³, Albuquerque, NM

Presentation session and time:

Multiple Dimensions of Dyspnea. May 15th, 2.00pm

Abstract:

Background: Change in dyspnea sensory quality in response to acute clinical treatment has only been investigated in asthma (Moy et al., AJRCCM 1998;158:749-53). The purpose of the present investigation was to explore the relative contributions of sensory quality descriptor-based intensity ratings to breathing distress over several days of acute hospitalization.

Methods: In this observational study, daily intensity ratings for breathing distress and for sensory quality descriptors were obtained from adults hospitalized for heart failure (N = 114). “Today” ratings were obtained on the day of enrollment (Study Day 1) and on the two following days (Study Days 2 and 3). A recall rating for the day of admission (Study Day 0) was also obtained on Study Day 1 (median hospital day 1). Daily breathing distress ratings (how bothered by breathing: 0 = not at all; 10 = as bothered as I could possibly be) were regressed on equally weighted mean intensity ratings for 3 sensory quality factors (SMOTHERING-AIR HUNGER, WORK-EFFORT; TIGHTNESS). Acute treatment was based on clinical judgment and was unrelated to study participation.

Results: There was a significant main effect of Study Day on the breathing distress rating, F(3, 240) = 138.3, p < .001, partial h² = .63, with significant paired differences between Study Day 0 and each subsequent study day (p < .001) but no significant difference between Study Days 1 and 2, or 2 and 3. Mean intensity ratings for the 3 sensory quality factors accounted for approximately half of the variance in the breathing distress rating on each day, but the relative contributions of each sensory quality factor varied considerably by study day (Table).

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<tr>
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<th>Study Day 1</th>
<th>Study Day 2</th>
<th>Study Day 3</th>
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<tr>
<td>TIGHTNESS</td>
<td>-10</td>
<td>.33†</td>
<td>.22*</td>
<td>.06‡</td>
</tr>
<tr>
<td>WORK-EFFORT</td>
<td>.39†</td>
<td>.29*</td>
<td>.49‡</td>
<td>.09</td>
</tr>
<tr>
<td>SMOTHERING-AIR HUNGER</td>
<td>.43†</td>
<td>.19</td>
<td>.09</td>
<td>-.03</td>
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<tr>
<td>P²</td>
<td>.51</td>
<td>.58</td>
<td>.51</td>
<td>.50</td>
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<td>P²adj</td>
<td>.50</td>
<td>.54</td>
<td>.49</td>
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*p < .02; † p < .01; ‡p < .001

Conclusion: In response to acute treatment for heart failure, the sensory quality of dyspnea continues to change, even when substantial relief has occurred and overall breathing distress ratings are stable. Results also suggest that in adults hospitalized for heart failure, sensations of SMOTHERING-AIR HUNGER resolve more rapidly than sensations of WORK-EFFORT.

Support: National Institute of Nursing Research-1 R15 NR008883-01A
Title: Emotional Distress and Breathing Distress in Adults Hospitalized for Heart Failure

Authors: M Parshall, PhD, RN; S Stokely, MSN, ACNP; U Ice, MSN, RN & J Silva, BSN, RN.

University of New Mexico College of Nursing, Albuquerque, NM

Presentation session and time: Multiple Dimensions of Dyspnea. May 15th, 2.15pm

Abstract:

Background: Few, if any, studies have investigated the extent to which dyspnea ratings are biased by nonspecific emotional distress or the extent of autocorrelation in dyspnea ratings over successive days of acute hospital treatment for exacerbated cardiopulmonary disease. In this observational study, we sought the answer to two research questions: (1) Does nonspecific emotional distress bias ratings of breathing distress in hospitalized patients? and (2) To what extent are daily ratings of breathing distress autocorrelated during a hospital stay?

Methods Adults hospitalized for heart failure were recruited as soon as feasible after admission (N = 119; Median hospital day (HD) at enrollment = HD 1; interquartile range [IQR] HD 1 to 2). Exclusions were: ST-elevation MI, pulmonary embolus, trauma, malignancy, BNP<100, inability to understand English, or heart failure not the focus of hospitalization. Questionnaires were administered for up to three consecutive days, beginning the day of enrollment (Study Day 1), at which time a dyspnea questionnaire was completed in a “today” version and a recall version for the day of admission (Day 0), and in a “today” version for up to 2 successive days thereafter (Day 2, Day 3). Breathing distress was rated by the item, How bothered are/were you by your breathing? (0 = not at all, 10 = as bothered as I could possibly be), previously validated in HF (Parshall et al., Heart Lung. 2001;30:47-56) and COPD (Res Nur Health. 2002;25:331-344). On Day 1, participants completed the K6, a reliable (Cronbach’s α=.82), valid 6-item scale of nonspecific emotional distress over the preceding month (range: 0-24; ≥13=severe; Kessler et al., Arch Gen Psychiatry. 2003; 60(2):184).

Results The sample was 71% male, 8% Black, 7% American Indian, and 39% Hispanic. Mean (SD) age was 58.9 (13.7) years. Median [IQR] ejection fraction was 34.5% [20%, 45%] and length of stay was 5 [4, 8] days. The mean (SD) K6 score was 9.1 (5.1), Median [IQR] = 8.0 [5, 13], with 30/119 (25%) scoring ≥13. Median [IQR] breathing distress scores were 9.0 [7.0, 10.0 ], 3.0 [1.0, 5.0 ], 2.0 [0, 5.0 ] and 2.0 [0, 5.0 ] for Days 0-3, respectively, Kendall's W = .54, c2(3) = 132.2, p < .001 with significant pairwise differences between Study Day 0 and Day 1 and between Day 1 and Day 2, Wilcoxon signed ranks test, p < .001 and p < .005, respectively. Spearman rank-order correlations (rs) between K6 and breathing distress were nearly zero (|rs| ≤.08, p ≥ .41). There was no significant difference in breathing distress ratings on any Study Day between those whos K6 scores were in the severe range (≥13) versus lower (<13) (p < .001, h2 ≤ .012 all comparisons). Autocorrelations (rs) of breathing distress were:

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<tr>
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<tr>
<td>Day 0</td>
<td>.25 (p = .014)</td>
<td>.07 (ns)</td>
<td>.16 (ns)</td>
<td>.56 (~&lt; .001)</td>
<td>.53 (~&lt; .001)</td>
<td>.52 (~&lt; .001)</td>
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Conclusions Ratings of breathing distress are independent from, hence unbiased by, nonspecific emotional distress and, at most, only moderately autocorrelated from day to day in patients hospitalized for HF who are willing to participate in an observational study.

Support: National Institute of Nursing Research-1 R15 NR008883-01A1
An earlier version of this abstract, based on preliminary data, was presented at the 2007 ATS International Conference.
Title:
The impact of panic disorder on dyspnea perception in chronic obstructive pulmonary disease

Authors:
N. Giardino
Department of Psychiatry, University of Michigan

Presentation session and time:
Multiple Dimensions of Dyspnea. May 15th, 2.30pm

Abstract:

Rationale: The prevalence of panic disorder (PD) in patients with chronic obstructive lung disease (COPD) is 3 to 10 times higher than that in the general population. Comorbid anxiety disorders in COPD is associated with increased hospitalizations for acute exacerbations, more severe dyspnea, greater disability, more impaired functional status, and decreased quality of life. However, little is known about the mechanisms by which PD affects patients with COPD. We hypothesize patients with COPD and PD will have greater affective, but not somatosensory, sensitivity to dyspnic stimuli.

Methods: Ten patients with COPD and panic disorder, 10 patients with COPD without panic, and 10 healthy, age-matched subjects were compared. Subjects were administered the Structured Clinical Interview for DSM-IV-TR to obtain a diagnosis of PD and to exclude other Axis-I disorders. Subjects completed questionnaire measures including the Beck Anxiety Inventory and Anxiety Sensitivity Index. Perceived dyspnea, respiratory behavior and other autonomic indeces were recorded in response to increasing inspiratory resistive loads.

Results: Subjects with panic disorder had higher anxiety and anxiety sensitivity scores and reported greater dyspnea in response to resistive loads. However no group differences were found in resistive load sensitivity. Subjects with panic disorder exhibited greater respiratory irregularity following the resistive load epochs.

Conclusion: Patient with COPD and PD do not show heightened sensitivity, but do report greater dyspnea, to inspiratory resistive loads.
Abstract:
Healthy subjects and COPD patients were exposed to several different uncomfortable respiratory interventions in the laboratory; after each exposure they completed a Multidimensional Dyspnea Profile (MDP). The COPD patients and normals underwent the following laboratory interventions: 1) minute ventilation was limited to 0.13 L/min and PETCO2 was raised to a level (mean 8 torr above resting) producing moderate discomfort ['limited ventilation hypercapnia', LVH, n=18], 2) the same intervention was intensified with higher PETCO2 until the subjects tolerance limit was reached (mean PETCO2 11 torr above resting), [n=17], 3) the subject voluntarily increased minute ventilation and at the same time a lung volume activated solenoid valve progressively forced the subject to breathe at higher end-expiratory volume (EEV) – target ventilation and EEV were progressively increased until the subject reached his/her maximum task performance ['Fessler', n=13], 4) the subject voluntarily increased minute ventilation while inspiring through a 13.8 cmH2O/L/sec resistance (measured at 1 L/sec) – target ventilation was progressively increased until the subject reached maximum task performance, [n=5] 5) the subject breathed with no ventilation target or added CO2 through a 26.5 cmH2O/L/sec resistance (measured at .3 L/sec) [n=4]. 6) After completing laboratory studies, each COPD patient was sent home with 14 copies of the MDP to be completed after episodes of dyspnea experienced during activities of daily living (ADL). The study is in progress; we report here preliminary results on a small sample.

Salient findings at this stage: a) The only stimulus able to consistently produce intolerable discomfort in the laboratory was maximal LVH. b) Emotions of anxiety, frustration, and fear were elicited in the laboratory by maximal LVH, showing that dyspnea can induce emotional responses independent of cognitive connections to disease. COPD patients showed slightly less emotional response to laboratory interventions. c) In COPD patients dyspnea associated with activities of daily living elicited greater fear than maximal LVH (although levels of discomfort were much less in daily living because ambulatory patients limited their dyspnea by reducing activity). [Supported by NIH NR10006]
**Title**

**Determination of cannabinoid effects on ventilatory control and breathlessness: a study of efficacy and safety.**

**Authors:**

Elspeth Pickering, Stephen J. Semple, Muhummad S. Nazir, Kevin Murphy, Andrew R. Cummin, Abraham Guz, Shakeeb H. Moosavi and Anita Holdcroft.

Magill Department of Anaesthesia, Imperial College London and Department of Respiratory Medicine National Heart and Lung Institute Imperial College London.

**Presentation session and time:**

Therapy and management of Dyspnea. May 15th, 3.30pm

**Abstract:**

Background. In humans Cannabinoids lack ventilatory depressant effects. We hypothesised that they may ameliorate breathlessness in normal subjects and in patients with chronic obstructive pulmonary disease (COPD); their ability to do so was determined using carbon dioxide (CO2) simulated breathlessness using 3 pre-determined fixed loads of CO2 (ml.min⁻¹).

Methods. Five normal and 4 COPD subjects entered a double blind randomised placebo-controlled crossover pilot trial with two test days a week apart. Each subject received sublingual sprays of cannabis based medicinal extract (CBME) or placebo up to a maximum of 4 sprays, equivalent to a single dose of 10.8mg of tetrahydrocannabinol (THC) and 10mg cannabidiol (CBD). Three 7 min periods of air breathing, low, moderate and high CO2 loads (0, 963, 1424 and 1881ml.min⁻¹) were imposed in random order, before and after drug and placebo administrations. Breathlessness was rated every 30s using a 100mm visual analogue scale (VAS). Minute ventilation (MV), end-tidal PCO2 (PETCO2), respiratory rate (RR), and tidal volume (TV) were measured breath-by-breath. Immediately following each CO2-loaded breathing period, subjects characterised their breathlessness by selecting respiratory descriptors from a standard list of 8, including 3 of the ‘work/effort’ cluster and 3 of the ‘air hunger’ cluster. Mood, arousal and anxiety scores were also recorded using the Spielberger Anxiety Inventory (S-Anxiety) and the Activation-Deactivation Adjective Check List of Thayer.

Results. The combined results for normal and COPD subjects showed no difference in VAS, respiratory measurements or psychological test scores before and after placebo or drug. There was no statistically significant difference in these measurements between normal and COPD subjects. However, COPD subjects chose the work/effort descriptors 25% more frequently and choose the air hunger descriptors 33% less frequently after cannabinoids in the absence of change in anxiety or arousal. This change in choice of descriptors was not seen after placebo, or after cannabinoids in normal subjects.

Conclusion. This study shows a lack of effect of cannabinoids on breathlessness ratings using a conventional visual analogue scale in a small group of subjects. Our findings with descriptor selections suggest that cannabinoids may ameliorate the unpleasantness of breathlessness but that a stimulus more specific for air hunger will be needed to determine a drug effect on breathlessness.
# Palliative oxygen versus medical air for relief of dyspnea: Results of an international, multi-site, randomized controlled trial

**Authors:**
Amy P. Abernethy, MD¹, Christine McDonald, MBBS, PhD, FRACP², Peter Frith, MBBS, FRACP³, Katherine Clark, MBBS, FRACP/FACHPM⁴, James E. Herndon, PhD⁵, Jennifer Marcello, MS¹, David Woods, MBBS, FRACP⁵, Iven Young, MBBS, PhD, FRACP⁶, Janet H. Bull, MD⁷, Andrew Wilcock⁸, Sara Booth, MBBS, FFARCSI⁹, Bernadette Kenny³, Jane L. Wheeler, MSPH¹, Belinda Fazekas³, Alan Crockett, MPH¹ and David C. Currow, MPH, FRACP³

(1) Duke University Medical Center, Durham, NC, (2) Austin Health, Melbourne, Australia, (3) Flinders University, Adelaide, Australia, (4) University of Sydney, Sydney, Australia, (5) Tasmania Statewide Palliative Care Service, Tasmania, Australia, (6) Sydney Area Health Service, Sydney Cancer Centre, Sydney, Australia, (7) Four Seasons Hospice & Palliative Care, Flat Rock, NC, (8) Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom, (9) Cambridge University, Cambridge, United Kingdom

**Presentation session and time:**
Therapy and management of Dyspnea. May 15th, 3.45pm

**Abstract:**

I. Background: Although the survival benefit of oxygen therapy for severely hypoxemic COPD patients (PaO2≤55 mmHg) is well-established, its symptomatic effectiveness for patients with intractable dyspnea due to life-limiting illness, but with PaO2>55 mmHg, is unclear.

II. Research Objectives: To evaluate oxygen vs. medical air for relief of breathlessness in patients with intractable dyspnea and PaO2>55 mmHg.

III. Methods: This randomized double-blind controlled trial recruited patients from 9 sites in the United States, United Kingdom, and Australia. Participants received oxygen or medical air via nasal cannulae at a blinded concentrator at 2 liters/minute, for at least 15 hours/day for 7 days. Primary outcome was breathlessness on a 0-10 numerical rating scale (NRS) measured twice daily; quality of life (QOL) via McGill QOL Questionnaire was secondary. Longitudinal repeated measures mixed models with unstructured covariance matrices were used to assess effects of time, intervention, and their interaction. Significant responders were individuals with >1 point NRS improvement; predictors of response were explored.

IV. Results: Participants (n=239) were: mean age, 73 (SD 10); 62% male; 64% COPD; mean PaO2, 77 (SD 12). Neither gas proved superior in relieving the sensation of dyspnea (p=0.456) or improving QOL (p=0.281). Dyspnea and QOL improved over the 7-day study period in both arms (p<0.0001 for each outcome). Significant predictors of morning response were: oxygen vs. air (OR 1.86, p=0.0344), low vs. high baseline breathlessness (OR 0.20, p=0.0003), moderate vs. high baseline breathlessness (OR 0.32, p=0.007). Responders were somewhat more likely to want to continue treatment than non-responders (51% vs 39%; p=0.0753); 56% of those with NRS response reported symptomatic improvement with treatment.

V. Conclusions: Overall, palliative oxygen conferred no additional benefit over medical air for relieving dyspnea or improving QOL in this study population. People with more severe breathlessness may derive more benefit from palliative oxygen. Patients could differentiate whether they symptomatically improved after a trial of medical gas.

VI. Implications for research, policy, or practice: Widespread use of palliative oxygen for the symptomatic management of dyspnea in non- or mildly-hypoxemic patients is not supported by this adequately-powered randomized trial, however select patients may benefit from the intervention.
Combined Effects of Obesity and COPD on Dyspnea and Exercise Tolerance

Josuel Ora, Pierantonio Laveneziana, Dror Ofir, Katherine A. Webb, Denis E. O'Donnell.
Respiratory Investigation Unit, Department of Medicine, Queen’s University and Kingston General Hospital, Kingston, Ontario, Canada.

Therapy and management of Dyspnea. May 15th, 4.00pm

Abstract:

Rationale: Among patients with chronic obstructive pulmonary disease (COPD) with similar degrees of airway obstruction, severity of lung hyperinflation is known to influence the extent of dyspnea and exercise intolerance. Lung volume components, in turn, are consistently affected by body mass index (BMI) both in health and in disease.

Objective: To explore the complex interactions between obesity, lung hyperinflation, dyspnea and exercise performance in COPD.

Methods: We compared dyspnea intensity ratings and ventilatory responses (breathing pattern, operating lung volumes and gas exchange) during symptom-limited incremental cycle exercise in well characterized groups of 18 obese (BMI = 35±4 kg/m2; mean±SD) and 18 normal-weight (BMI = 22±2 kg/m2) patients with moderate to severe COPD.

Measurements and Main Results: Groups were well matched for FEV1 (mean 49 %predicted) and diffusing capacity (means >70 %predicted) but resting lung hyperinflation [end-expiratory lung volume (EELV)] was significantly reduced in association with increasing BMI (p<0.005). In the obese patients, peak symptom-limited oxygen uptake was increased (p<0.01) and dyspnea ratings at a standardized ventilation were decreased (p<0.01) compared with normal-weight patients. Ratings of dyspnea intensity at a standardized ventilation during exercise correlated well with the concurrent dynamic EELV/TLC ratio (r=0.68, p<0.00001), as well as with the resting EELV/TLC (r=0.67, p<0.00001).

Conclusion: The combined mechanical effect of obesity and COPD was to reduce operating lung volumes at rest and throughout exercise with consequent favorable influences on dyspnea perception and exercise tolerance during cycle ergometry.

Sources of support: Ontario Thoracic Society.
**Title**
Mechanical Ventilation: Tidal volumes used in ICU are likely to induce inescapable air hunger

**Authors:**
Andrew Binks, Ph.D., Jamie Gellock, B.S.
University of New England, Portland, ME.

**Presentation session and time:**
Therapy and management of Dyspnea. May 15\textsuperscript{th}, 4.15pm

**Abstract:**

Background: A significant proportion of mechanically ventilated patients develop psychological injuries ranging from depression to PTSD. Current clinical protocols prescribe small tidal volumes (VT) to reduce the risk of lung injury in susceptible patients. However, VT reduction induces air hunger (AH; a desperate urge to breathe) that may promote the reported psychological harm. In a brief survey of 11 ICU patients the mean AH score was 48\% (where 100\% represented ‘extreme’ AH). We have determined the VT during mechanical ventilation at which AH arises and compared it to tidal volumes given to ventilated ICU patients.

Methods: 14 healthy subjects (10 female; 19-38 years) were mechanically ventilation via a mouthpiece. Tidal volumes were periodically reduced while subjects scored AH using an electronic scale. Blood gases were kept constant through manipulation of inspired gases. AH threshold was determined by linear regression of AH scores and VT.

Results: During mechanical ventilation air hunger arose when VT was reduced below 1033 ± 313ml. In the ICU, our subjects would have been given tidal volumes of approximately 670ml or less (10ml/kg body weight). Regression analysis predicted this clinical VT would induce AH scores of 34\% full scale; a score consistent with those of the ICU patients we surveyed.

Discussion: Tidal volumes currently given to ICU patients are the likely cause of their reported AH and may contribute to the occurrence of psychological injury. The underlying reasons why larger tidal volumes are required for comfort during mechanical ventilation compared to spontaneous breathing are unclear. We postulate that changes in respiratory muscle afferent activity and/or psychological factors may play a role.
CONTROL OF BREATHING PATTERNS WITH A SIMPLE SPEAKING TASK

Authors: RW Lansing and JD Hoit
Dept. Speech, Language, and Hearing Sciences, Univ. Arizona, Tucson AZ 85721

Presentation session and time:
Therapy and management of Dyspnea. May 15th, 4.30pm

Abstract:
Dyspnea during speaking presents problems in communication for many patients with pulmonary disease (O'Driscoll et al. 1999; Hodgev et al. 2003; Hixon & Hoit 2005). When increased respiratory drive impairs their ability to meet both metabolic and phonatory needs, they may employ a variety of speech-breathing strategies to minimize breathing discomfort: changes in tidal volume (VT), frequency (f), end-expiratory lung volume (EEV), flow, or non-phonated expirations. It is not known how these adjustments affect their dyspnea during speaking. Preliminary to studying these changes in patients, we tested a simple speaking task (counting) in healthy subjects to see if we could use it to vary VT and f, without altering minute ventilation (VE). Counting is a familiar, well-learned act that avoids the cognitive load of visual and auditory targets and is easy to use in the clinic or home.

Method
Six healthy subjects counted to 5, 10, 13, or 16 (5, 11, 17 and 23 syllables) at a comfortable rate for 1 minute (e.g., 1, 2, 3, 4, 5, inspire, 1, 2, 3 etc.). We predicted that count length and rate of counting would set f, that VT would adjust to meet the expiratory demands of count length, and VE would remain relatively constant. After each 1-minute counting period the subject rated the feeling of "needing more air, a need to breathe more", and the feeling of "physical exertion" on a 0 to 10 labeled visual analog scale. VT, f, and VE were measured from respiratory magnetometer data.

Results
Data are for the 5 subjects who maintained a constant rate of counting with minimal non-phonatory expirations. (1) For each counting period VTs were maintained within 12% of the minute's average. (2) As count length increased, VT progressively increased from .56 to 1.5 liters on average while f decreased from 20 to 6.9 bpm. Differences were significant across count lengths for both VT and f (p < .001). VE was maintained at 1.3 l/min above resting (average, 10.5 l/min; range, 10.0 to 11.5), The small differences in VE across count lengths were not statistically significant. Oxygen saturation did not change. (3) EEV varied above and below FRC within single counting tasks and with no consistent pattern among subjects. (4) Dyspnea: Three subjects rated dyspnea as LVAS 0 or 1 across counting tasks. Two subjects reported ratings of 2 to 6 for “needing more air” and 2 to 3 for “physical exertion”, with higher ratings generally associated with longer count length.

Conclusions
Subjects unguided by visual and auditory targets, with minimal training, can systematically vary tidal volume and breathing frequency with little change in minute ventilation. Other speaking tasks should allow control of other breathing parameters such as expiratory pressure (loudness) with minimal guidance. These methods may be useful in laboratory or clinical situations when it is desirable to alter breathing parameters without instrumentation for control and measurement.
Title
Dyspnea during Eating and Drinking: a possible contributor to Dysphagia in COPD.

Authors:
K. Dean, J., Hoit, A. Lederle, R. Lansing, J. Parrott.
Dept. of Speech, Language, and Hearing Sciences, University of Arizona, Tucson, AZ 85721

Presentation session and time:
Therapy and management of Dyspnea. May 15th, 4.45pm

Abstract:
Dyspnea in people with chronic obstructive pulmonary disease (COPD) is intensified by physical exercise and other activities that compete with or interrupt spontaneous breathing. Because the act of swallowing requires momentary breath-holding, it is possible that eating and drinking evoke or exacerbate dyspnea in people with COPD. The present study was designed to determine if this is true.

We developed a 1-page questionnaire that includes five major questions (“Do you ever experience...?”), checkboxes for situation-specific items, and places for providing additional comments. Respondents to the questionnaire were 133 adults with COPD and 13 healthy adults. Most (115) completed the questionnaire via the internet (http://fly2.ws.copd) and the remainder completed it on paper.

Results showed that 74% of the respondents with COPD experienced dyspnea (“breathing discomfort”) when eating or drinking, whereas none of the healthy respondents did. The respondents who experienced breathing discomfort did so most often when eating a large meal and when drinking a glass of water without stopping, and less often when eating a small snack and drinking a sip of water. The vast majority of those who experienced breathing discomfort reported that breathing discomfort caused them to change the way they eat or drink by taking smaller bites or smaller sips, eating or drinking less overall, avoiding walking while eating or drinking, taking frequent breaks while eating or drinking, avoiding talking during a meal, avoiding certain foods or drinks, and other less common adjustments. About half of those who reported breathing discomfort also reported that they change their breathing behaviors when eating or drinking, usually by taking deeper breaths.

This survey suggests that it is common for people with COPD to experience breathing discomfort while eating or drinking and that they change the way they eat and drink and the way they breathe to reduce or avoid discomfort. Their heightened drive-to-breathe may create competition between breathing and swallowing, which, in turn, may contribute to the higher prevalence of dysphagia (disordered swallowing) and malnutrition so common among people with COPD.
Patients suffering from acute pneumothorax experience intense dyspneic sensation. They struggle for air and present with rapid deep breathing, or rapid shallow breathing if chest movement causes pain. Airway sensors activated by lung collapse are believed to be responsible for such dyspneic sensation. In experimental animals, lung deflation cuts short expiration and stimulates inspiration, causing the Hering-Breuer deflation reflex. Airway sensors stimulated by lung deflation should be responsible. Two main types of mechanosensors operate in the lung and airways: inflation activated and deflation activated receptors (DARs). The inflation activated receptors can be subdivided into slowly adapting receptors (SARs) and rapidly adapting receptors (RARs). Activation of SARs and RARs, according to Paintal, may produce relief of dyspneic sensations. In small animals, DARs often form pure deflation units, whereas in large animals, DARs are usually associated with SARs or RARs to form a sensory unit responding to both lung inflation and deflation. Many reflex effects previously attributed to RARs are now assigned to DARs. DAR activation shortens $T_e$, and increases respiratory rate and inspiratory depth. If the dyspneic sensation during pneumothorax is mediated by lung mechanosensors, the DAR is the most likely candidate.

(supported by NIH HL58727)
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<th><strong>Title</strong></th>
<th><strong>Blockade of Airway Sensory Nerves and Dyspnea.</strong></th>
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| **Authors:** | **Burki N, Lee L-Y**  
University of Connecticut and University of Kentucky |
| **Presentation session and time:** | **Physiological mechanisms of Dyspnea. May 16th, 1.45pm** |

**Abstract:**

Anecdotal evidence (News Physiol Sci 1995;10: 238-243) suggested that vagal fibers in the lungs were involved in the genesis of dyspnea. In a series of studies in animals (J Physiol. 1998;508:109-18; J Appl Physiol. 1998;84:417-24; J Appl Physiol. 2003;95:1315-24.) we established that adenosine directly activates vagal C fibers and affects ventilatory pattern. Our subsequent series of human experiments (J Appl Physiol. 2005;98:180-5; Respir Res. 2006;7:139; Pulm Pharmacol Ther. 2008;21:208-13) strongly implicated a role for vagal C fibers in the genesis of dyspnea. We have now analysed the relative effects of blockade of vagal C fibers by two methods and routes of delivery: by inhibition of the sodium channel and interruption of action potential conduction in the nerve by inhaled local anesthetic (lidocaine), and by blockade by systemic theophylline, a known, nonselective adenosine receptor antagonist. Both techniques significantly (p<0.05) attenuated the dyspneic response to intravenous adenosine. However, the attenuation of the dyspnogenic response was significantly (p<0.05) greater with pretreatment with systemic theophylline (mean change in response, AUC - 44%) versus pretreatment with inhaled lidocaine (mean change in response, AUC -11.8%). These differences in the results of airway sensory nerve blockade probably reflect different populations of C fiber receptors and may explain conflicting results of previous studies of dyspnea and airway anesthesia.
<table>
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<th>Title</th>
<th>Diaphragm activity in voluntary breath-holds</th>
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| Authors: | Anna L. Hudson, Jane E. Butler and Simon C. Gandevia  
Prince of Wales Medical Research Institute and University of New South Wales |
| Presentation session and time: | Physiological mechanisms of Dyspnea. May 16\textsuperscript{th}, 2.00pm |
| Abstract: | It has been proposed that tonic contraction of the diaphragm may accompany a voluntary breath-hold to ‘suppress the expression of the central respiratory rhythm’ (1), but tonic activity is minimal or absent in recordings with an intra-oesophageal electrode (2). After a short period of hyperventilation, subjects (n = 5) performed breath-holds at the usual end tidal volume and were instructed to close their glottis. Costal, and crural (3 subjects only) diaphragm electromyographic activity (EMG) were recorded with an intramuscular electrode, and a multi-electrode gastro-oesophageal catheter, respectively. End-tidal CO2 (ETCO2), ECG, rib cage and abdominal movements, and abdominal EMG (surface electrodes) were monitored. Hyperventilation decreased ETCO2 by ~15% from eupnoeic values of ~ 5.5%, and the average breath-hold duration was 51.4 ± 13.6 sec (mean ± sd). Dyspnoea at breakpoint was reported as 5 ± 2 on a Borg scale. Throughout voluntary breath-holds there was low-amplitude tonic contraction of the diaphragm in all subjects (28.2 ± 13.3% of activity in eupnoea for costal and 25.4 ± 17.5% for crural EMG). Tonic single motor units discharged at 8.5 ± 3.1 Hz (n = 12 units from 4 subjects). Bursts of phasic activity were superimposed on tonic contraction, but the time at which they appeared differed between subjects. In three subjects, they appeared late in the breath-hold, after ~30 s, but in two subjects, there was phasic activity within the first ~ 5 s. Sinus arrhythmia was associated with phasic diaphragmatic bursts, but also occurred during tonic contraction without phasic activity. This suggests that during a breath-hold, voluntary drive to the medulla can transiently suppress phasic inspiratory activity, but some low-threshold diaphragm motor units discharge tonically and sinus arrhythmia persists.  
Title

Effect of breathing pattern and type of ventilatory constraint on hypercapnic air-hunger induced in healthy volunteers

Authors:
T Georgiou Delisle, K Murphy, ARC Cummin and SJG Semple, SH Moosavi

National Heart and Lung Institute, Imperial College London, Charing Cross Campus, St. Dunstan’s Road, London W6 8RP, UK.

Presentation session and time:
Physiological mechanisms of Dyspnea. May 16th, 2.15pm

Abstract:

Introduction: A previous study in healthy subjects indicated that dyspnoea is influenced by overall ventilation not the pattern of breathing (Remmers et al., Respiration Physiology 1968;4:78-90). However, there is a prevailing view that adopting particular breathing patterns is beneficial for clinical dyspnoea. Taking advantage of recent advances in experimental dyspnoea techniques, we re-tested the hypothesis that breathing pattern influences air hunger (AH), a particularly unpleasant form of dyspnoea. We also tested the hypothesis that respiratory muscle tension in response to ventilatory constraint contributes to AH.

Methods: AH was induced in 8 healthy males (aged 22±1years) by raising inspired CO2 (PETCO2=52±4mmHg). Ventilation was constrained (8.9±2.5l/min) by breathing to a metronome and either: 1) breathing from a bag with limited flow of fresh gas, or 2) voluntary matching of tidal volume (VT) to a visual target. For each method, three breathing pattern were imposed: a baseline breathing pattern (pattern 1; 12 breaths/minute and naturally adopted VT), faster, shallower breathing (pattern 2; 15 breaths/minute, 80%VT), and slower, deeper breathing (pattern 3; 10 breaths/minute, 120%VT). Subjects rated AH every 20s using a 100mm visual analogue scale (VAS). Peak inspiratory airway pressure was measured breath-by-breath at the mouthpiece as an index of respiratory muscle tension during ventilatory constraint.

Results: Changes in breathing pattern in either direction from baseline did not produce significantly different AH irrespective of breathing constraint method (52±19, 64±16, and 59±14 mmVAS for patterns 1, 2 and 3 with ‘bag limit’; 48±18, 63±16 and 51±13 mmVAS for patterns 1, 2 and 3 with ‘voluntary targeting’). The tendency for AH to be lowest with baseline breathing pattern, was not significant. AH levels were no different between methods of constraint, though inspiratory pressures were markedly lower with ‘voluntary targeting’ (1.9±0.2 versus 7.9±5.2 cmH2O). Inspiratory capacity did not change with breathing pattern indicating that end-expiratory lung volumes remained constant.

Conclusions: For a given level of hypercapnia, AH is unaffected by change in breathing pattern or by the generation of respiratory muscle tension. This is consistent with the notion that afferent feedback from pulmonary mechanoreceptors encoding overall ventilation is the key factor in mitigating hypercapnic AH.
**Title**

Impact of Obesity and Gender on Perception of Dyspnea during Induced Bronchoconstriction and Dynamic Lung Hyperinflation in Asthma.

**Authors:**


Department of Medicine, Queen’s University & Kingston General Hospital, Kingston, Ontario, Canada.

**Presentation session and time:**

Physiological mechanisms of Dyspnea. May 16th, 2.30pm

**Abstract:**

During methacholine provocation testing in females, obese asthmatics (OBA) undergo greater dynamic lung hyperinflation (DH) for a given level of bronchoconstriction than normal weight asthmatics (NWA) [Sutherland T, et al. AJRCCM 2008]. We examined the sensory consequences and the influence of gender on these obesity-related effects on operating lung volumes during acute bronchoconstriction. Methods: High-dose methacholine challenge (MCh) tests up to a 50% decrease in FEV1 or 256 mg/mL were conducted in 51 NWA (BMI 18.5-24.9 kg/m2, 29% male) and 46 OBA (BMI ≥30 kg/m2, 35% male) between 20-60 years of age. Serial FEV1, inspiratory capacity (IC) and plethysmographic end-expiratory lung volume (EELV) were measured and analyzed. Results: At rest, FEV1 was similar, IC/TLC was higher (p<0.001) and EELV/TLC was lower (p<0.001) in OBA compared with NWA. At PC20: EELV increased more in OBA (25%) than NWA (12%) (p=0.002); while dyspnea ratings (Borg scale) were not different. At maximum response in NWA and OBA, respectively: there was a 48 and 49% decrease in FEV1, a 33 and 47% increase in EELV, and dyspnea intensity reached 4.0 and 4.2 Borg units. For a standardized 25% increase in EELV, the increase in dyspnea intensity was less by 0.9 Borg units in OBA compared with NWA (p=0.012). Within the OBA group, the increase in dyspnea intensity for a given increase in EELV were significantly less in males than females (p=0.04). Conclusions: During MCh bronchoconstriction, the relatively reduced resting EELV in OBA was mechanically advantageous in that it allowed these individuals to accommodate greater increases in dynamic EELV with less respiratory discomfort than NWA. Perceptual responses to MCh-induced increases in EELV were blunted in obese males compared with obese females.

**Funding:** Ontario Thoracic Society
**Title**
Effects of Human Pregnancy on the Intensity of Perceived Breathlessness during Hypercapnia-Induced Hyperventilation.

**Authors:**
Queen’s University & Kingston General Hospital, Kingston, ON, Canada.

**Presentation session and time:**
Physiological mechanisms of Dyspnea. May 16th, 2.45pm

**Abstract:**
We examined the effects of pregnancy on the intensity of perceived respiratory discomfort (breathlessness) during hypercapnia-induced hyperventilation. Thirty-five healthy young women performed an isoxic hyperoxic CO2 rebreathing (RBR) procedure in the third trimester (TM3; 36.3±0.2 wks gestation, mean±SEM) and again 20.0±1.3 wks post-partum (PP). Borg ratings of perceived breathlessness were measured at the end of each min during RBR, and at the end of RBR. In TM3 vs. PP the central chemoreflex ventilatory recruitment threshold for PCO2 (VRTCO2) decreased, while subVRTCO2 ventilation (VEB) and central chemoreflex sensitivity (CcS) increased (all p<0.01). Breathlessness intensity ratings were identical in TM3 vs. PP (5.0±0.3 vs. 5.0±0.4 Borg units, p=0.96) at an isoVE of 40.2±1.7 L/min during RBR, despite significant differences in PETCO2 (TM3, 47.4±0.6 vs. PP, 59.0±0.5 mmHg, p<0.01). Pregnancy-induced reductions in PETCO2 at isoVE were associated with concurrent changes in VRTCO2 (r²=0.46, p<0.01) and VEB (r²=-0.25, p=0.01), but not CcS (r²=0.06, p=0.14). Breathlessness intensity ratings were 2-fold higher in TM3 vs. PP (6.4±0.4 vs. 3.2±0.4 Borg units, p<0.01) at an isoPETCO2 of 53.8±0.7 mmHg during RBR. This difference could be explained, in part, by a 28.3±2.8 L/min (200%) increase in VE at isoPETCO2 (r²=0.28, p<0.01), which in turn correlated with pregnancy-induced alterations in VRTCO2 (r²=0.32, p<0.01) and VEB (r²=0.26, p<0.01), but not CcS (r²=0.05, p=0.30). In conclusion: 1) breathlessness-VE relationships were similar in TM3 and PP during hypercapnia-induced hyperventilation; 2) pregnancy-induced increases in perceived breathlessness at isoPETCO2 reflected the normal awareness of increased VE; and 3) aside from its established effects on VE, CO2 did not have a significant independent effect on the intensity of perceived breathlessness during isoxic hyperoxic RBR in healthy young women.

[Funded by: Ontario Thoracic Society; WM Spear]
The neural response to air hunger shares temporal dynamics with subjective interoception

Ka’rleyton C. Evans, MD, MSc, Andrew Binks, PhD, Andrea Vovk, PhD, Robert B. Banzett, PhD


(*) Indicates shared first authorship

Brain Imaging May 16th, 3.30pm

Abstract:

Background: Dyspnea is an extremely unpleasant respiratory sensation experienced by patients with pulmonary and anxiety disorders. There is an unmet medical need to treat dyspnea as non-narcotic agents are currently unavailable. The identification of objective profiles of neural activity underlying dyspnea may lead to targeted drug development for this subjective symptom. Recent neuroimaging studies suggest the perception of air hunger (a form of dyspnea experienced as an uncomfortable urge to breathe) to be mediated by the amygdala, anterior cingulate and insular cortices (i.e., cortico-limbic circuitry). However, the genesis of air hunger and its relief within this circuitry remains poorly understood. The present study sought to characterize the dynamic stimulus-response of laboratory-induced air hunger within cortico-limbic circuitry of healthy individuals.

Methods: Six healthy subjects underwent fMRI scanning under constant elevated partial pressure of end-tidal CO2 (mean PCO2 = 46.1 mmHg) during mechanical ventilation. Air hunger was provoked and relieved during alternating 90 second periods of low tidal volume (0.53 liters) and high tidal volume (1.01 liters). Subjective air hunger ratings were made via visual analogue scale every 15 seconds. Voxel-wise fMRI analyses were performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Given previously published findings, the amygdala, anterior cingulate and anterior insular cortices served as a priori cortico-limbic regions of interest (ROIs), where the statistical threshold was set at p < 0.05 (corrected for region size). Subsequent neural time-course data were extracted from functionally identified cortico-limbic ROIs and compared with subjective reports of air hunger.

Results: As hypothesized, air hunger was associated with significant activation of cortico-limbic circuitry, specifically within the anterior insula, anterior cingulate and amygdala. The present findings confirmed previously published findings, with nearly overlapping localization of regional maxima. Neural time-course data extracted from cortico-limbic ROIs were observed to mirror the time course of subjective reports of air hunger.

Summary: The findings from the present study of air hunger in healthy individuals confirm and extend the findings from previous neuroimaging studies of dyspnea, specifically air hunger. The demonstration that neural activity within cortico-limbic circuitry is coincident with subjective ratings of air hunger serves to significantly advance our knowledge of the neural dynamics of air hunger sensation. It is hoped that this work will inform future efforts toward targeted drug development for dyspnea.

Supported by RO1HL46690, The Executive Committee on Research of the Massachusetts General Hospital and Pfizer, Ltd.
### Abstract:

**RATIONALE:** Dyspnea is the frightening key feature of asthma, which patients repeatedly experience in the course of disease. Recent studies have suggested that habituation processes might lead to a reduced perception of dyspnea. However, the underlying brain mechanisms of dyspnea are still not well explored and respective imaging studies in patients with asthma are absent. By using functional magnetic resonance imaging (fMRI), we examined whether patients with asthma show distinct brain activations during perceived dyspnea when compared to healthy controls. These brain activations were compared with brain activations during perceived pain to study neuronal generalisation processes to another unpleasant bodily sensation, which shares several characteristics with dyspnea.

**METHODS:** While laying in the scanner, 14 patients with mild to moderate asthma and 14 matched healthy controls repeatedly underwent conditions of mild and severe resistive load induced dyspnea and mild and severe heat pain. Mild and severe levels of both sensations were individually matched for intensity levels.

**RESULTS:** Ratings of the sensory intensity of dyspnea and pain were similar for patients and controls, whereas ratings of the affective unpleasantness of both sensations were lower in patients. When compared with controls, patients with asthma showed reduced insular cortex activity, but increased activity in the periaqueductal grey (PAG) during dyspnea and pain. Connectivity analyses demonstrated that the reduced activation of the insular cortex during dyspnea and pain in patients was moderated by increased PAG activation, which was not observed in controls.

**CONCLUSIONS:** The findings demonstrate a down regulation of insular cortex activity by the antinociceptive PAG in patients with asthma during perceived dyspnea, but also pain. This might represent a neuronal habituation mechanism reducing the affective unpleasantness of dyspnea in asthma, which generalizes to other unpleasant physical sensations such as pain.

**Funding source:** DFG LE 1843/5-1
# Dyspnea and Pain Share Affect-Related Homeostatic Brain Network

**Authors:** Andreas von Leupoldt\(^1\), Tobias Sommer\(^2\), Daniela Schön\(^1\), Hans Jörg Baumann\(^3\), Hans Klose\(^3\), Michael Rosenkranz\(^4\), Bernhard Dahme\(^1\), Christian Büchel\(^2\)

\(^1\)Department of Psychology, University of Hamburg, Hamburg, Germany, \(^2\)Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, \(^3\)Department of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, \(^4\)Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

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**Presentation session and time:**

Brain Imaging May 16\(^{\text{th}}\), 4.00pm

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**Abstract:**

**RATIONALE:** Dyspnea and pain share many characteristics. Both are subjectively perceived physiological sensations with a similarly alarming and unpleasant character, which signals homeostatic threat. Furthermore, similarities in the neuronal processing of both sensations have been assumed, including activations of the limbic system, but not yet tested. Therefore, we compared the perception of dyspnea and pain and their respective brain processing in three thematically related studies by using different methodological approaches.

**METHODS:** In study 1, we investigated the association between perceived dyspnea, pain and negative affect during resistive load breathing, the cold-pressor test and affective picture viewing in 22 healthy volunteers. In study 2, 14 healthy volunteers repeatedly underwent conditions of mild and severe resistive load induced dyspnea and mild and severe heat pain while laying in a fMRI-scanner. In study 3, the perception of resistive load induced dyspnea and cold-pressor pain was compared between 4 patients with right-hemispheric insular cortex lesions and 4 matched healthy controls.

**RESULTS:** In study 1, a positive correlation between ratings for perceived dyspnea and pain was observed in the affective unpleasantness dimension, but not in the sensory intensity dimension, which was further related to negative affect during picture viewing. Besides specific brain activations for either dyspnea or pain in study 2, common activations for both sensations were found in affect-related limbic areas such as the insular cortex, dorsal anterior cingulate cortex, amygdala and medial thalamus. In study 3, patients with insular lesions demonstrated reduced perceptual sensitivity for dyspnea and pain, in particular for the affective unpleasantness of both sensations, when compared to healthy controls.

**CONCLUSIONS:** The results of these three studies suggest that dyspnea and pain are at least in part processed by a common human brain network, which is also frequently observed in studies examining the processing of affective states. In particular the insular cortex plays an important role for the perception of both sensations, but also for other homeostatic processes. This affect-related homeostatic network seems particularly relevant for processing the affective unpleasantness of dyspnea and pain.

**Funding source:** DFG LE 1843/5-1 and LE 1843/6-1
Title
Analgesia-inducing properties of dyspnea: a comparison of "air hunger" with "sense of excessive inspiratory effort"

Authors:
Capucine Morelot-Panzini, Julien Mayaux, François Hug, Jean-Claude Willer, Thomas Similowski

Université Paris 6, ER10UPMC and INSERM U731, Paris, France, Université de Nantes, JE 2438, Nantes, France.

Presentation session and time:
Brain Imaging May 16th, 4.15pm

Abstract:
Background and hypothesis: Dyspnea and pain, both major symptoms signalling harm threatening conditions, have a lot of common features. A recent electrophysiological study conducted in healthy humans has shown that inspiratory threshold loading, inducing a form of dyspnea best described as "a sense of excessive inspiratory effort", is associated with a marked inhibition of a spinal nociceptive reflex (RIII)(1). This corresponds to the classic pain physiology phenomenon of "counter-irritation", that is specifically elicited by noxious stimuli, and that involves the stimulation of Aδ and C-fibers. Therefore, a link between the stimulation of C-fibers -of whatever nature- and the perception of a "sense of excessive inspiratory effort" is among the hypotheses that could be raised to explain the analgesia-inducing effect of this type of dyspnea. This would be consistent, for example, with the respiratory muscle length-tension inappropriateness theory. Among the various dyspneic sensations, "air hunger" is markedly different from the sense of excessive inspiratory effort. It is elicited by different stimuli and its underlying mechanisms are bound to be of a different nature. For example, air hunger could be the result of direct chemoreceptors stimulation with corollary discharge. We hypothesized that these differences would result in different analgesia-inducing properties.

Methods: We studied 8 healthy caucasian subjects (5 men and 3 women, age 26-40), who gave written consent to participate, after external ethical approval by the appropriate French authority. Ventilatory airflow (V') was measured to determine usual ventilatory variables, with concomitant recordings of end-tidal CO2 partial pressure (PETCO2) and of the ECG. The RIII reflex was studied by measuring the EMG response of the biceps femoris to trains of five rectangular electrical shocks of 1 ms duration delivered over 20 ms, 6 times per minutes, with a constant-current stimulator. Alpha-motoneuronal excitability was assessed through the Hoffmann (H) reflex (soleus). The subjects underwent 5 minutes inspiratory threshold loading (ITL) sessions with a threshold set at 2/3 of maximal static inspiratory pressure and 10 minutes steady-state hypercapnic challenge sessions (CO2) —5% Fi CO2, first 5 minutes unrestrained, last 5 minutes with controlled hypoventilation—. Dyspnea was characterized in terms of intensity, unpleasantness and "Simon's descriptors" (2)

Results: ITL induced a very intense dyspneic sensation (intensity 6-8 on a visual-analog scale, VAS), predominantly of the "excessive effort type". It was associated with RIII inhibition, statistically significant after the second minute and maximal after 5 minutes. There was no discernible change in the amplitude of the H-reflex. The subjects experienced little dyspnea during unrestrained 5% Fi CO2. Controlled hypoventilation increased their dyspnea intensity ratings to values comparable with the ITL ones (VAS 6-8), with "air hunger" as the predominant descriptor. The subjects were unanimous in considering air hunger as more unpleasant than excessive effort for a given sensation intensity. No RIII inhibition was observed during the CO2 challenges, at any point in time, and in spite of a slight H facilitation.

Conclusions: "Air hunger" and the "sense of excessive inspiratory effort" seems to be associated with radically different analgesia-inducing properties. This study therefore provide an additional neurophysiological substrate to the different natures of these two dyspneic modalities. Given the current conceptions regarding the mechanisms underlying the counter-irritation phenomenon, one hypothesis to be tested is that the "sense of excessive inspiratory effort" involves C-fibers whereas air hunger does not.

ABSTRACTS OF POSTER PRESENTATIONS

(oral presentations also presented as posters)
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<th>Title</th>
<th>DYSPNEA DESCRIPTORS FOLLOWING EXPOSURE TO SEPARATE DYSPNOGENIC STIMULI</th>
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<tr>
<td>Authors:</td>
<td>CR O’DONNELL, RB BANZETT, RM SCHWARTZSTEIN, RW LANSING, DM ELKIN.</td>
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<tr>
<td>Div Pulm Crit Care &amp; Sleep Med, Beth Israel Deaconess Med CTR and Harvard Med. Sch, Boston</td>
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<td>Presentation session and time:</td>
<td>Poster</td>
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<td>Abstract:</td>
<td>To assess distinguishable qualities of dyspnea, we exposed healthy volunteers (N = 9) and patients with COPD (N = 5) to stimuli designed to evoke a sense of air hunger (AH), or work and effort (WE). Following, subjects rated the intensity of different breathing sensations on a ten point visual analog scale. Several words or phrases were employed to capture each type sensation (AH or WE)</td>
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<td>To evoke AH, minute ventilation was limited to 0.13 L/m/kg while partial pressure of inspired CO2 was increased (limited ventilation hypercapnia, LVH). To evoke a sense of WE end-expiratory lung volume was elevated during normocapnic hyperpnea (Fessler). A subset of healthy volunteers were also exposed to target driven normocapneic hyperpnea with added inspiratory resistance (VE-R).</td>
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<td>Factor analysis identified two components comprised of descriptors associated with either AH or WE that accounted for 76% of the variance associated with correlations among quality descriptors. One component contained the phrases 'air hunger’, 'want more air’, and 'breaths don't satisfy’, while the other contained phrases 'work and effort’, 'rapid deep breathing’, 'muscle work’, and 'concentration/mental effort’. Despite overall correlation among descriptors, there was considerable overlap of ratings in response to LVH and Fessler stimuli. When exposures were matched on overall sensory intensity: work and effort =7.1 following Fessler, and 6.1 following VE limit; air hunger = 4.8 following exposure to Fessler and 5.1 following LVH. Many subjects rated highly the sense of concentration/mental effort associated with either task, and this might have contributed to high work effort ratings following LVH. Multiple linear regression revealed that a sense of muscle work and a sense of mental work contributed independently to prediction of work and effort rating, irrespective of experimental exposure.</td>
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<td>Conclusions</td>
<td>1) There is considerable overlap between ratings of AH and WE following exposures designed to evoke each response separately. 2) Mental effort or concentration contributes to an overall sense of work and effort for either stimulus. 3) A sense of AH during Fessler may result from limited tidal volume excursion as inspiratory capacity is reduced. 4) the phrase 'breaths don’t satisfy’ is largely synonymous with air hunger. Supported by NIH NR10006.</td>
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**Effect of morphine on laboratory dyspnea and respiratory drive**

**Authors:**

L Adams1, CR O'Donnell, DM Elkin, RM Schwartzstein, RW Lansing, SA Gilman, RB Banzett

Div. Pulm, Crit Care & Sleep Med, Beth Israel Deaconess Med. Ctr. & Harvard Med. Sch., Boston, MA USA; 1 Sch PT & Ex Sci, Griffith University, Qld, Australia.

**Abstract:**

Recent systematic reviews provide weak support for use of opiates in palliation of refractory dyspnea. However their use, dose and optimal route of administration remain controversial with concomitant respiratory depression perceived as a major risk. This abstract reports preliminary data from a blinded randomised controlled study on the effect of i.v. morphine on a standard laboratory dyspnea challenge and associated respiratory drive. After informed consent and appropriate familiarization, 3 healthy volunteers received either 0.07mg/kg morphine sulphate (over 5 mins) or saline on separate days. Before, and for 2 hours following administration, subjects performed (i) dyspnea responses to increasing PETCO2 with ventilation (VE) clamped at resting levels (ii) ventilatory responses to increasing PETCO2 to assess respiratory drive. With clamped VE, all subjects tolerated an elevated PETCO2 of 53-54 torr; dyspnea ratings of 94%, 95% and 81% of the maximum tolerable before morphine fell to 66%, 47% and 30% after morphine respectively. Reduced dyspnea was reported within 20 mins and was sustained for 2 hours. No changes in dyspnea scores were seen following saline. With VE unclamped, equivalent levels of PETCO2 (52-53 torr) were accompanied by ventilatory depression in each subject (42 to 26, 37 to 22 & 33 to 16 l/min) for up to 2 hours following morphine but not with saline. To assess whether morphine-induced reductions in dyspnea could be explained by respiratory depression, dyspnea scores were compared pre and post morphine at the different PETCO2 levels (clamped VE) that induced equivalent unclamped VE levels. In 2 subjects, morphine-induced dyspnea was “proportional” to ventilatory depression; the 3rd subject showed “proportionally” greater fall in dyspnea. These early results show that a clinically moderate dose of morphine results in substantial and sustained relief of laboratory dyspnea in healthy subjects. Whether this can be accounted for solely by the accompanying respiratory depression remains to be determined.
## Faculty and Presenter names and contacts:
*(listed alphabetically)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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</tr>
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<tr>
<td>Banzett, Robert B.</td>
<td>Harvard University, Boston, MA, USA</td>
<td><a href="mailto:rbanzett@bidmc.harvard.edu">rbanzett@bidmc.harvard.edu</a></td>
</tr>
<tr>
<td>Binks, Andrew P.</td>
<td>University of New England, Portland, ME, USA</td>
<td><a href="mailto:abinks@une.edu">abinks@une.edu</a></td>
</tr>
<tr>
<td>Burki, Nausherwan</td>
<td>University of Connecticut, USA</td>
<td><a href="mailto:nburki@uchc.edu">nburki@uchc.edu</a></td>
</tr>
<tr>
<td>Deesomchok, Athavudh</td>
<td>Queen's University, Ontario, Canada.</td>
<td><a href="mailto:7ad25@queensu.ca">7ad25@queensu.ca</a></td>
</tr>
<tr>
<td>Delisie, T. Georgiou</td>
<td>Imperial College London, UK.</td>
<td><a href="mailto:s.moosavi@imperial.ac.uk">s.moosavi@imperial.ac.uk</a></td>
</tr>
<tr>
<td>Evans, Karl C.</td>
<td>Massachusetts General Hospital, Boston, MA</td>
<td><a href="mailto:KCEVANS@PARTNERS.ORG">KCEVANS@PARTNERS.ORG</a></td>
</tr>
<tr>
<td>Giardino, Nicholas</td>
<td>University of Michigan, USA</td>
<td><a href="mailto:ngiardin@med.umich.edu">ngiardin@med.umich.edu</a></td>
</tr>
<tr>
<td>Gracely, Richard</td>
<td>University of North Carolina, USA</td>
<td><a href="mailto:rgracely@unc.edu">rgracely@unc.edu</a></td>
</tr>
<tr>
<td>Hoit, Jennifer</td>
<td>University of Arizona, Phoenix, USA</td>
<td><a href="mailto:hoit@email.arizona.edu">hoit@email.arizona.edu</a></td>
</tr>
<tr>
<td>Hudson, Anna</td>
<td>Prince of Wales Medical Research Institute, Australia</td>
<td><a href="mailto:a.hudson@powmri.edu.au">a.hudson@powmri.edu.au</a></td>
</tr>
<tr>
<td>Jensen, Dennis</td>
<td>Queen's University, Ontario, Canada.</td>
<td><a href="mailto:dennis.jensen@queensu.ca">dennis.jensen@queensu.ca</a></td>
</tr>
<tr>
<td>Lansing, Robert</td>
<td>University of Arizona, Phoenix, USA</td>
<td><a href="mailto:rlansing@bidmc.harvard.edu">rlansing@bidmc.harvard.edu</a></td>
</tr>
<tr>
<td>McCrimmon, Donald</td>
<td>North Western University,</td>
<td><a href="mailto:dm@northwestern.edu">dm@northwestern.edu</a></td>
</tr>
<tr>
<td>Morelot-Panzini, Capucine</td>
<td>Université Paris 6, Paris, France</td>
<td><a href="mailto:capucine.morelot@psl.aphp.fr">capucine.morelot@psl.aphp.fr</a></td>
</tr>
<tr>
<td>Ora, Joshua</td>
<td>Queen’s University, Ontario, Canada.</td>
<td><a href="mailto:josuel@alice.it">josuel@alice.it</a></td>
</tr>
<tr>
<td>Parshall, Mark</td>
<td>University of New Mexico, USA</td>
<td><a href="mailto:mparshall@salud.unm.edu">mparshall@salud.unm.edu</a></td>
</tr>
<tr>
<td>Semple, Stephen J.G.</td>
<td>Imperial College London, UK.</td>
<td><a href="mailto:s.semple@imperial.ac.uk">s.semple@imperial.ac.uk</a></td>
</tr>
<tr>
<td>Tracey, Irene</td>
<td>Oxford University, UK.</td>
<td><a href="mailto:irene@fmrib.ox.ac.uk">irene@fmrib.ox.ac.uk</a></td>
</tr>
<tr>
<td>Undem, Bradley</td>
<td>John Hopkins University, Baltimore, USA</td>
<td><a href="mailto:bundem@jhmi.edu">bundem@jhmi.edu</a></td>
</tr>
<tr>
<td>Von Leupoldt, Andreas</td>
<td>Universität Hamburg, Germany</td>
<td><a href="mailto:andreas.vonleupoldt@uni-hamburg.de">andreas.vonleupoldt@uni-hamburg.de</a></td>
</tr>
<tr>
<td>Wheeler, Jane L.</td>
<td>Duke University, North Carolina, USA</td>
<td><a href="mailto:jane.wheeler@duke.edu">jane.wheeler@duke.edu</a></td>
</tr>
<tr>
<td>Yorke, Janelle</td>
<td>University of Salford, Manchester, UK</td>
<td><a href="mailto:J.Yorke@salford.ac.uk">J.Yorke@salford.ac.uk</a></td>
</tr>
<tr>
<td>Yu, Jerry</td>
<td>University of Louisville, Louisville, USA</td>
<td><a href="mailto:j0yu0001@louisville.edu">j0yu0001@louisville.edu</a></td>
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CME Evaluation Form

1) Select your title:

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2) What influenced you to take this CME activity?

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3) Please rate the projected impact of the following objectives

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4) This CME activity

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<td>Was presented in the appropriate learning format</td>
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<td>Quality of the meeting site was excellent</td>
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5) Open questions:

How could this activity be improved?

Based on your educational needs, please provide us with suggestions for future topics and formats:

Comments: