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On the Individual Variations in Dyspnea and its Prediction Using Non-Invasive Methods

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by

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DEDICATIONS

I dedicate this dissertation to all the scientists of the world. Scientists are some of the most passionate, driven, and dedicated people I have met in my life. They work tirelessly and endlessly towards the goal of ushering humanity forward. Some are altruistic, while others are needlessly self-centered; most are somewhere in between. Regardless, their contributions add to the ever-evolving and expanding pool of human knowledge. We learn from others, build upon their work, and contribute new data with the hope that someone, anyone, will do the same and benefit from it. We see a future in which we want to live, a hopelessly impossible future, and work towards realizing it. Through late night reading and thinking sessions to early morning experiments, we toil away for a future most of us are certain we will never see. A future free of pollution, a future free of disease, a future free of suffering. That being said, we are not merely dreamers and romantics; we are the very sculptors of reality. The future, when viewed from a wide lens, is determined by those who dare to turn their dreams into reality. By those who are incapable of hearing the word “impossible” without the words “for now” following it, even if only in their minds. By those who are not interested in simply repeating the work or lives of others, but making a unique mark on the world, however small the impact and however large the cost to themselves. That is what a scientist is; a wild force of imagination and willpower who has been set free upon reality, stripped of the limitations of a rigid mind. To all my fellow scientists, dreamers, and sculptors of reality; thank you for all that you do. Always remember that imagination is the uncharted land upon which

the roads of reality are paved. Keep on imagining, keep on solving problems, keep working towards that impossible (for now) future. Godspeed.

ABSTRACT OF THE DISSERTATION

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by

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Dyspnea is the subjective sensation of breathing discomfort. It is prevalent in patients with chronic and critical illness and associated with poor clinical outcomes and long-term psychological trauma. The multidimensional nature of dyspnea and individual variation in its presentation make identification difficult, particularly in non-communicative patients. To address this critical need, I aimed to (1) better understand the factors contributing to individual variation in dyspnea severity by identifying its physiological and psychological drivers, and (2) produce a novel tool for monitoring dyspnea based on noninvasive biomarker inputs. I recruited healthy adults and administered demographic and psychological evaluations to evaluate their health, anxiety levels and interoceptive awareness traits. I then induced dyspnea using a semi-rebreathing, forced end-tidal system to control arterial partial pressures of oxygen and carbon dioxide while collecting self-reported dyspnea scores during free breathing. I also collected clinically-relevant noninvasive biomarker data including respiratory air flow rates, inspiratory and end-tidal gas tensions, electrocardiogram (ECG), and oxygen saturation. Video was recorded to allow physician estimates of dyspnea during experiments. Dyspnea severity was

positively associated with physiological factors including the hypercapnic ventilatory response (HCVR) ($p = 0.006$), respiratory rate ($p < 0.001$), tidal volume ($p < 0.001$), minute ventilation ($p < 0.001$), and heart rate ($p = 0.006$). Through mixed linear model analysis, I found that trait anxiety has a positive association with dyspnea severity ($p = 0.042$). “Attention regulation”, “emotional awareness” and “self regulation” also influenced dyspnea severity ($p < 0.001$, $p = 0.004$, $p = 0.004$ respectively). Using a combination of demographic and physiological data I trained categorical machine learning models to determine if a multivariate method would achieve higher accuracy in identification of dyspnea than observational estimates by healthcare professionals. Ensembled and classical models were tested. Random forest performed best overall with an F1 score of 0.805. We then recruited physicians and nurses to view the videos and assess participant dyspnea using the respiratory distress observation scale. They achieved a precision-recall F1 score of 0.608, meaning our model performed 32.4 percent better. This study highlights the multivariate nature of dyspnea, and the need for further evaluation of identification methods.

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Chapter 1: Introduction

Dyspnea, commonly known as "shortness of breath", represents a complex and often debilitating symptom that encompasses both physiological and psychological dimensions.[1,2] From a clinical perspective, dyspnea is not merely an uncomfortable sensation but a significant indicator of underlying cardiopulmonary pathologies, affecting millions globally and leading to substantial disability by deteriorating daily quality of life.[2–4]

Dyspnea is a common symptom in several chronic and acute pathologies including chronic obstructive pulmonary disease (COPD), asthma, heart failure, interstitial lung disease, neuromuscular disorders, lung cancer, and acute conditions including pneumonia and pulmonary embolism.[5–11] The presence of dyspnea is a potent predictor of mortality for COPD patients who have been discharged from the ICU and surpassed some seemingly obvious measurements such as heart failure FEV1, positive air pressure use on discharge, and recent hospital admissions in prognostic value.[12,13]

The subjective nature of dyspnea, like hunger or thirst, means its severity and qualitative aspects vary widely among patients, making its assessment and management a challenge in clinical practice. Therefore, a deeper understanding of its mechanisms, comprehensive assessment strategies, and effective management approaches are imperative to improve patient outcomes and reduce suffering.

Efforts to address the issue of dyspnea assessment via observation have been met with some success over the years. Namely, the development of the Respiratory Distress Observation Scale (RDOS) has equipped healthcare practitioners with a valuable tool to assess dyspnea, which is particularly important for noncommunicative patients.[14] However, observation scales come with their own limitations such as requiring in-person observation and leaving the times when a patient is not directly under observation unaddressed. A tool which can accurately predict or monitor dyspnea in noncommunicative people, and could be deployed continuously, is greatly needed. The development of such a tool is a focal point of this dissertation and the research presented herein.

Physiology of Dyspnea, and its Three Main Dimensions

The pathophysiology of dyspnea is fundamentally complex, integrating signals from a wide array of sources throughout the body, making it an interoceptive experience distinct from discomforts like localized pain. A prevailing unifying theory exists that dyspnea results from a mismatch between the central respiratory motor command and the incoming afferent information from receptors in the airways, lungs, and chest wall structures.[1,15–17] This concept was explained by Godfrey in the late 1960s as "length-tension inappropriateness," which he described in the context of breath hold experiments. He concluded that motor output from the respiratory center which was mis-matched because the muscles were not allowed to shorten during the voluntary breath holds caused the sensation of dyspnea.[18] This definition has evolved to encompass neuro-

mechanical, or efferent–reafferent dissociation as our understanding of the specific roles of the central nervous system, chemoreflexes, and peripheral signaling in modulating dyspnea developed.[17,19,20]

The brain assesses the effectiveness of motor commands issued to ventilatory muscles by comparing the expected flow and volume response with actual afferent feedback from peripheral sensory receptors. When this comparison reveals an inadequacy in respiratory pressure, airflow, or movement of the lungs and chest wall given the outgoing motor command, the intensity of dyspnea is heightened.[1,15] This mechanism explains how dyspnea can arise from different sources such as breath-holding, insufficient tidal volumes, and insufficient minute ventilation. Patients with mechanical loads (resistive or elastic) or respiratory muscle abnormalities also experience this efferent-afferent dissociation, contributing to dyspnea intensity.

Generally, the sensation of dyspnea includes three dimensions:

> **Air Hunger:** This sensation is characterized by an increased respiratory drive, usually associated with increased ventilation. It is considered a "primal sensation" and a primary element of dyspnea.[21] The sensation of air hunger is strongly related to chemoreceptor stimulation, particularly by increased partial pressure of arterial carbon dioxide ($PaCO_2$), and can persist even with complete neuromuscular blockade, demonstrating its independence from muscular work or

effort.[22] Studies have shown that when drive is increased while voluntary breathing is suppressed, dyspnea escalates rapidly.[23,24] Brain imaging studies have specifically identified limbic, paralimbic, and cerebellar activation during air hunger.[25] Some studies suggest the unpleasantness of this sensation is greater than that of work/effort in laboratory settings, although due to the highly subjective nature of what people find to be "more unpleasant", this should only be taken as a rough generalization.[26]

Chest Tightness: This dimension is thought to originate from the stimulation of pulmonary sensory receptors via vagal pathways, specifically slow-adapting receptors, irritation receptors (fast-adapting), and C-fibers in the lung, which respond to local airway inflammation and muscle fiber contraction.[2,20,27] Clinical observations and practice show that relaxation of bronchial smooth muscle via β-agonists alleviates chest tightness, even when effort and airway obstruction persist.[1] This indicates that chest tightness is a distinct form of breathing discomfort from work/effort and air hunger.

Increased Effort or Work: This sensation is a common feature in conditions characterized by abnormal mechanical loads on the respiratory system, such as COPD and interstitial lung disease, which reduce compliance of the lung, and neuromuscular weakness, which require increased efferent neural activity to maintain baseline respiratory output.[7] The sensation of increased effort or work of

breathing reflects the conscious perception of an increased central respiratory motor output, especially directed to the intercostal muscles.[16,28] The intensity of this sensation correlates with the increase in the effort-to-displacement ratio during exercise.[29] Fatigue and weakness of respiratory muscles can also intensify this sensation, as more effort is required to drive a weak muscle. While respiratory muscle activity is not essential for dyspnea perception *per se*, the perception of effort is intrinsically linked to the magnitude of the centrally generated motor command signal.[23]

It is important to note that more than one of these dimensions of dyspnea can be at play during a bought of dyspnea, and experimentally isolating one from the other is difficult. For the purposes of the study presented in this dissertation, air hunger was the primary mechanism by which dyspnea was stimulated. Specifically, we used stimulation of central and peripheral chemoreceptors by modulating inhaled oxygen and carbon dioxide levels, which will be explained in more detail in the methods chapter. However, various degrees of each dimension of dyspnea could have been experienced by the participants of our study. This is particularly true of work/effort, as the increase in ventilatory drive over multiple minutes can increase the unpleasant sensation of increased breathing effort.

Chemoreflexes

Oxygen levels in the blood are primarily monitored by highly specialized cellular structures known as peripheral chemoreceptors.[30] The main peripheral sensor for acute oxygen changes is the carotid body, a small arterial chemoreceptor located at the bifurcation of the common carotid artery.[31] Other peripheral chemoreceptors include those located in the aortic bodies.[30] The sensory and neurosecretory cells within chemoreceptors are the glomus cells**.** These cells are essential for oxygen (O_2) homeostasis. The glomus cells are grouped in clusters called glomeruli, enveloped by glia-like sustentacular cells.[31]

Recent studies suggest that the molecular mechanism of oxygen sensing is via a mitochondria driven model. Under hypoxic conditions, the decrease in oxygen availability causes a buildup of electrons along the electron transport train, which slows down the processes of mitochondrial complex I, leading to accumulation of NADH and production of reactive oxygen species.[31] These molecules act as signals that modulate ion channels, namely K^+ channels, which leads to glomus cell depolarization. This depolarization causes voltage-dependent Ca^{2+} channels to open, and subsequently an influx of calcium ions and neurotransmitter release.[31] This activates the glossopharyngeal nerve which then sends the signal to the central nervous system, primarily the nucleus tractus solitarius.[15,31]

While multiple brain and brainstem regions may be involved in carbon dioxide (CO_2) sensing, there is evidence that it is primarily conducted in the medulla *via* detection of changes in local concentrations of H^+ ions.[30,32] A well-studied region involved in central chemoreception is the retrotrapezoid nucleus (RTN). The RTN is located on the ventral surface of the medulla, and is involved both in sensing of changes in CO_2 and also sending signals to other brain regions when it detects these changes.[32] The RTN innervates the preBötzinger complex, which is implied to be heavily involved in the generation of breathing rhythm.[32] It also innervates the Bötzinger region as well as the rostral and caudal respiratory groups.[32] Due to its broad innervation with multiple brainstem components, it has been implicated in the modulation of both breathing rhythm and intensity.[32] Outside of direct nerve innervation, the RTN also creates and releases neuropeptides which affect breathing. These are namely pituitary adenylate cyclase-activating peptide, galanin, and neuromedin-B.[32]

When either a lack of oxygen or an increase in carbon dioxide are detected via the sensors described above, an increase in ventilatory drive occurs leading to increased ventilation (assuming pathology, medications or mechanical ventilation do not interfere). As touched on previously, the importance of chemoreception to air hunger lies in the balance between the stimulus and the respiratory drive it causes. The increase in ventilation in response to a set change in either the partial pressure of oxygen (PaO_2) or carbon dioxide ($PaCO_2$) will be generally referred to as chemosensitivity, although each has a distinct name and measurement: hypoxic ventilatory response (HVR) and

hypercapnic ventilatory response (HCVR), respectively. HVR and HCVR can vary broadly from person to person, meaning that while breathing the same concentrations of oxygen and carbon dioxide, two individuals could have different increases to their total breathing output, or total ventilation. It can be hypothesized that those with higher chemosensitivity are at higher risk of developing dyspnea, which will be investigated in the first research chapter of this dissertation.

Clinical Importance of Dyspnea

Impact on Patients' Daily Lives: Dyspnea severely limits patients' daily activities, exercise capacity, and overall functional status, often leading to a "negative spiral" in conditions like COPD.[33,34] Patients with dyspnea frequently experience a reduction in physical activity, which further deconditions them and exacerbates their breathlessness. This limitation can be so severe that it prevents patients from performing basic self-care activities like dressing. The impact of dyspnea extends beyond physical limitations to significantly impair health-related quality of life across all adult age groups.[35]

Psychological impact: Dyspnea is intimately linked with psychological distress, particularly anxiety, fear, and depression.[33,36–38] Up to 74% of COPD patients experience anxiety symptoms and up to 55% have clinical anxiety, which can manifest as restlessness, motor tension, insomnia, difficulty swallowing, palpitations, and suppressed appetite.[39,40] This strong association leads to a "dyspnea-anxiety-dyspnea cycle," where

the experience of breathlessness causes anxiety, which in turn creates muscle tension, intensifying dyspnea and leading to panic.[41] Patients describe feeling "frightened," experiencing "panic," and thinking about death during severe dyspnea episodes.[37,41,42] The anticipation of discomfort from physical exertion further contributes to psychosocial symptoms like anxiety and depression. The quality and intensity of dyspnea are shaped by patient experience, expectation, behavioral style, and emotional state, which may explain why its relationship with lung function impairment is often weak. Those who are more dependent, anxious, or excessively focused on their health may experience severe dyspnea with minor increases in ventilatory impedance.[4,34,43]

Patient Outcomes: All patients reporting any dyspnea at hospital admission are at an increased risk of in-hospital death, with greater dyspnea correlating with a higher risk of mortality regardless of cause of presentation.[3] Dyspnea at admission or recalled within 24 of admission interview can be predictive of mortality within 2 years of discharge, even for those without cardiovascular or pulmonary pathologies.[3] Similarly, severe dyspnea is extremely predictive of hospital re-admission and mortality for COPD patients being discharged from the ICU after surviving acute hypercapnic respiratory failure, even after adjusting for age, BMI, airflow obstruction (measured FEV1), and heart failure.[13]

Dyspnea is frequent and intense in mechanically ventilated patients in the ICU and is associated with adverse outcomes such as anxiety, prolonged mechanical ventilation, noninvasive ventilation failure, and mortality.[44–46] It is often linked to ventilator settings

such as low tidal volume, low inspiratory flow rate, and lack of synchronization between ventilator and patient breathing efforts.[47–49] Moderate-to-severe dyspnea is independently associated with noninvasive ventilation failure and higher mortality rates.[45] Furthermore, adjusting ventilator settings to better meet patient needs improves dyspnea in 35 percent of patients, meaning proper identification of dyspnea and intervention can assist a large percentage of mechanically ventilated patients.[50] In addition, dyspnea during the hours following extubation of mechanically ventilated patients is correlated with extubation failure, showcasing the importance of continued monitoring of dyspnea.[51] The ability to monitor and predict dyspnea would allow healthcare professionals to intervene and drastically improve patient outcomes.

Identification and Assessment of Dyspnea

Assessment of dyspnea in noncommunicative patients: The RDOS and its derivative scales including the MV-RDOS adapted for mechanically ventilated patients and the IC-RDOS made for quick use in intensive care units fulfill the crucial clinical role of objectively measuring respiratory distress when standard self-report measures, such as the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), are infeasible.[14,52,53] The RDOS is composed of eight items, each given a score between 0 and 2, for a score range of 0-16. These items are respiratory rate, heart rate, accessory muscle use, paradoxical breathing pattern, nasal flaring, grunting at end-expiration, look of fear and restlessness. The RDOS shows strong consistency in scoring between trained users of the scale, which

is critical for a tool with such widescale use.[14,54] The nature of the scale also allows it to detect changes with treatment, meaning healthcare professionals can understand the effectiveness of their intervention by re-assessing the patient. In a recent study, the RDOS was used to guide ventilator withdrawal, and showed promise as a method for reducing patient distress.[55]

Limitations of observational assessment: While the RDOS is an excellent tool, it suffers from limitations including universal reliability, accuracy, and difficulty determining the intensity of dyspnea. For example some of the measures such as heart are objective, while others can be masked by patient behavior or sedation, such as look of fear. Some studies have noted that despite training, some healthcare professionals struggle to maintain consistent scoring on certain items (such as restlessness) in the RDOS, and others tried to alter the RDOS categories in an attempt to make it more useable for their specific needs.[56,57] Also, the relationship between RDOS scores and self-reported dyspnea has been moderate at best, and generally is found to be weak.[44,58] Some recent studies have also found that the use of the RDOS causes an underestimation of suffering, as nurse and physician assessments of dyspnea are lower than patient self-report.[59] It is important to note that the RDOS, which was developed to bring standardization to dyspnea assessment, was not intended to be a catch-all; during initial testing the authors clearly considered and discussed the limitations of the observational tool they created.[14] Despite this, the serious need for a tool of this nature has led to continuous research of its use case and limitations.

Machine learning may show promise as a valid method of predicting dyspnea severity: While the use of machine learning for the monitoring of dyspnea is not well established, research into the use of machine learning algorithms for the prediction of other subjective sensations (such as pain) based on noninvasive biomarker inputs has been under investigation for some time.[60–62] Pain, like dyspnea, is an important subjective symptom and can similarly be masked by difficulties with communication, sedation, and obstruction of proper assessment by healthcare professionals. Despite the large efforts into making advancements in prediction, the effectiveness of such methods for consistent, accurate monitoring of subjective sensations remains uncertain. Machine learning has also been explored as a method for predicting subjective psychological symptoms such as fear, anxiety, and even the development of Post Traumatic Stress Disorder.[63–67] The lack of application of machine learning techniques in the prediction of dyspnea presents a gap which a portion of this dissertation attempts to begin to fill, although much more work is needed in this realm before any confident remarks can be made about the use of machine learning in monitoring dyspnea.

Study Aims

Proper identification of dyspnea is critical for improving patient outcomes in the ICU setting. However, there are still many things that are not well understood regarding the manifestation and intensity of dyspnea. Namely, while work exists to describe some of the drivers of dyspnea in patients, less work has been done in a younger, healthier

population to understand fundamental patterns or correlates in dyspnea cases without the complications accompanied by the presence of pathology. This is important not only for understanding dyspnea more thoroughly, but also as a starting point for what factors to implement in tools which can address dyspnea identification in the wide variety of pathologies/presentations in the hospital/ICU. While it is unknown whether a single tool can encompass all the variance in the range of pathologies and reasons for hospital visits which may complicate dyspnea, the importance of a foundational model to build, modify and compare future iterations to cannot be overstated. Thus, the overarching goal of the work presented in this dissertation is the generation of such a tool. More granularly, the general structure of the goals of this dissertation can be divided as follows:

1. To determine physiological drivers of individual variation in dyspnea onset and severity, including potential relationships between age, sex, BMI, and chemoreflex sensitivity in hypercapnic and hypoxia induced air hunger in free breathing individuals.
2. To determine if general anxiety characteristics, namely state anxiety, trait anxiety, and interoceptive awareness are linked to dyspnea severity.
3. Produce a novel tool for the monitoring of dyspnea, which can assist physicians in determining if a patient is in need to direct attention or intervention due to dyspnea.

Note: Some of the research described in this dissertation has been used for the filing of a patent with the USPTO.

Chapter 2: Methods

Ethical Approval: This study was approved by the University of California, Riverside Clinical Institutional Review Board (IRB #22063). Participants were informed of the study's purpose and risks and provided written informed consent in their native language (English). The work was conducted in accordance with the *Declaration of Helsinki*, except for registration in a database.

Participant recruitment: Sixty-eight participants were recruited for the study from winter 2023 to winter 2025. Of these 68, three were removed due to a failing sensor which provided inaccurate data, one participant was removed due to being unable to pass the safety testing, and four were removed due to unusable data. These unusable data included issues such as excessive sensor noise, a poor air seal on the mask which led to being unable to hold treatment conditions to acceptable standards, and unfixable sensor misreads such as issues with EKG, pulse oximeter, etc. 60 participants' data was included in the final dataset. 35 women and 25 men with an age range of 18 to 49 years (mean 23.10 ± 5.83 years).

The study took place at the University of California, Riverside (elevation ~200 meters). Participants were recruited from the university as well as the local community through flyers and word of mouth. Inclusion criteria included individuals between the ages of 18-65 who were fluent in English, had no history of cardiovascular or pulmonary disease,

were not currently taking any anti-inflammatory medications, were not currently pregnant, had no recent travel above 8,000 feet elevation within one month of the experiment, and did not smoke regularly (exceptions were made if the participant smoked once or twice a year, but was not a regular smoker). Participants did not take corticosteroids, aspirin, or other anti-inflammatory medications within 48 hours of their visit and were asked to eat a small meal prior to the start of their study appointment.

General survey: A general health and demographic survey was administered after the consenting process which involved participants filling out information about their age, weight, height, blood pressure, any medications they were taking and background questions. These questions consisted of a history of smoking, pregnancy, and ethnic background. If participants were unsure of their recent height or weight, a mechanical medical scale was used to measure height and weight. Participants completed all surveys via Redcap on a computer stationed in the room where the experimental treatments were also conducted. The researchers stayed in the room and were available to answer any questions the participants had but did not directly observe the participants completing the surveys.

Psychological surveys: The State-Trait Anxiety Inventory (STAI) and Multidimensional Assessment of Interoceptive Awareness (MAIA) were administered after the general survey but before the dyspnea experiments.[68,69] The STAI was always administered first followed by the MAIA. The scores were counted using the respective survey's

documentation. Participants completed all surveys via Redcap on a computer stationed in the room where the experimental treatments were also conducted. The researchers stayed in the room and were available to answer any questions the participants had but did not directly observe the participants completing the surveys.

To study the difference between baseline anxiety and anxiousness due to a negative stimulus, the STAI divides it into two categories with separate questions: trait anxiety and state anxiety. Similarly, the MAIA divides interoceptive awareness into eight categories. Below is a description of each category:

- **Trait anxiety**: The general anxiety level that a person feels in their day-to-day life.
- **State anxiety**: The anxiety a person feels when there is a negative stimulus that triggers anxiety.
- **Noticing**: The ability to gain awareness of and be able to properly focus on internal stimuli. This can be most closely compared to mindfulness.
- **Not distracting**: A person's inclination not to distract themselves when something unpleasant happens.
- **Not worrying**: The ability to avoid mental stress when faced with physical discomfort
- **Attention regulation**: The ability to maintain focus on bodily sensations
- **Emotional awareness**: The ability to understand that a specific physical sensation leads to a specific emotional response or reaction.

- **Self-regulation**: The ability to control stress by paying attention to the bodily sensation
- **Body listening**: A person's inclination to intentionally listen to their bodily sensations for possible insights.
- **Trusting**: A person's confidence in the safety and trustworthiness of their body sensations.

Safety testing: To ensure that participants were physically eligible to participate in the experiments, a spirometry test was done to measure lung function. Participants were handed a Hans Rudolph flow meter (model ML1000) attached to a filter (model MLA304) and disposable cardboard mouthpiece. They were then instructed to take three normal breaths, after which they would perform a maximal inhalation followed immediately by a forced expiration at maximum force. The spirometry plugin in LabChart 8 (Ad Instruments, Colorado Springs CO, USA) was used to obtain the FEV_1/FVC ratio. Each participant completed this test a minimum of three times (some participants repeated measurements due to mistakes or the need for further instructions), and the FEV_1/FVC ratio from three high-quality recordings was averaged. In order to be eligible to participate, an FEV_1/FVC of at least 0.70 was required, indicating the likely absence of underlying pulmonary pathology such as asthma.

Dyspnea stimulation experiments: To induce dyspnea, we used a forced end-tidal gas method to maintain constant inspiratory PO_2 (P_{IO2}) and end-tidal PCO_2 (P_{ETCO2}) over a

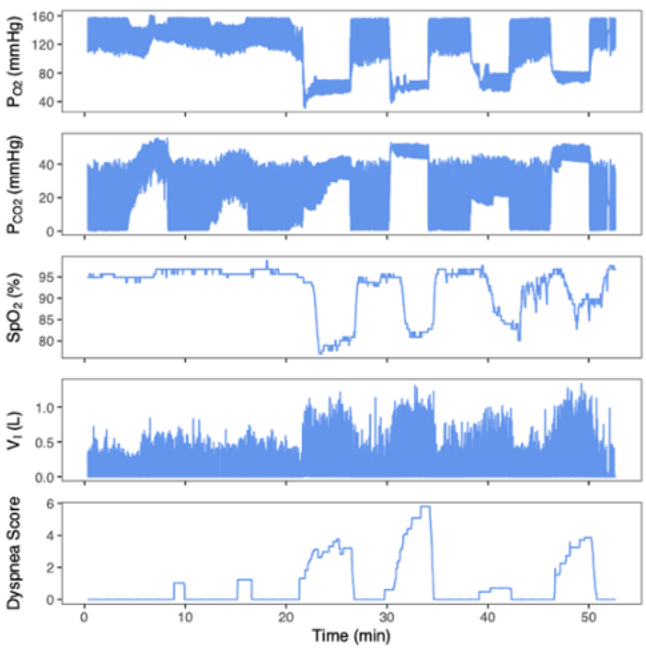
four-minute period. This method was modified from a similar protocol used previously by our laboratory.[70] Using a gas mixer rotameter, O_2, N_2, and CO_2 were manually adjusted to maintain target gas tensions at six pre-determined test conditions (**Figure 1A**). Trial orders were randomized using Google's random number generator.[71] Each participant underwent these six trials in a randomized, participant-blinded order which each lasted four minutes, interspaced by four-minute rest periods where the participants inhaled room air.

Figure 1: Experimental treatments and a representative trace

A

Trial	Inspiratory pO_2 (mmHg)	End-tidal pCO_2 (mmHg)
1	149	45
2	149	52
3	80	45
4	80	52
5	68	45
6	68	52

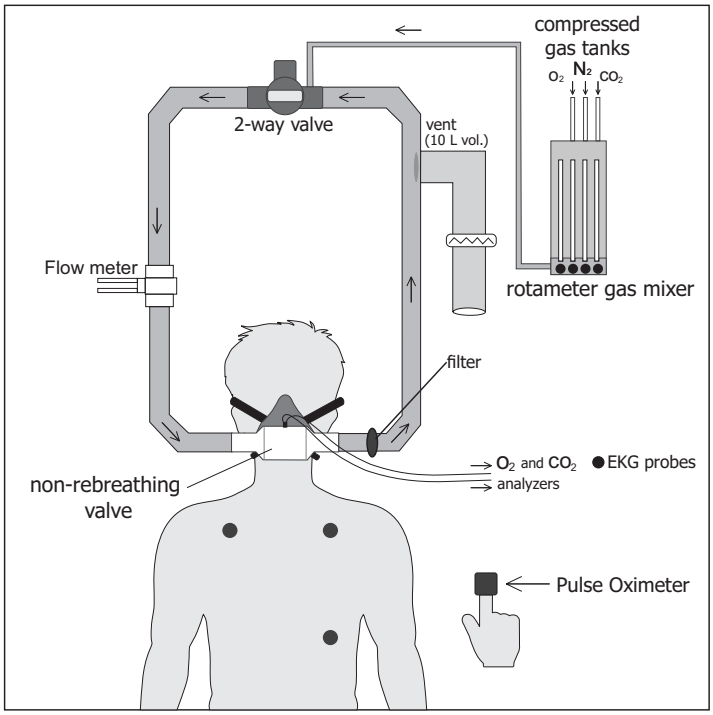
B



Footnote 1: (A) Table of experimental treatments in numerical order. (B) Representative trace of data collected during experiments.

Collection of physiological data: Participants were seated in a semi-recumbent position and fitted with an oronasal face mask (7450 Series V2 Mask, Hans Rudolph, Cole Palmer, Shawnee, KS, USA) attached to the semi-rebreathing circuit via a two-way non-rebreathing valve (Model 2600, Hans Rudolph). The experimental setup is shown in **Figure 2** and adapted from an illustration in Heinrich et al 2020.[70] SpO_2 was measured using a Nellcor N600x pulse oximeter (Medtronic, Minneapolis, MN, USA) with a finger probe. This pulse oximeter has been validated to accurately measure SpO_2 at levels as low as 68.5%.[72] A three-lead ECG was recorded using an ADInstruments (Colorado Springs CO, USA) Bioamp. Partial pressures of oxygen (pO_2) and carbon dioxide (pCO_2) were subsampled from the non-rebreathing valve directly in front of the mouth. CO_2 was measured with an infrared CO_2 analyzer (Model 17630, Vacumed, Ventura, CA, USA) pulling air at a rate of 200 ml/min and O_2 was measured via a paramagnetic oxygen analyzer (Model 17620, Vacumed) pulling air at a rate of 200 ml/min. A respiratory flow head (Model MLT1000L,

Figure 2: Illustration of the semi-rebreathing forced end tidal system used to stimulate dyspnea



Footnote 2: Adapted from illustration originally in Heinrich et al 2020.

ADInstruments) was placed directly upstream of the inspiratory port of the non-rebreathing valve to measure inspiratory air flow rates.

Analog signals from CO_2, O_2, SpO_2, EKG, and respiratory flow measures were collected by an ADInstruments PowerLab 8/30 (model ML870) and output as a digital signal to a PC and recorded in LabChart8 pro software (AD Instruments).

To measure self-reported dyspnea severity, participants were either provided with (1) a laser pointer and were prompted at the end of each 4-minute experimental and rest treatment period to indicate their level of breathing discomfort on a large 1-10 dyspnea scale placed directly in front of them, or (2) a knob attached to a linear potentiometer which allowed them to give a continuous rating of their breathing discomfort which was recorded directly into LabChart. Participants were specifically instructed to rate their level of breathing discomfort, and if they asked for further instruction were told to give a rating of the severity of unsatisfied breathing or shortness of breath. They were informed that a score of zero indicated no presence of breathing discomfort and that ten indicated the worst possible breathing discomfort. Statistical analyses (T-test, $p = 0.466$) were conducted to verify that the method of dyspnea identification did not influence the severity of the sensation.

Data Extraction: Inspiratory tidal volumes were determined using the spirometry plug in on LabChart which utilizes the integral of the inspiratory flow rate. Heart rate was

determined from the R-R interval of the ECG channel. Respiratory rates were determined by counts of change from negative spirometry flow to positive. Total ventilation was calculated from tidal volumes and respiratory rate. Partial pressures of oxygen and carbon dioxide were calculated from the respective sensors percentage reading and multiplying by the total atmospheric pressure, or 760 mmHg. Physiological biomarker and self-reported dyspnea score data was extracted from LabChart in 1-minute increments at the end of each 4-minute trial. This allowed the participant's minute ventilation and end-tidal gas tensions to equilibrate to the treatment during the first three minutes. Means, maximums, and minimum values were gathered for each physiological variable described above. 1-minute data periods were also collected at the end of each rest cycle. Chemoreflex values were calculated using the equations

$$HVR = \frac{\Delta \dot{V}_E}{\Delta SpO_2}$$

and

$$HCVR = \frac{\Delta \dot{V}_E}{\Delta P_{ETCO2}}$$

To measure hypoxic ventilatory response, treatments 1 (P_{IO2} = 149 mmHg, P_{ETCO2} = 45 mmHg) and 3 (P_{IO2} = 80 mmHg, P_{ETCO2} = 45 mmHg) were use since both treatments had the same target P_{ETCO2}, to ensure a change in ventilation due to HCVR did not confound the calculation. Hypercapnic ventilatory response was calculated by using treatments 1 (P_{IO2} = 149 mmHg, P_{ETCO2} = 45 mmHg) and 2 (P_{IO2} = 149 mmHg, P_{ETCO2} = 52 mmHg), since both treatments shared the same target P_{IO2}.

Statistical Analysis

Data pre-processing: All data was checked for outliers visually and via the ROUT method. If an outlier existed that was within normal physiological limits, it was kept in the dataset. If a data point was outside possible physiological limits (for example a tidal volume of 15 liters) the LabChart file was first checked to ensure that incorrect data extraction did not occur. Data points that were determined to be outliers due to a sampling error or addressable sensor error were re-collected and added to the dataset; otherwise, they were removed. Data rows missing values were removed. In total, 9 participant data were removed due to incomplete data.

Correlations: Data was first tested for normality using the Shapiro-Wilk test. As nearly all variables in the data were found to be not normally distributed, Spearman rank correlations were used for all correlation analyses. To correct for multiple comparisons, Benjamini-Hochberg corrections were done.

Mixed effect models: Mixed linear models were used to investigate multivariate effect on dyspnea severity. Models were generated with Python using the libraries *numpy* and *pandas* for data management, *statsmodels* for model parameters, and *matplotlib* and *seaborn* for data visualization.[73–78] All models used mean dyspnea severity as the dependent variable and the restricted maximum likelihood method of estimating variance components due to the imbalanced data. Covariance between random effects was factored

in, but interactions between variables was not considered. Random intercept was used. The other factors used to generate the models are listed below:

Model	Dependent Variable	Grouping Factor	Random Effects	Fixed Effects
Chemoreflex	Mean Dyspnea	Treatment	Participant ID	Sex, BMI, Age, HVR, HCVR
Anxiety	Mean Dyspnea	Sex	P_{ETCO2}, P_{IO2}, Participant ID	State Anxiety, Trait Anxiety
Interoception	Mean Dyspnea	Sex	P_{ETCO2}, P_{IO2}, Participant ID	All interoceptive awareness dimensions

Machine learning: All algorithms were developed using the Anaconda distribution of packages for python, models were carried out using the *Sci-kit Learn* toolkit, and models were re-validated using the same parameters in R.[79] Models included dyspnea severity as the supervised label and input variables including sex, BMI, age, and mean, maximum, minimum, and standard deviation of the following: end tidal pCO_2, inspiratory pO_2, heart rate, total ventilation, tidal volume, respiratory rate, inspiratory flow rate, and SpO_2. Dyspnea severity was divided into two categories (present or absent), with a variety of cut off points for the categories ranging from a self-reported dyspnea score of two to five. Six classification models were chosen to evaluate performance. Cross-validation was

done with a 30-70 split of the data for testing and training, respectively. Random forest was selected as the top-performing model to evaluate based on precision-recall performance results. Below is a list of the models included in the analysis as well as a brief description on their core functionality and the parameters that were set during their generation for this study:

- **K-Nearest Neighbor (KNN):** The KNN algorithm constitutes a non-parametric method used for both classification and regression. For a given query point, the algorithm identifies the k closest training examples within the feature space based on a specific distance metric. In classification tasks, the algorithm assigns a class label via plurality voting among the k neighbors, whereas in regression, it computes the average of the property values of the neighbors.[80]
- **Extreme Gradient Boosting (XGBoost):** XGBoost is a scalable implementation of gradient boosted decision trees (GBDT). Unlike Random Forest, which builds trees in parallel, XGBoost constructs an ensemble sequentially. Each new tree attempts to correct the residual errors of the preceding ensemble. Systemically, XGBoost introduces innovations such as sparsity-aware split finding, which learns default directions for missing data, and a weighted quantile sketch for approximate tree learning on large datasets.[81]
- **Support Vector Machines (SVM):** SVMs are supervised learning models rooted in Statistical Learning Theory and Vapnik-Chervonenkis theory. The fundamental objective of an SVM is to identify an optimal hyperplane that separates data classes with the maximum possible margin. The data points closest to this

decision boundary are termed "support vectors," and the model is defined exclusively by these points, offering resilience to outliers. The algorithm solves a constrained optimization problem, typically minimizing the hinge loss function with a regularization parameter that controls the trade-off between maximizing the margin and minimizing classification errors on the training set. [82]

- **Random Forest:** Random Forest is an ensemble learning method that aggregates a multitude of decision trees to mitigate the inherent variance and overfitting associated with individual trees. The algorithm operates on the principle of bootstrap aggregating (bagging), where multiple trees are trained independently on bootstrapped subsets of the data. Crucially, Random Forest introduces an additional layer of randomness: at each node split, the algorithm selects a random subset of features for consideration. This mechanism decorrelates the individual trees, ensuring that strong predictors do not dominate every tree structure, thereby reducing the variance of the aggregate model.[83]
- **Logistic Regression:** Logistic Regression is a parametric statistical model used primarily for binary classification. It models the probability that a dependent variable Y belongs to a specific class given input X. Unlike linear regression, which outputs continuous values, logistic regression applies the logistic (sigmoid) function to a linear combination of inputs. The core mathematical concept is the logit, or log-odds, defined as the natural logarithm of the odds (shown below).

$$\ln\left(\frac{p}{1-p}\right)$$

The model assumes a linear relationship between the input variables and the log-odds of the event. Parameters are estimated using Maximum Likelihood Estimation, which seeks coefficients that maximize the likelihood of observing the given sample data.[84]

- **Naïve Bayes:** This classifier is a generative model based on the application of Bayes' Theorem. It assigns class labels by calculating the posterior probability P(Y|X) derived from the prior probability P(Y) and the likelihood P(X|Y). The algorithm is termed "naive" due to its strong independence assumption: it postulates that all features are conditionally independent given the class variable. Even though this independence assumption rarely holds in real-world data, Naive Bayes performs surprisingly well, particularly in high-dimensional domains. Despite the model confidence being inaccurate due to the independence assumption, the classification decision often remains correct.[85,86]

Model	Parameters
KNN	tuned via neighbors considered over range 5 to 30 weight function = optimal distance power = Minkowski engine = kknn
Logistic Regression	tuned via penalty over range 10^{-4} to 1 regularization = lasso engine = glmnet

Random Forest	parameters per tree = $\sqrt{number\ of\ variables}$ nodes = minimum number of trees = 500 engine = ranger
XGBoost	tuned via learn rate over range 0.001 to 0.1 trees = 1000 tree depth = 6 engine = xgboost
Naïve Bayes	smoothness = Laplace smoothing engine = naivebayes
Support Vector Machines	tuned via cost values over range 0.001 to 100 engine = kernlab

Note: any parameters not specifically listed were left default.

Physician dyspnea severity rating

Participants were video recorded from a front-facing and profile view during the experiments. 30-second clips were collected and paired with simultaneous screen recordings of heart and respiratory rates. A custom MATLAB program was created to display the clips one-by-one and prompt the viewer to score criteria of the RDOS. MICU and ED physicians and nurses completed these ratings (n =19). Each video was labeled

with “presence of dyspnea” if the total RDOS score was equal to or above the threshold used. Initial threshold was set to 3. Due to difficulty observing nasal flaring, this criterion was removed.

Chapter 3: The Role of Ventilatory Chemoreflex Sensitivity in Hypoxia- and Hypercapnia-induced Dyspnea Severity During Free Breathing

Introduction

Despite being a common symptom in hospitalized patients, dyspnea remains challenging to identify in many cases.[2,44,87,88] Due to the large variations between individuals, as well as the wide variation in pathologies and how they affect dyspnea, understanding what drives individual variation in dyspnea is paramount for being able to properly identify it in real time at the individual level. Understanding what drives variation in dyspnea in a healthy population creates a platform upon which a better understanding of dyspnea in the context of pathology can be studied.

Prior studies indicate that a variety of factors may contribute to dyspnea severity. For example, the partial pressure of arterial carbon dioxide (P_ACO_2) has been found to be a major driver of dyspnea.[15,89] Lower arterial oxygen levels can also lead to increased respiratory drive and subsequent increase in the sensation of breathing discomfort.[21,30] Although hypercapnia is generally considered to be a more potent stimulator of dyspnea than hypoxia, some studies have shown that when matched for ventilatory drive, hypoxia and hypercapnia lead to similar levels of discomfort.[90]

While a wide variety of factors can contribute to dyspnea severity, focusing on the relationship between basic variables such as age, sex, BMI and chemoreflexes is required to gain a better foundational understanding of the individual variation seen in dyspnea. For example, prior studies have highlighted that dyspnea increases with age in both healthy cohorts and COPD patients.[91,92] However, these studies use large datasets that rely on a patient to inform them of their shortness of breath, and ask about general dyspnea or breathlessness. They also tend to bias towards older populations and those with chronic cardiovascular or pulmonary pathologies. Collecting dyspnea severity data during dyspnea stimulation of a healthy population allows for better investigation of the relationship between age and dyspnea.

An individual with higher chemoreflex sensitivity would have a larger ventilatory response to hypoxic and hypercapnic conditions, leading to further potential respiratory discomfort since higher chemoreflex sensitivity leads to higher respiratory drive, which is a primary component of the neural mechanism underlying dyspnea. A study conducted on patients with chronic heart failure found that the use of dihydrocodeine (an opioid used for suppression of cough) suppressed the participants HVR and HCVR, increased their tolerance to exercise and also reduced dyspnea during peak exercise.[93] While these findings imply that chemoreflex modulation played a role, dihydrocodeine is a known to suppress cough through alteration of activity in the medulla. It is difficult to determine from these findings whether the chemoreflex signaling was in fact suppressed, or if the results were due to lowered respiratory motor signaling/activation. In another study

researchers found that even at early stages of disease progression, Parkinson's patients exhibit reduced HVR and a lower perception of dyspnea compared to a control group.[94] Both of these studies highlight that chemoreflexes play a role in dyspnea severity. However further study is needed to understand how differences in chemosensitivity between people influences the severity of dyspnea.

Biological sex appears to have a multifaceted relationship with the prevalence of dyspnea. In larger studies, women have been shown to be more likely than men to report dyspnea.[95] While this does not definitively imply that women are inherently at greater risk of experiencing dyspnea, it does imply that there may be a difference in the way the sensation is perceived in women vs men. However, when comparing dyspnea severity to the percentage of maximum ventilation capacity used during the stimulus rather than total ventilation, the differences between men and women's dyspnea diminishes.[96,97] Women with COPD are more likely to suffer from anxiety and depression compared to their male counterparts, which can alter perception of dyspnea.[33,96,98] While its exact mechanism and interactions with other factors which influence dyspnea are not entirely clear, sex is an important factor in dyspnea and requires further study.

Body Mass Index (BMI) is another critical clinical factor which has been found to play a role in dyspnea. A study which utilized data from the Third National Health and Nutrition Examination Survey (over 16,000 participant samples were used from the dataset) found that obese individuals use bronchodilators more frequently, experience dyspnea when

walking up a hill more often, and are less likely to perform basic cardiovascular exercise such as walking greater than one mile.[99] In particular, the prevalence of dyspnea on exertion increased as BMI increased. Another study done on a small cohort of men found that obese but otherwise healthy men report dyspnea at rest more frequently than men with lower BMI.[100] Obesity was found to be correlated with lower dyspnea and higher peak oxygen consumption during exercise compared to non-obese individuals with COPD, suggesting that there may be some effect of BMI which is not yet well understood.[101] This can potentially be caused due to some reduction in hyperinflation in the obese patients from the mechanical differences in obese and normal weight COPD patients. It is unclear which aspects of dyspnea BMI may influence outside of lung mechanics, and more work is needed to understand the relationship between BMI and dyspnea across a range of both BMIs and varied intensities and dimensions of dyspnea stimuli.

In this study, I recruited a healthy patient population of men and women across a wide range of age and BMI levels and experimentally induced dyspnea through controlled modulation of arterial blood gas pressures of oxygen and carbon dioxide while collecting self-reported dyspnea severity scores during each treatment. The goal of this study was to investigate the relationship between chemoreflex sensitivity, BMI, sex, and age with self-reported dyspnea during free breathing. I hypothesize that the individual variation present in these factors contributes to variation in dyspnea severity given physiologically similar conditions. Specifically, I hypothesize that chemoreflexes, age and BMI will have

positive correlations with dyspnea severity, and that women will report higher dyspnea than men on average within the same stimulus.

Results

Univariate Analysis reveals HVR and HCVR are Associated with Dyspnea Severity

Table 1 shows the results of the univariate correlation analysis with dyspnea.

Table 1: Summary of correlation analysis of individual factors with dyspnea severity

Corrected Univariate Spearman Correlations: Variable vs Mean Dyspnea

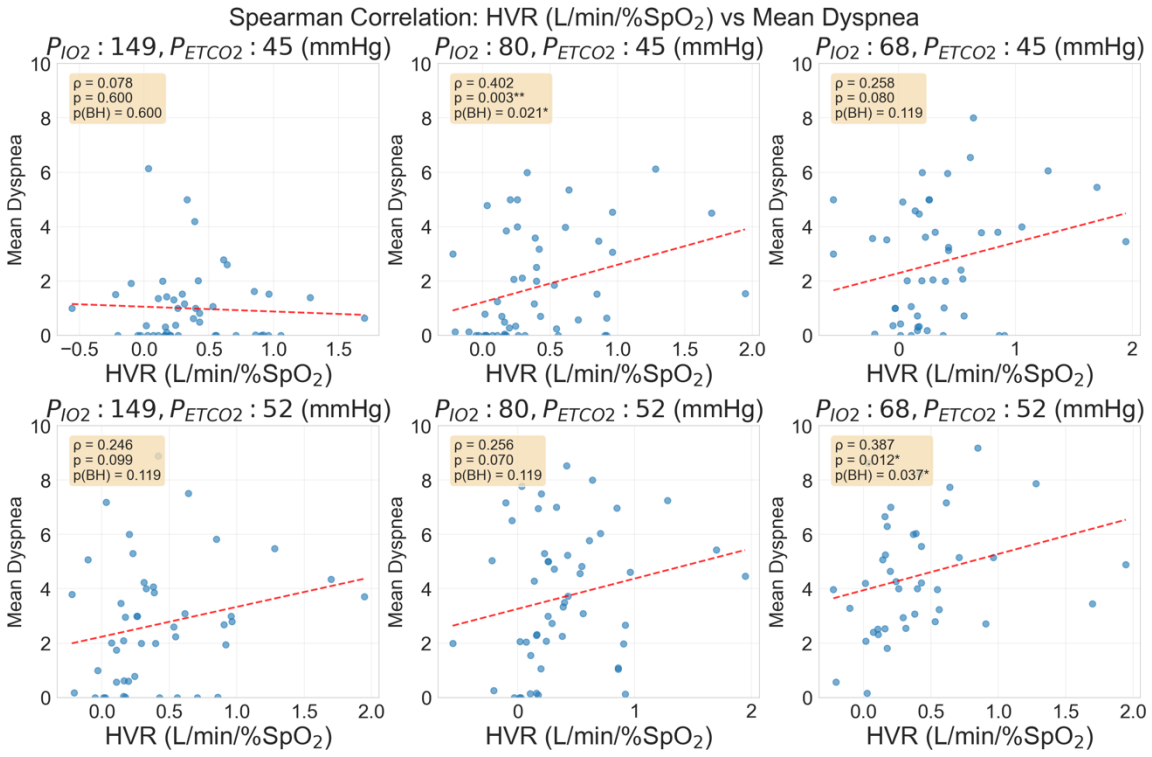
	P_{IO2}: 149 mmHg P_{ETCO2}: 45 mmHg		P_{IO2}: 149 mmHg P_{ETCO2}: 52 mmHg		P_{IO2}: 80 mmHg P_{ETCO2}: 45 mmHg		P_{IO2}: 80 mmHg P_{ETCO2}: 52 mmHg		P_{IO2}: 68 mmHg P_{ETCO2}: 45 mmHg		P_{IO2}: 68 mmHg P_{ETCO2}: 52 mmHg	
Variable	**ρ**	**p p(BH)**	**ρ**	**p p(BH)**	**ρ**	**p p(BH)**	**ρ**	**p p(BH)**	**ρ**	**p p(BH)**	**ρ**	**p p(BH)**
HVR (L/min/%SpO_2)	0.08	0.600 0.600	0.25	0.099 0.119	0.40	**0.003** **0.021** *	0.26	0.070 0.119	0.26	0.080 0.119	0.39	**0.012** **0.037** *
HCVR (L/min/mmHg CO_2)	0.26	0.078 0.233	0.35	**0.017** 0.104	0.12	0.403 0.483	0.13	0.346 0.483	0.09	0.527 0.527	0.17	0.278 0.483
Age (years)	-0.15	0.304 0.675	-0.14	0.338 0.675	-0.03	0.817 0.834	-0.23	0.110 0.663	0.03	0.834 0.834	-0.08	0.610 0.834
BMI (kg/m^2)	-0.00	0.990 0.990	-0.08	0.597 0.946	0.04	0.788 0.946	0.05	0.714 0.946	0.14	0.354 0.946	0.21	0.189 0.946

Footnote 3: Spearman's rho is represented by "ρ", p-value by "p", and corrected p value by p(BH).

To determine if age, sex, BMI, HVR or HCVR were associated with dyspnea severity, I first conducted univariate analyses on each factor. HVR and HCVR were significantly correlated to self-reported dyspnea severity under some conditions. HVR was positively correlated with self-reported dyspnea under conditions of moderate hypoxia (P_{IO2} = 80 mmHg, P_{ETCO2}. = 45 mmHg, p = 0.003) and under hypoxic, hypercapnic conditions (P_{IO2} = 68 mmHg, P_{ETCO2}. = 52 mmHg, p = 0.012) (**Table 1**, **Figure 3**). HCVR showed a

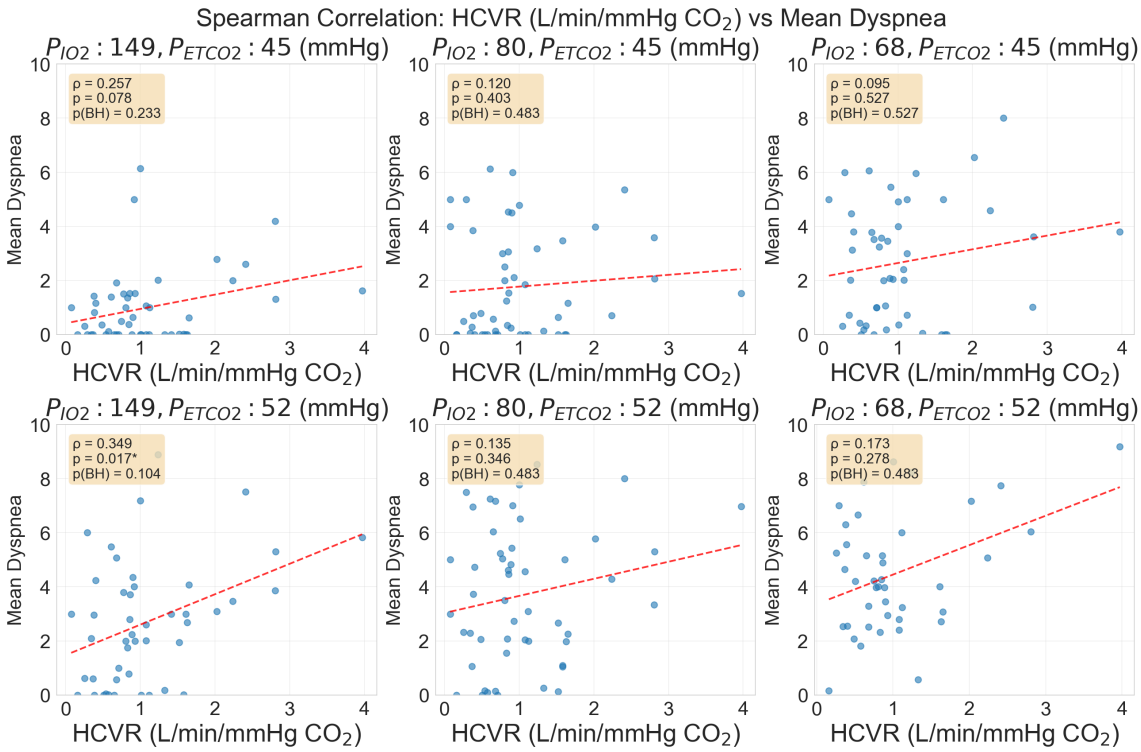
significant positive correlation with self-reported dyspnea severity during normoxic hypercapnic conditions (P_{IO2} = 149 mmHg, P_{ETCO2}. = 52 mmHg, p = 0.017) (**Table 1**, **Figure 4**). After family-wise adjustment for multiple comparisons only HVR results remained statistically significant. Age, and BMI did not show univariate correlations with dyspnea severity under any treatment condition (**Table 1**). No difference was found between dyspnea reporting of men and women (**Figure 5**).

Figure 3: Individual Spearman rank correlation of HVR with dyspnea



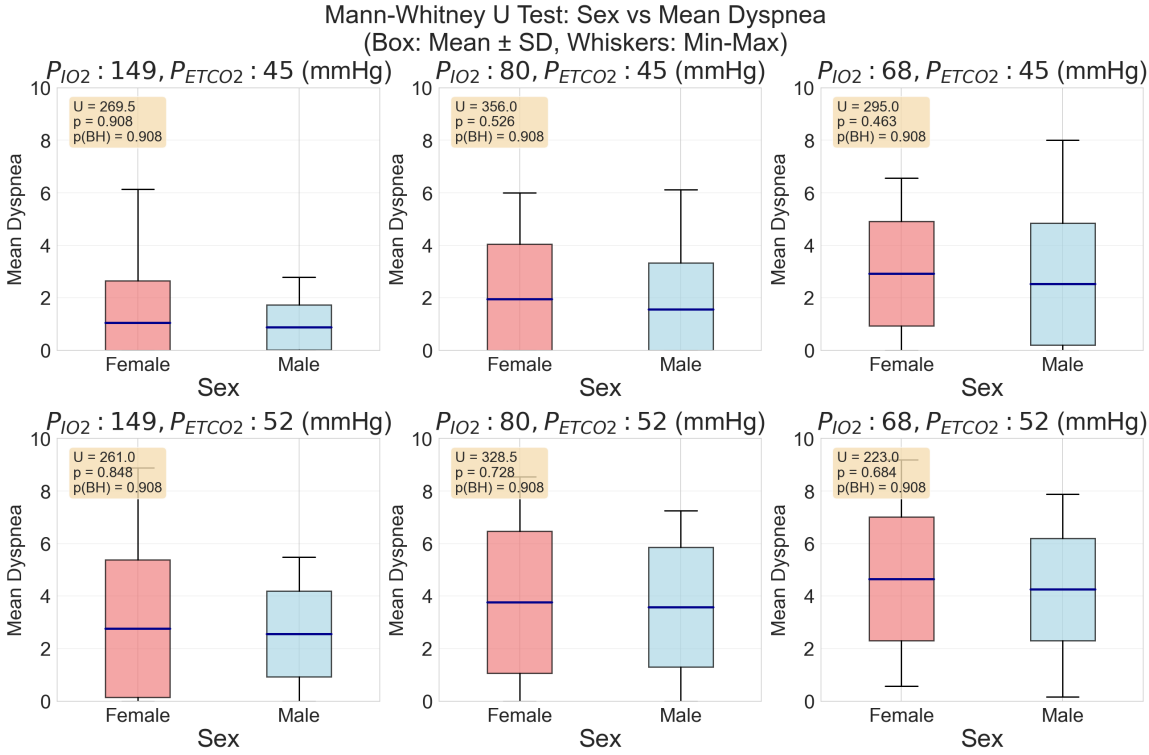
Footnote 4: Individual participant data is indicated by blue dots. A linear fit is provided for illustrative purposes only. Asterisks indicate statistical significance (p <0.05).

Figure 4: Individual correlation analysis of HCVR with dyspnea severity



Footnote 5: Individual participant data is indicated by blue dots. A linear fit is provided for illustrative purposes only. Asterisks indicate statistical significance ($p < 0.05$).

Figure 5: Mann-Whitney U test results for sex differences in dyspnea reporting

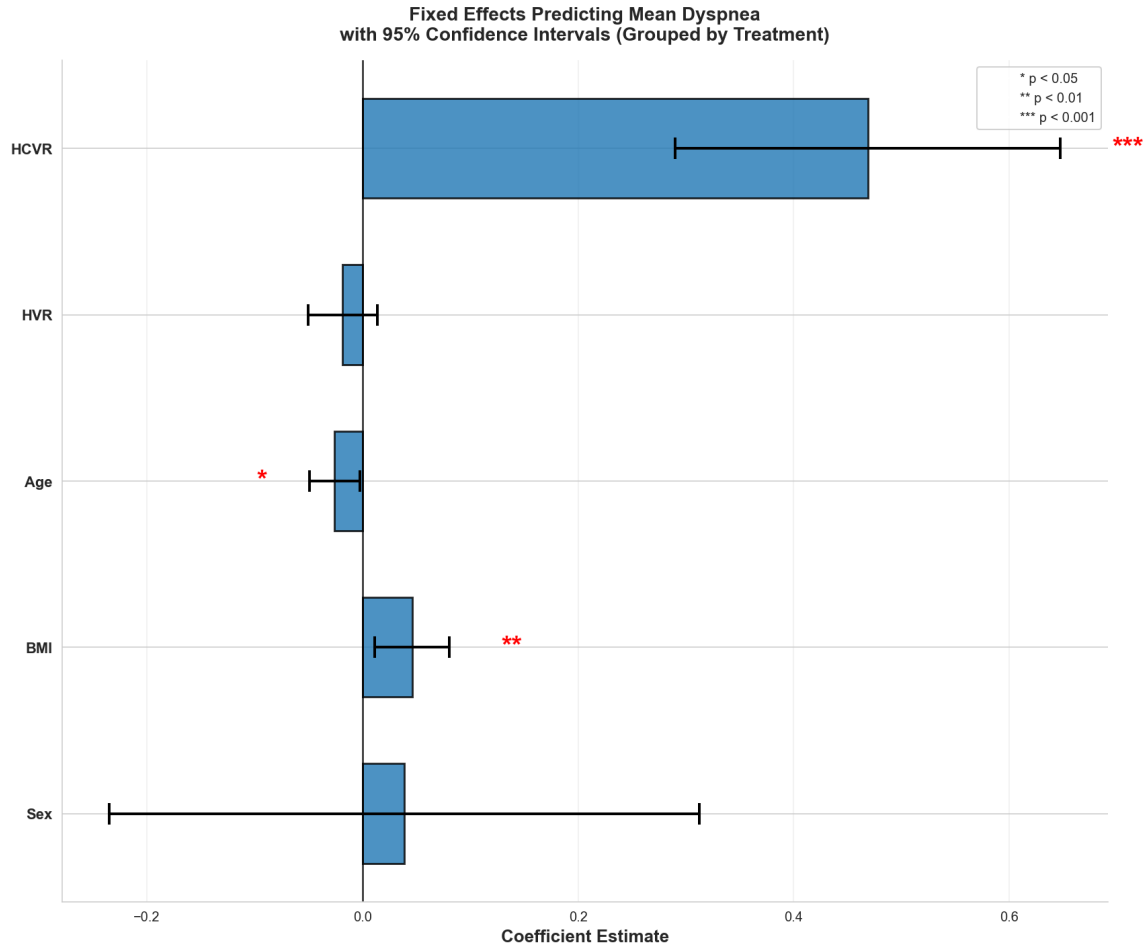


Footnote 6: Mann-Whitney U test results for sex differences in dyspnea reporting. Whiskers represent minimum and maximum, blue line represents mean value, box is mean ± SD.

Multivariate analysis reveals age and BMI effects on dyspnea severity

To determine if age, sex, BMI and chemoreflexes account for a considerable portion of the variance in dyspnea severity at fixed gas tensions, I employed a mixed linear model as described in the methods section. HCVR, BMI, and age showed significant main effects with dyspnea severity ($p < 0.001$, $p = 0.009$, and $p = 0.031$ respectively). However, there were no main effects of sex or HVR on dyspnea severity. **Figure 6** shows a summary of these findings.

Figure 6: Demographic and chemoreflex mixed linear model



Footnote 7: The "Coefficient Estimate" as listed describes the units of change of the dependent variable (in this case, dyspnea severity) per unit of the variable listed.

Discussion

Hypoxic and hypercapnic ventilatory responses are positively correlated with dyspnea severity: While both hypoxic and hypercapnic stimuli have been shown to be involved in dyspnea manifestation, hypercapnia is generally considered to produce a

more unpleasant sensation than hypoxia.[2,5,15,89] This may explain why there was a main effect of HCVR, and not HVR, on self-reported dyspnea severity in the multivariate model in our study (**Figure 6**), despite showing a univariate correlation with HVR. The lack of significance of HVR in our multivariate model aligns with recently observed phenomenon of "happy" or "silent" hypoxemia, where patients with COVID-19 with hypoxemia presented to care centers with relatively low dyspnea.[102,103] It is suggested that arterial CO_2 remains relatively normal in early COVID-19, so the main active chemoreflex is HVR in these patients.[103] This suggests that HVR was not a primary driver of dyspnea in these patients. Outside of pathology, HVR may have limited involvement in the sensation of air hunger even in healthy people. A study done on a small group of divers suggests that they end their dive not due to air hunger, but due to cognitive changes which they notice.[104] This is important because divers have low P_aCO_2 due to hyperventilation before diving, so they would not have a strong air hunger stimulus HCVR, instead primarily from HVR due to hypoxia. Even with the hypoxic conditions of a long dive, the air hunger stimulus was not sufficient to force the dive to end. Similarly, Nakano et al investigated how hypoxia affects dyspnea severity using a hypobaric hypoxic chamber, and found that hypoxia was not an independent factor in dyspnea.[105] The results from these studies may suggest that HVR is not a potent stimulus for air hunger, which aligns with our univariate findings that HVR does not correlate with dyspnea severity during severe hypoxia (P_{IO2} = 68mmHg, p(BH) = 0.119), although it does not explain why our moderate hypoxia (P_{IO2} = 80mmHg, p(BH) = 0.021) stimulus showed a significant trend.

Other studies show more mixed results. Onodera et al found that in early stages of Parkinson's disease normal HCVR was found, but HVR was lower than the control.[94] These patients experienced significantly reduced dyspnea during hypoxic tests compared to control, but only a slight decrease in dyspnea during hypercapnic tests which was not found to be significant. However, it must be noted that the samples size was relatively small and the p value for the difference in dyspnea under hypercapnic conditions was nearly significant ($p = 0.065$). While chemosensitivity to hypoxia may still play a significant role in air hunger in some cases, our findings suggest that the primary chemoreceptor signaling which triggers the unpleasant sensation of air hunger in free breathing individuals is HCVR.

Dyspnea severity at controlled arterial PO_2 and PCO_2 tensions does not differ across healthy men and women during free beathing: No sex differences in dyspnea severity are observed in our study (**Figure 5**). Similarly, Cory *et al.* (2015) looked at sex differences in dyspnea severity reporting of active, healthy participants during exercise. While there was a sex difference in dyspnea intensity at equal work rates and total ventilation rates, these sex differences disappeared when they looked at the relationship between dyspnea intensity and the fraction of maximal voluntary ventilation used.[97] They also reported that female participants took shorter, shallower breaths than the males, which may be attributed to their heightened sensation of breathing discomfort. This highlights that sex effects in exercise related dyspnea are diminished when the

physiological differences are accounted for. Interestingly, while there was no difference in dyspnea reporting close to rest and at maximum work rates and minute ventilations, the female group reported higher dyspnea during moderate work rates and ventilations. This study's findings are largely in line with the present study, as our multivariate model also found no sex effect. However, it must be noted that the method of dyspnea stimulation was different, primarily relying on work/effort, and this does not mean that differences in other factors (such as chemosensitivity) could not modulate air hunger related dyspnea severity. Despite the lack of sex-specific findings in our study, clinical data exists showing evidence for a sex affect in dyspnea and dyspnea reporting. In patients with COPD, women have generally expressed greater dyspnea both at rest (general reporting) and during exercise.[96,98] While these observations seem to be caused by physiological differences between men and women, they may also be due to the method of dyspnea stimulation. Many of the studies provided use work/effort based reporting, and there is less data on differences in chemosensitivity between men and women reporting dyspnea.

Determining the role of age in dyspnea severity requires a more chronologically diverse participant population: While our univariate analysis found no correlation between age and dyspnea severity, our multivariate model found age to have a weak negative association with dyspnea severity. This is in contrast to some of the existing literature, which demonstrates that age has a positive correlation with dyspnea prevalence.[2,33,106] Age was also reported to be positively correlated with dyspnea during

exercise, even at relatively moderate intensities.[107] It is important to note that the age diversity in our study cohort was relatively small and within a young range, meaning we did not gather data within the ranges where clinical differences are found. Generally speaking, the age-related changes in dyspnea within the cited studies are reported within populations that greater than 65 years old, exceeding the age distribution of our study cohort.[12,91] More data must be collected before any conclusive comparisons can be made in this regard.

High BMI may lead to higher dyspnea severity: We found no univariate correlation between BMI and dyspnea severity. However, our linear model revealed a slight inclination for individuals with higher BMI to experience more severe dyspnea. This seems to mainly align with clinical findings, where high BMI is generally associated with higher dyspnea severity, both at rest and during exercise.[33,91,99,100] Most studies show this relationship during pathology or during exercise, which is not directly comparable to air hunger stimulation. Here we provide evidence that BMI plays a role in air-hunger driven dyspnea severity.

Limitations

The primary limitation which much be addressed is that some participants self-reported their height, weight, or both. While participants were informed that their height and weight could be measured if they were uncertain, this does not remove the potential errors that could have been caused by misreporting these values

Conclusion

Chemoreflex, and particularly HCVR, is one of many variables which drives dyspnea severity in free breathing adults. Age and BMI seem to also play roles in the manifestation of dyspnea severity in healthy adults. Due to the multivariate nature of dyspnea and the nuances of the patient condition (particularly in clinical settings, outside of the lab), it is critically important to consider and investigate the relationships of the other variable on dyspnea severity to develop a better foundational understanding of what drives dyspnea its three dimensions. More research is needed to finalize a conclusive foundational model for dyspnea severity.

Chapter 4: Anxiety and Interoceptive Awareness are Linked to Dyspnea in Free-Breathing Individuals

Introduction

Dyspnea is a highly distressing, unpleasant, and threatening sensation, capable of summoning a primal fear response.[21] Patients describe experiencing thoughts of impending death, intense fear, and panic during episodes of acute dyspnea.[37,108] Unidentified or inadequately addressed dyspnea generates feelings of helplessness, frustration, and fear, which are significant contributors to post-traumatic psychological consequences.[38] This is particularly evident in critically ill, mechanically ventilated patients in intensive care units (ICUs), where dyspnea is a major stressor leading to "dark respiratory recollections" and a heightened risk of post-traumatic stress disorder (PTSD). The subjectivity of dyspnea means that its severity and qualitative characteristics vary considerably among patients. The self-reported intensity of dyspnea often correlates poorly with individual objective physiological measures of underlying disease severity.[1,2,46,58,109] Earlier studies found that even multivariate predictive models of dyspnea severity only accounted for a small amount of the variance in self-reported dyspnea scoring within specific patient populations, such as those with advanced cancer.[110] This incongruity may be attributable to the influence of psychological factors on the perception and experience of dyspnea, extending beyond the physiological and pathological underpinnings.

The neural basis of dyspnea involves activity in the brainstem, cortex, and limbic system. Functional imaging studies demonstrate that both air hunger and increased resistive loads leading to increase work/effort correlate with activations in cortico-limbic areas, including the insular cortex, anterior cingulate cortex, and amygdala.[4,34] These regions are also implicated in interoception and nociception, suggesting shared processing pathways for aversive bodily sensations. Attentional focus also plays a critical role. While attentional distraction can reduce the affective dimension of dyspnea, hypervigilance towards respiratory sensations can amplify dyspnea perception.[33,92,111] This highlights the central role of emotional processing in the subjective experience of dyspnea.

While many studies have investigated the physiological and neurological correlates to dyspnea severity, further research is needed to elucidate how a person's psychological state alters their dyspnea perception.[2,15,34,111–113] Specifically, there is a gap in understanding how psychological metrics such as anxiety and interoceptive awareness are correlated to dyspnea severity in healthy, free breathing individuals. This understanding would clarify the importance of collecting this information in the clinical setting, as it could inform clinicians the risk of a patient experiencing severe dyspnea, and the nature of the intervention required to alleviate it. With a deeper understanding of the contribution of mental state on dyspnea severity, monitoring and treatment for dyspnea can be more personalized, and future monitoring systems can account for person's anxiety to potentially make more accurate predictions. In this study, we investigated the

interoceptive and emotional processing of individuals experiencing dyspnea to find links between these qualities and dyspnea severity. I hypothesized that anxiety and detrimental interoceptive awareness qualities would be positively correlated with dyspnea severity, positive interoceptive awareness qualities would be negatively correlated with dyspnea severity.

Results

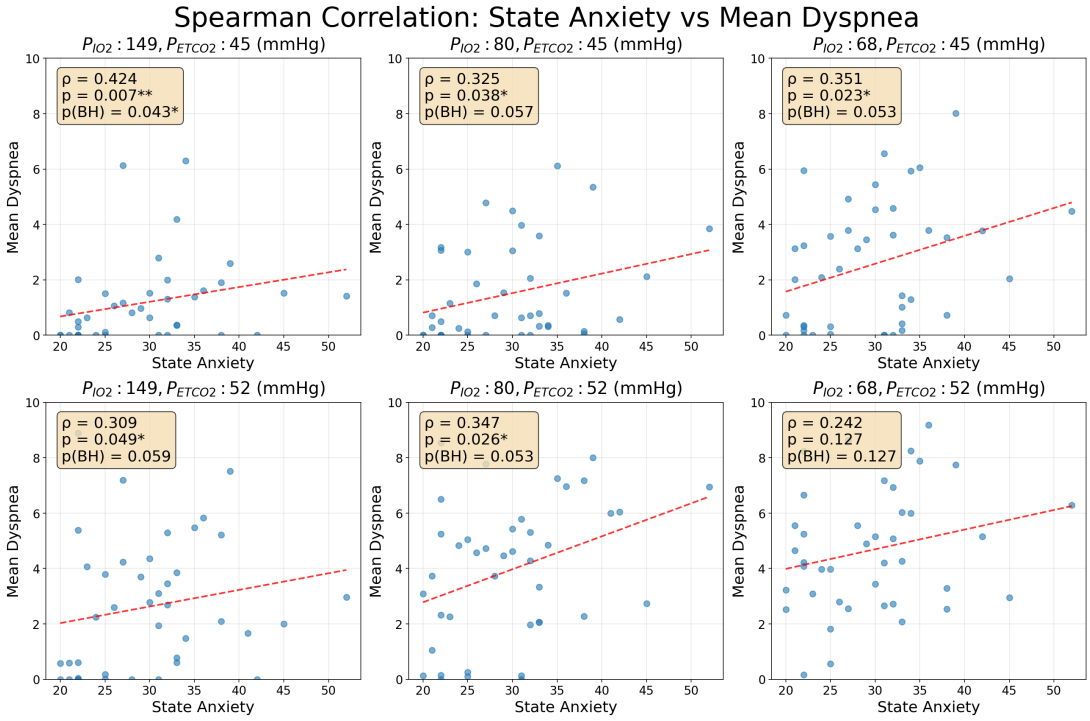
State anxiety correlates with self-reported dyspnea in hypoxic and hypercapnic conditions, but not when combined

To determine if state anxiety traits were associated with self-reported dyspnea severity in response to hypoxia and/or hypercapnia during free breathing, I first looked at univariate relationships between anxiety and interoceptive awareness with dyspnea severity. **Figure 7** shows the relationship between state anxiety and dyspnea severity under each hypoxic and hypercapnic stimuli.

State anxiety score was positively correlated with dyspnea severity during all treatments except for the combination of hypercapnia and hypoxia seen in treatment 6 (P_{ETCO2} = 52 mmHg, P_{IO2} = 68 mmHg). However, after correcting for multiple comparisons this correlation only remained significant under treatment 1 conditions (P_{ETCO2} = 45 mmHg, P_{IO2} = 149 mmHg), ($r = 0.424$, $p_{BH} = 0.043$). However, state anxiety does follow a moderate trend with dyspnea severity for all treatments and remains within one-one-hundredth of our significance threshold ($p = 0.05$) with the exception of the results from

treatment 6 (P_{ETCO2} = 52 mmHg, P_{IO2} = 68 mmHg). There was no difference between men and women in state anxiety reporting (t-test, p = 0.276).

Figure 7: Spearman correlation of state anxiety vs dyspnea severity

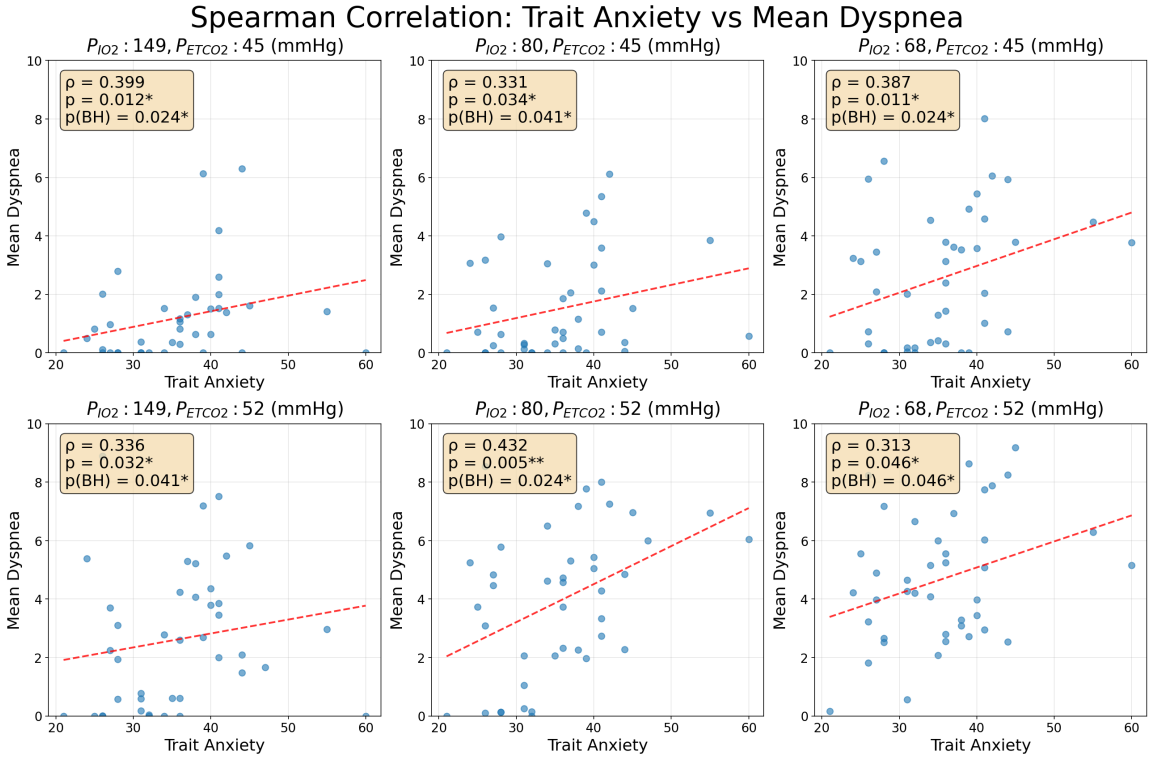


Footnote 8: Asterisks represent statistical significance, red line is for illustration and visualization purposes only. State anxiety shows a positive trend with dyspnea severity but is only significant in treatment 1 after p-value corrections.

Trait anxiety is correlated with dyspnea severity

Unlike state anxiety, trait anxiety was significantly correlated to dyspnea severity across all treatments after correction for multiple comparisons. **Figure 8** shows the results of the spearman correlations separated by treatment. There was no difference between men and women in trait anxiety reporting (t-test, p = 0.425).

Figure 8: Spearman correlation of trait anxiety vs dyspnea severity



Footnote 9: Asterisks represent statistical significance; red line is for illustration and visualization purposes only. All treatments showed a significant positive relationship.

Interoceptive awareness and self-reported dyspnea

To determine if interoceptive awareness traits were related to self-reported dyspnea severity in response to hypoxia and hypercapnia in free breathing people, I used spearman correlations using mean dyspnea as the dependent variable. No interoceptive awareness variables were individually correlated with dyspnea severity. Sex differences were found in the reporting of the “not distracting”, “not worrying”, “attention regulation”, and “trusting” dimensions of interoceptive awareness (t tests, p = <0.001, 0.021, 0.030, 0.010, respectively). Since there was a significant effect of sex on several

interoceptive awareness traits, I then evaluated the impact of these traits on dyspnea separately within sex groups using spearman correlations. Here we found that male participants had a significant negative correlation between attention regulation and dyspnea severity during normoxic, hypercapnic conditions (pO_2 = 149, pCO_2 = 52), (r = -0.707, p(BH) = 0.013). No other treatment conditions showed significant correlations for men nor women between interoceptive awareness dimensions and dyspnea severity.

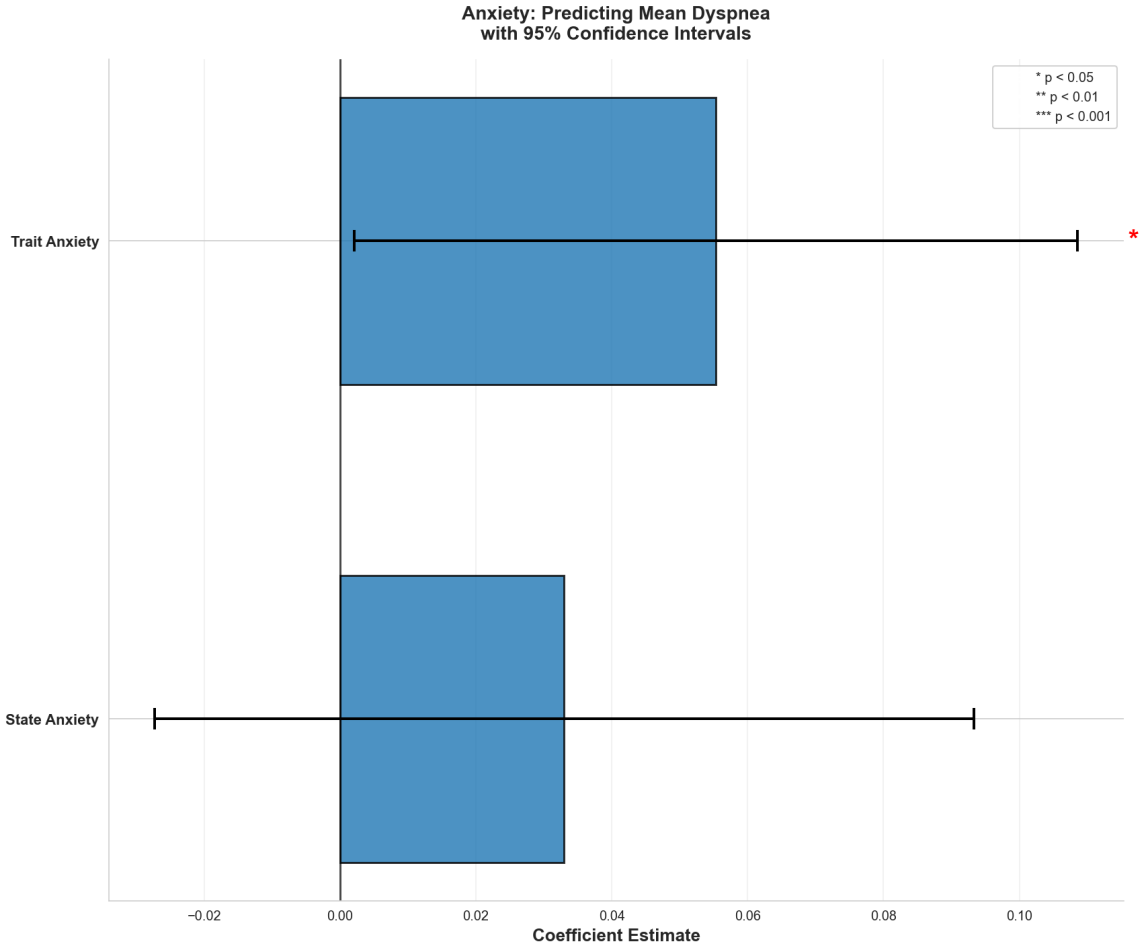
Multivariate analysis reveals effect of interoceptive awareness dimensions on self-reported dyspnea severity

To determine the role of the psychological variables on dyspnea severity while accounting for sex, individual variation, and gas tensions (P_{ETCO2} and P_{IO2}), I analyzed two multivariate models: one for anxiety and one for interoceptive awareness. When testing anxiety variables and adjusting, many of the trends remain the same. In our mixed linear model, state anxiety was not related to dyspnea severity. However, trait anxiety had a significant effect on dyspnea severity (Coefficient = 0.06, p = 0.042). **Figure 9** contains the full results of the analysis.

Unlike the univariate analysis, the mixed linear model showed that several dimensions of interoceptive awareness have an effect on dyspnea severity. Attention regulation,

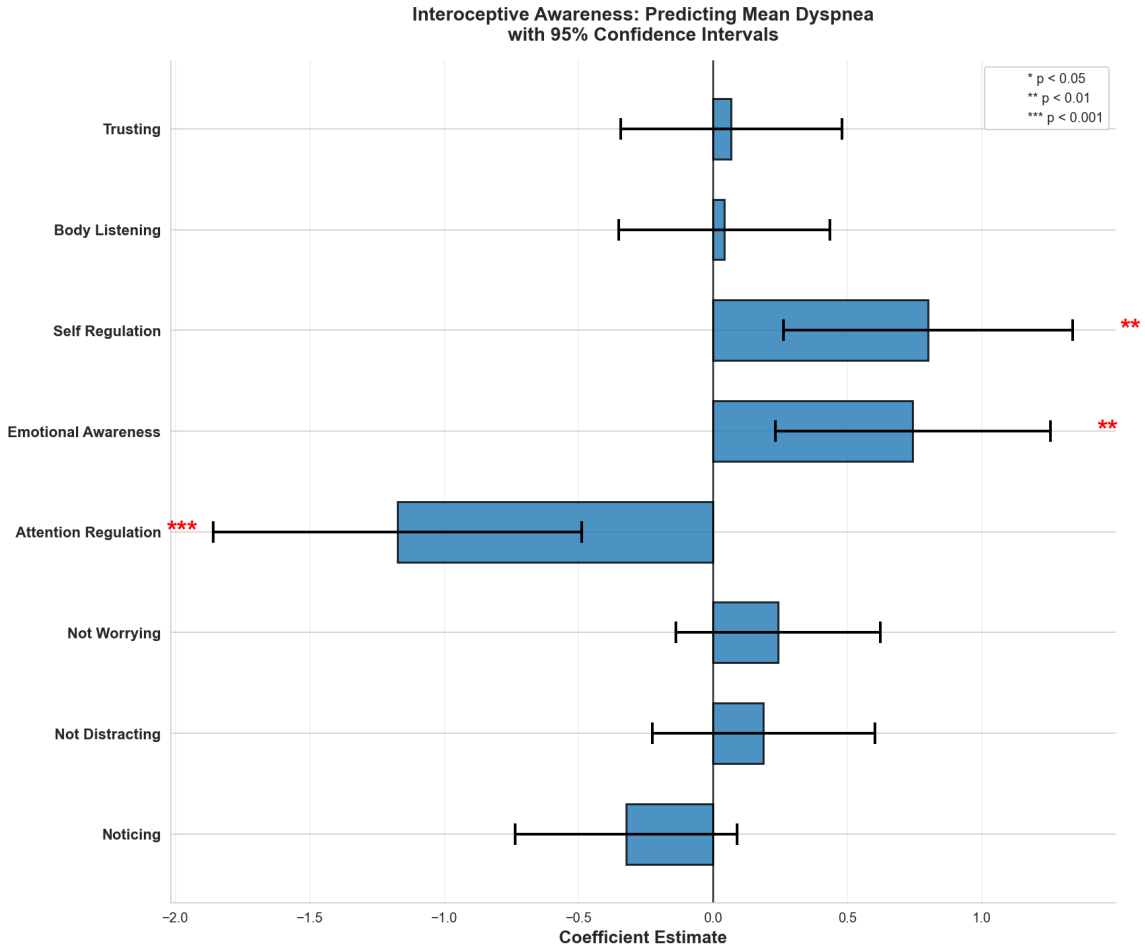
emotional awareness and self regulation all had significant effects ($p < 0.001$, $p = 0.004$, $p = 0.004$, respectively). **Figure 10** shows the results of this model.

Figure 9: Mixed linear model for anxiety vs dyspnea severity



Footnote 10: The lines through the bars represent the 95% confidence intervals, asterisks represent significance.

Figure 10: Mixed linear model for interoceptive awareness vs dyspnea severity



Footnote 11: The lines through the bars represent the 95% confidence intervals, asterisks represent significance.

Discussion

Dyspnea severity increases with elevated trait anxiety

Previous studies found links between dyspnea and anxiety. For example, COPD patients with anxiety report higher dyspnea and a greater impact of breathing problems on their quality of life compared to COPD patients without anxiety. [36,113] While it is not possible

to separate the contribution of state and trait anxiety in those clinical experiments, the STAI has been found to be generally correlated with other anxiety indices such as the Taylor Manifest Anxiety Scale and the Cattell and Scheier's Anxiety Scale Questionnaire.[114] However, there are important factors to consider such as the psychological impact of COPD. Patients with COPD in these studies also showed a fear of dyspnea, likely due to negative experiences with breathlessness which is typical of the pathology. Our healthy participants were unlikely to have this pre-conditioned fear of dyspnea. As we did not collect a history of our participants' previous experiences with breathlessness, we were not able to make a comparison of participants with and without possible fear of dyspnea. It is important to note that we used air hunger in our study which may have a different psychological impact than work effort. More research is needed to make proper comparisons between studies. Despite the limitations, our data aligns with the clinical findings that elevated anxiety leads to elevated dyspnea severity, and trait anxiety may be a good marker for understanding an individuals' pre-disposition towards dyspnea of a high severity.

The combined stimulus of hypercapnia and hypoxia increases the number of participants experiencing a dyspnea severity greater than zero. This trend can be seen in **Figure 6**. It is particularly noticeable in the participants with somewhat lower trait anxiety. This suggests that there may exist an air hunger stimulation threshold at which point trait anxiety no longer positively correlates to dyspnea severity, meaning that individuals with and without anxiety would feel similar levels of discomfort. It may also be due to a

plateau in the effect of trait anxiety on dyspnea severity as the stimulus increases, but this is difficult to determine in the current study due in part to the lower sample size of individuals with high trait anxiety and the limitations of the six treatments. Further study is needed to determine potential mechanistic reasons for these observations.

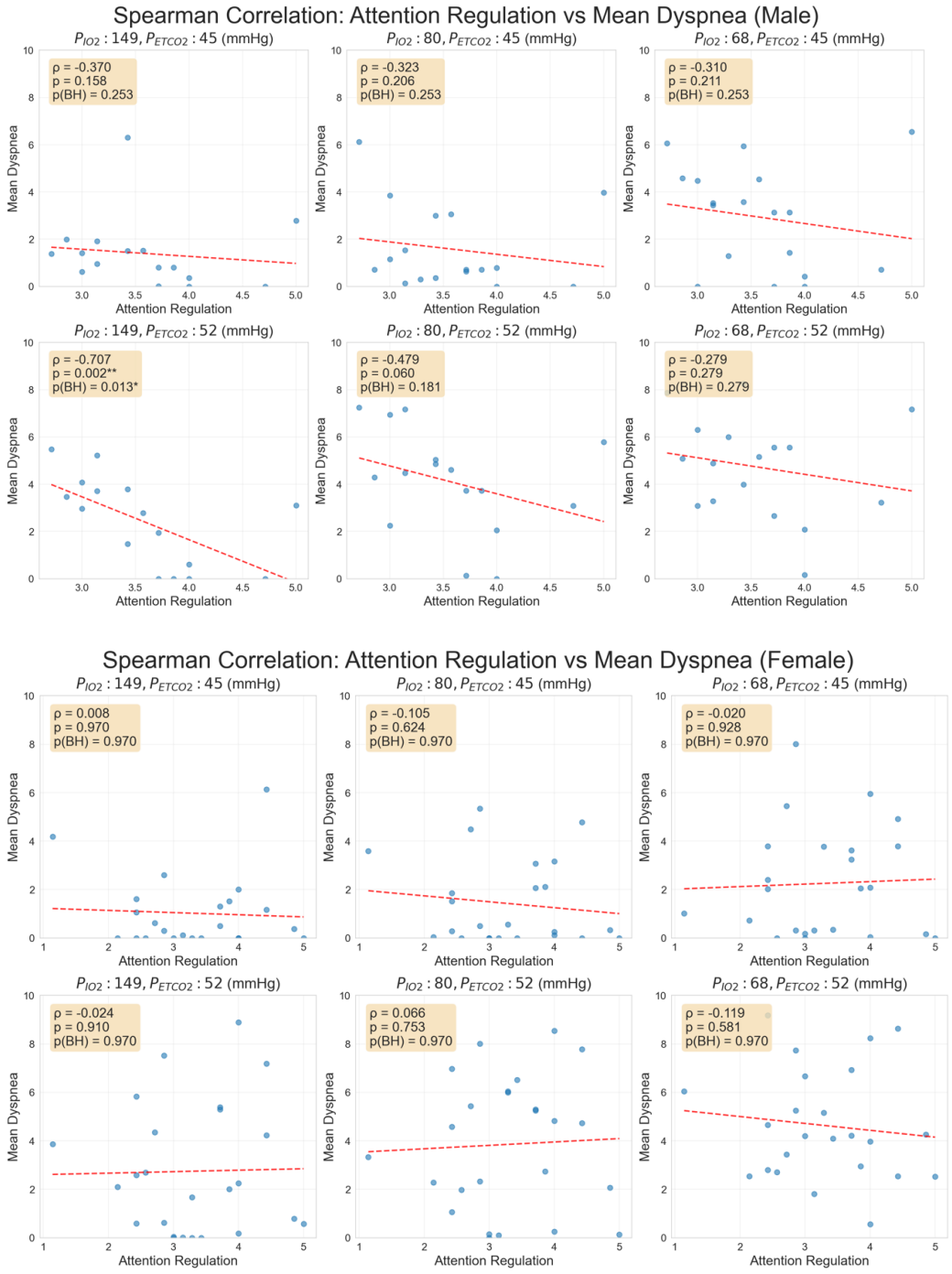
High "emotional awareness" and "self regulation" lead to increased dyspnea severity; High "attention regulation" leads to lower dyspnea

While a variety of studies have concluded that brain regions involved in awareness are activated during dyspnea manifestation, there has been a gap in studies which were able to quantify this relationship outside of imaging analysis. There is some evidence that attentional distraction can reduce the perception of dyspnea, but not the intensity.[27] This aligns with our findings, as the not distracting category showed no significant relationship with dyspnea severity. Our study suggests that the "emotional awareness" and "self regulation" dimensions of interoceptive awareness have a positive association with dyspnea. The result is somewhat expected for "emotional awareness" since this dimension is a metric of one's awareness of how their emotional state affects their body, with questions focused on how positive experiences cause positive changes in bodily sensations and how it can change negatively when they have a negative emotion (the questions specifically mention anger and "when something is wrong"). However, "self regulation" is a measure of reducing or controlling negative sensations. Upon closer inspection, the questions regarding "self regulation" focus on calming oneself through awareness of the body and specifically breathing. These qualities had the opposite of their

intended effect in this case, where additional attention to the participant's breathing as a method of comfort only brought more discomfort since that was their main stressor.

While scores for "not distracting", "not worrying", "attention regulation" and "trusting" were different across sexes, these differences did not manifest in significantly different relationships to dyspnea severity within sex groups. The one exception was "attention regulation", where men showed a significant negative correlation with their scores and self-reported dyspnea severity during normoxic hypercapnic (P_{IO2} = 149, P_{ETCO2} = 52) conditions only. In all other treatments men showed a negative trend, while women had no noteworthy trends across treatments (correlation coefficients of -0.1 or less). For some interoceptive dimensions where no significance was found in the univariate analysis, there was often a pattern where male and female participants displayed different trends between their interoception scoring and their self-reported dyspnea scores. This is most notably seen in "not worrying", where there was a general negative trend with dyspnea severity for male participants, and a positive trend for females. **Figure 11** shows the comparison between sexes for this interoceptive awareness dimension.

Figure 11: Sex differences in correlation trends for attention regulation



Footnote 12: Spearman's rho is represented by "ρ", p-value by "p", and corrected p value by p(BH)

Limitations

While we did our best to ensure that participants were calm and well prepared before participating in our study, entering an experiment of this nature is inherently stressful. The combination of fear and anticipation/catastrophizing which could have occurred before the start of the experiment, and throughout, was only controlled for during experiment administration, and not through additional data collection on these factors. As with all surveys there is also the limitation of errors in self-reporting to be considered.

Conclusion

Dyspnea is the unpleasant sensation of unsatisfied breathing commonly experienced in the hospital setting. While the consequences of dyspnea on the psychological well-being of patients are well documented, the role that a patient's psychological state plays on dyspnea severity is less understood. We found that trait anxiety is positively correlated to dyspnea severity. We also found that various dimensions of interoceptive awareness are correlated as well. Sex effects were found in interoceptive awareness reporting from participants. However, the only significant change shown was for attention regulation during normoxic hypercapnia (P_{IO2} = 149, P_{ETCO2} = 52), where male participants showed a significant negative correlation with dyspnea severity which was lost when the two sexes data were combined. Anxiety and interoceptive awareness are important aspects of peoples' experience and perspective on dyspnea and should be investigated further as sources of variation in dyspnea manifestation and self-reporting.

Chapter 5: A Machine Learning Approach to Predicting Dyspnea with Noninvasive Biomarkers

Introduction

As explained previously, dyspnea is considered highly subjective and when left untreated, can produce profound patient suffering.[17,46,108,115] Dyspnea causes delays in extubation in mechanically ventilated patients, and is correlated with an increase in noninvasive ventilation failure, generally leading to worse outcomes.[116] It can also cause lingering damage to psychological health well after physiological symptoms have subsided, and hospitalized patients who experience severe dyspnea are at high risk of developing depression, anxiety, or PTSD-like symptoms after their hospitalization.[33,38,108,117,118] As such, identifying and addressing it as quickly as possible is of high clinical value.

In the past decades, much progress was made in our understanding of the pathophysiology of dyspnea. Several qualitatively distinct sensations contribute to this symptom, including work of breathing, chest tightness or bronchoconstriction, and "air hunger" or unsatisfied inspiration.[2,15,58] These sensations are driven by several neural inputs which modulate respiratory drive, including information from chemoreceptor stimulation, chest wall mechanoreceptors, and vagal C fibers.[5,15,16,20,119] Dyspnea occurs when there is a mismatch between the expected result of central neural output and the actual perceived airflow or ventilation.[2,5]

Despite the widespread presence of dyspnea and its significant impact on patient quality of life, the detection of dyspnea in the hospital setting continues to be challenging. Current methods of detection, such as the respiratory distress observation scale (RDOS), rely heavily on subjective measures (such as look of fear) and observations that can be masked due to patient condition or medications administered (such as grunting and nasal flaring).[14] Furthermore, healthcare providers often "woefully" underestimate dyspnea severity based on observation alone.[37,41,58,59,120] In many cases, patients may be unable to communicate their discomfort, leading to unrecognized patient suffering.[46] It is likely that this disparity is due to the complex, multivariate nature of dyspnea, as well as individual variation in how patients experience, display, and describe their discomfort.

There is an urgent need for a clinical tool to improve detection of dyspnea and continuously monitor this symptom. Such a tool would empower physicians with novel information about patient discomfort and indicate when interventions are needed. To address this need, we aimed to determine if self-reported dyspnea severity can be accurately predicted using noninvasive biomarkers. To accomplish this, we experimentally stimulated dyspnea while measuring several easily monitored physiological factors and used a machine learning approach to create a model to predict self-reported dyspnea severity using these biomarkers as inputs. We hypothesized that self-reported dyspnea could be accurately predicted with these simple biomarkers and

that this model would score higher on performance metrics such as precision and recall than healthcare providers' observational estimates.

Some of the results of these studies have been previously reported in the form of abstracts.[121,122]

Results

Dyspnea severity as a function of gas treatments:

Self-reported dyspnea severity differed significantly across the 6 experimental treatments (main effect: $F(6,582) = 136.5$, $p < 0.001$) (**Figure 12**). These differences were driven by significant main effects of both P_{IO2} ($F(2,584) = 47.4$, $p < 0.001$) and P_{ETCO2} ($F(2,584) = 142.7$, $p < 0.001$). There was substantial variation in self-reported dyspnea severity across participants even under the same experimental treatments (**Figure 12**, **Table 2**). This is not driven by variance in the achieved pO_2 and pCO_2 treatment levels using the end-tidal forcing system. We achieved our target gas tensions within an average standard deviation inter-trial of ± 1.1 mmHg and intra-trial of ± 0.6 mmHg for P_{ETCO2}, and inter-trial of ± 3.0 mmHg for and intra-trial of ± 2.6 mmHg for P_{IO2} (**Figure 13**). Actual end-tidal pCO_2 and pO_2 values were utilized in machine learning models rather than grouping by treatment.

Figure 12: Dyspnea increases as air hunger stimulation increases

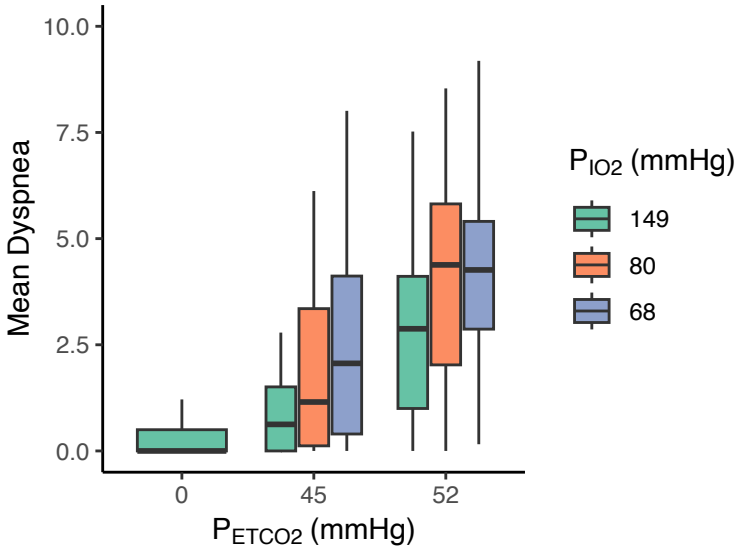
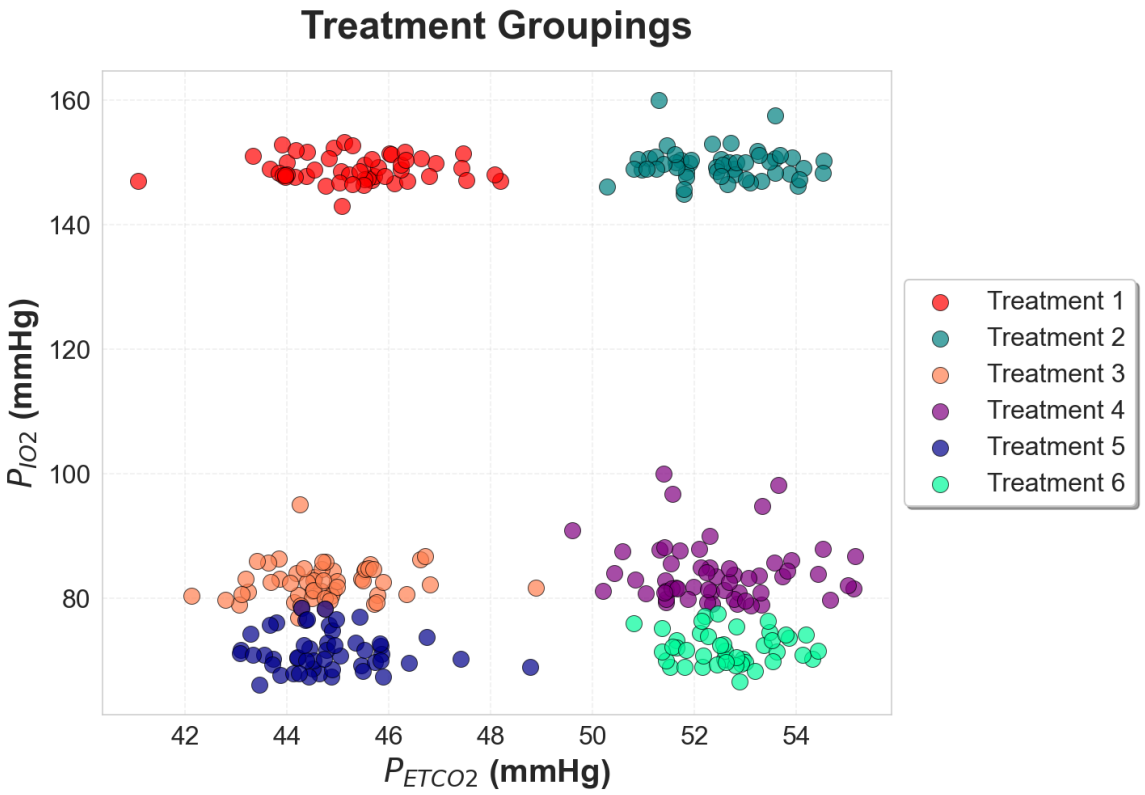


Table 2: Summary of variance in self-reported dyspnea throughout experimental treatments

		Self-reported Dyspnea Severity		
P_{O2} (mmHg)	P_{CO2} (mmHg)	Mean ± SD	Minimum	Maximum
149	45	0.961 ± 1.320	0	6.136
149	52	2.708 ± 2.181	0	8.887
80	45	1.763 ± 1.909	0	6.121
80	52	3.791 ± 2.461	0	8.5376
68	45	2.651 ± 2.186	0	8.010
68	52	4.542 ± 2.109	0.158	9.187

Figure 13: Groupings of treatments



Efficacy of traditional individual biomarkers:

Table 3 provides a summary of the independent effects of key biomarkers on mean dyspnea severity under each treatment via a mixed linear model which considers age, sex, BMI, P_{IO2} and P_{ETCO2} as covariates. All biomarkers except SpO_2 show significant main effects.

Table 3: Summary of effects of biomarkers when applied as fixed effects independently in a mixed linear model with age, sex, BMI, P_{IO2} and P_{ETCO2} as covariates

Biomarker	Coefficient (β)	P (Main Effect)	Std. Error	CI (0.025)	CI (0.975)
Respiratory rate (breaths/min)	0.102	<0.001	0.018	0.066	0.139
Tidal Volume (L)	1.682	<0.001	0.263	1.166	2.197
Minute Ventilation (L/min)	0.140	<0.001	0.014	0.114	0.167
Heart rate (beats/min)	0.028	0.006	0.010	0.008	0.048
SpO_2 (%)	0.036	0.158	0.026	-0.014	0.087

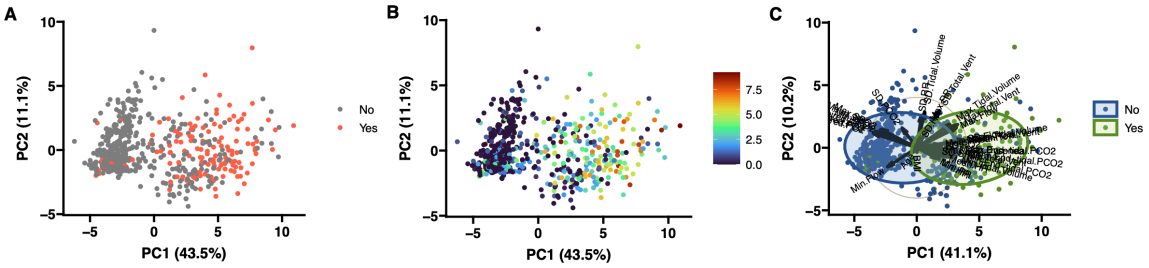
Selection of cut-off for binary classification of dyspnea during model training:

NRS scores of two through five were tested separately as cut-off points for classification due to the variety of cut-off points utilized in prior studies, though cut-offs of three to four are generally recommended for distinguishing moderate discomfort from mild/lack of.[123,124] A cut-off of three was ultimately selected based on highest performance. **Table 4** summarizes model performance across the various thresholds. PCA analysis shown in **Figure 14** also indicates more clear division of groupings with a dyspnea score greater than or equal to three.

Table 4: Summary of Random Forest performance using a variety of dyspnea severity scores as the cut off between "not dyspneic" and 'dyspneic"

	AUC Values		Values Based on Ideal Threshold			
Cut-Off	ROC	PR	Precision	Recall	F1	Threshold
2	0.882	0.783	0.776	0.804	0.789	0.35
2.5	0.865	0.726	0.644	0.826	0.724	0.33
3	0.923	0.832	0.816	0.795	0.805	0.42
3.5	0.864	0.666	0.535	0.697	0.605	0.36
4	0.888	0.649	0.652	0.556	0.600	0.51
4.5	0.928	0.601	0.475	0.905	0.623	0.25
5	0.903	0.576	0.405	0.833	0.545	0.29

Figure 14: PCA analysis of biomarkers vs dyspnea severity



Categorical prediction models:

All models performed with high accuracy; **Figure 15A** shows the testing results of all models. Area under the receiver operating characteristic curve (ROC-AUC) values were highest for the KNN (0.926) and random forest model (0.923) with all models performing with ROC-AUC values above 0.85. Due to the imbalanced nature of the results (presence of dyspnea severity ≥3 was less common), area under the precision-recall curve (PR-AUC) values were also calculated (**Figure 15B**). Random forest performed the best with

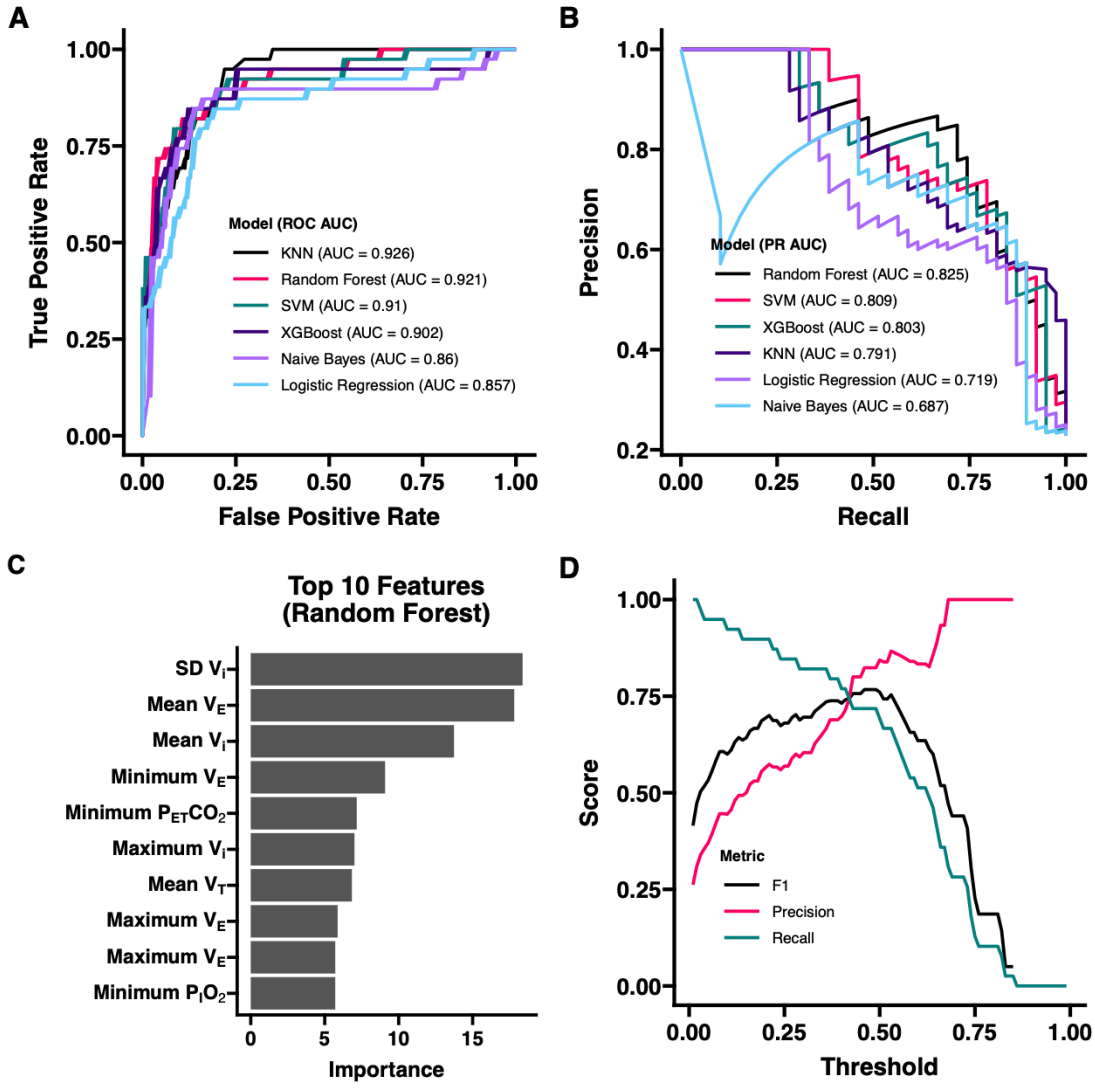
an PR-AUC of 0.832, with the nearest competitor being SVM at 0.809. Since the random forest model demonstrated highest performance, it was chosen as the focus of subsequent analyses. **Figure 15C** provides feature importance scores for the top ten biomarkers within the final random forest model. Standard deviation of flow rate, mean total ventilation and mean inspiratory flow rate were the top three features in this model. Beyond the top three features there is an initial sharp decline in feature importance, and the remaining features in the top 10 exhibit similar levels of importance. **Figure 16** shows an example visualization of one of the trees in the model.

In a separate analysis, we sought to verify if the final random forest model's performance was biased across sex groups. To do this, we tested the final model separately on test datasets derived only from male or female participants. We found no significant difference in performance for the prediction between sex groups (Male: precision = 0.980, recall = 0.909, F1 = 0.943; Female: precision = 0.915, recall = 0.974, F1 = 0.943; $p = 1$).

Next, we determined the threshold on the predicted probabilities for classification (**Figure 15D**). A threshold of 0.42 lead to the highest F1 score (0.805). Identifying patients who have dyspnea (positive result) is of key importance, so further experiments and clinical verification is needed to determine the ideal threshold balance between precision and recall in this application. For example, recall can be improved if the

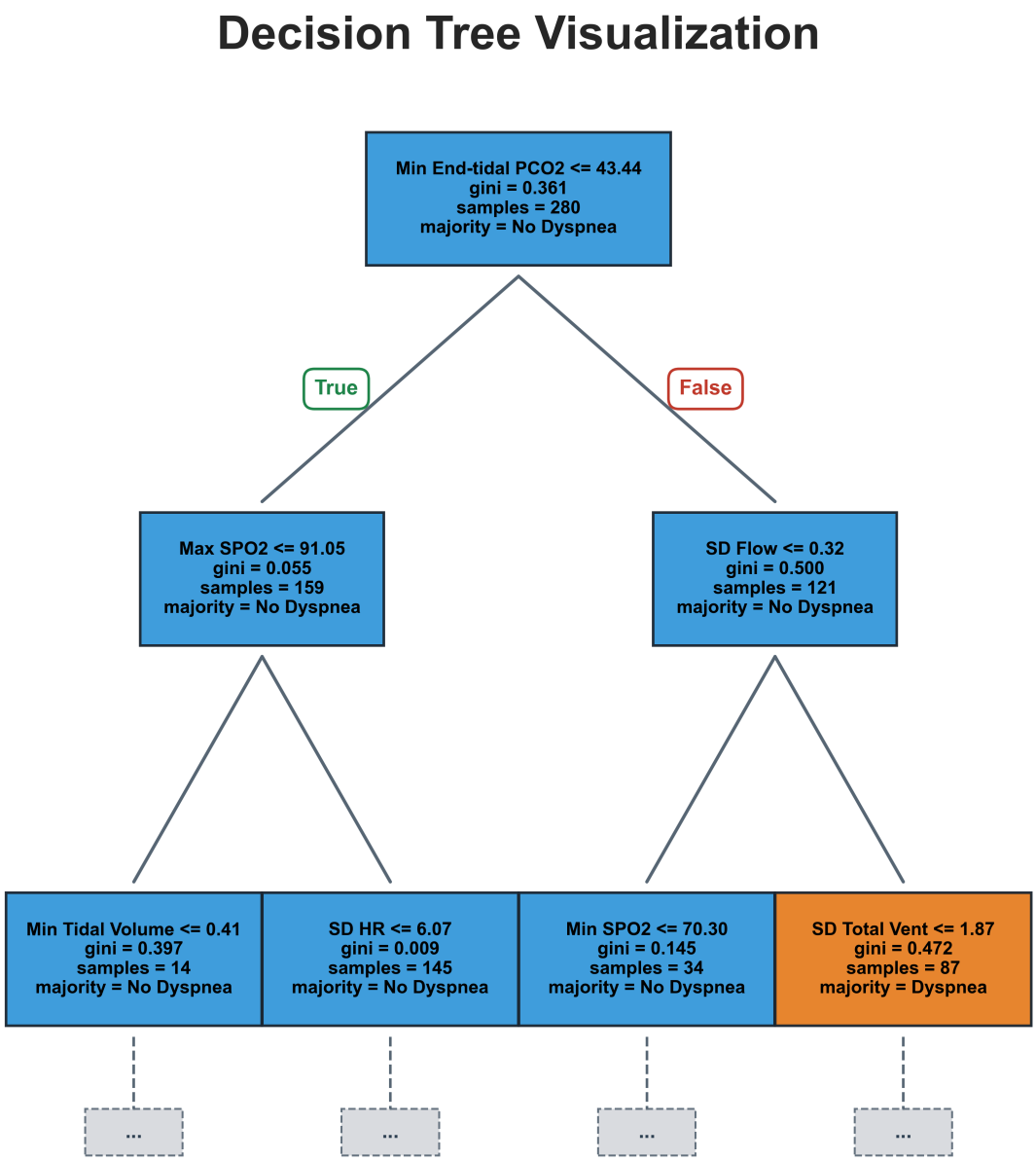
classification threshold is further reduced, at the expense of precision, which may be of value in an ICU setting where false negative estimates are harmful.

Figure 15: Results from machine learning algorithm performance analysis.



Footnote 13: (A) ROC performance showed KNN as top model with random forest close behind (B) Precision-Recall performance shows random forest as top performer (C) Top 10 features used by the model to predict dyspnea (D) Precision Recall performance across entire threshold range, intersect is used to determine ideal performance.

Figure 16: Visualization of a decision tree within the random forest classifier



Footnote 14: Only the first two nodes beyond the root are shown in illustration, but the decision tree can extend beyond as needed to complete the classification task. Gini tracks impurity of the node, where a score of zero indicates a pure node (all samples are of the same category) and 0.5 indicates a completely impure node, where there is an equal distribution of both classification categories.

Physician and nurse performance:

Physicians and nurses performing RDOS scoring on participants from the machine learning dataset achieved an accuracy of 58.82% using standard thresholds. The standard threshold of ≥ 3 was used for the RDOS, but a variety of self-report cut-offs were tested.[125] **Table 5** shows the confusion matrix and overall physician performance. Notably, recall rate was alarmingly low and was the primary reason for loss in accuracy. Recall performance did not improve across a variety of self-reported dyspnea score cut offs, although precision did improve markedly as the cut off was decreased. F1 and accuracy scores remain largely unchanged across all cut off points. As literature has expanded in recent years on the use of the RDOS and it has been adapted to various applications with changes in scale and cut off points, we also tested performance across a variety of RDOS thresholds.[44,56,126] **Table 6** shows the complete set of performance results. Generally, decreases in the RDOS threshold greatly increase recall with minimal loss of precision.

Table 5:Confusion matrix showing physician performance using a variety of self-reported dyspnea cut offs and standard RDOS scoring.

NRS Dyspnea Cut-Off	True Positive	True Negative	False Positive	False Negative	Precision	Recall	F1	Accuracy
2	27	11	2	28	0.931	0.491	0.643	0.559
2.5	24	13	5	26	0.828	0.480	0.608	0.544
3	24	13	5	26	0.828	0.480	0.608	0.544
3.5	22	18	7	21	0.759	0.512	0.611	0.588
4	22	18	7	21	0.759	0.512	0.611	0.588
4.5	17	22	12	17	0.5862	0.5	0.540	0.574
5	17	22	12	17	0.5862	0.5	0.540	0.574

Table 6:Hypothetical performance of physician scoring of dyspnea using RDOS across a range of dyspnea cut offs and RDOS thresholds

Dyspnea Cut-Off	RDOS Threshold	True Positive	True Negative	False Positive	False Negative	Precision	Recall	F1	Accuracy
2	1	49	4	9	6	0.845	0.891	0.867	0.779
2	2	40	7	6	15	0.870	0.727	0.792	0.691
2	3	27	11	2	28	0.931	0.491	0.643	0.559
2.5	1	46	6	12	4	0.793	0.92	0.852	0.765
2.5	2	37	9	9	13	0.804	0.740	0.771	0.676
2.5	3	24	13	5	26	0.828	0.480	0.608	0.544
3	1	46	6	12	4	0.793	0.920	0.852	0.765
3	2	37	9	9	13	0.804	0.740	0.771	0.676
3	3	24	13	5	26	0.828	0.480	0.608	0.544
3.5	1	39	6	19	4	0.672	0.907	0.772	0.662
3.5	2	33	12	13	10	0.717	0.767	0.742	0.662
3.5	3	22	18	7	21	0.759	0.512	0.611	0.588
4	1	39	6	19	4	0.672	0.907	0.772	0.662
4	2	33	12	13	10	0.717	0.767	0.742	0.662
4	3	22	18	7	21	0.759	0.512	0.611	0.588

Discussion

Individual variation in hypercapnia and hypoxia-induced dyspnea during free breathing:

Our data demonstrated that both end-tidal pCO_2 and inspired pO_2 levels were associated with self-reported dyspnea severity in free-breathing healthy individuals (**Figure 2**). These data support prior findings that hypoxia and hypercapnia induce dyspnea.[15,16,30,90] While our experimental treatments were effective in stimulating significant dyspnea in this population, we note that there was substantial variation in severity across participants under the same treatment conditions. In contrast, self-reported dyspnea severity is more severe and less variable across individuals in other studies utilizing fixed ventilation

protocols.[42] This may be due to several factors, including feedback from lung mechanoreceptors during larger tidal volumes in voluntary spontaneous breathing, alleviating some of the dyspnea stimulus. Based on these differences in dyspnea severity in free breathing individuals versus those experiencing fixed tidal volumes and/or frequency, future work will be required to validate our models in clinical populations to facilitate translation.

Predictive power of single biomarkers:

Our findings are consistent with prior work showing significant relationships between select individual biomarkers and dyspnea severity. Tachypneic breathing is often viewed as one of the main indicators of dyspnea, and is one of the scored criteria on the RDOS showing the highest predictive value.[127] This link is clear in previous experiments by Izumizaki et al. (2011) who show that the threshold for dyspnea is positively associated with the threshold for increases in respiratory rate during CO_2 rebreathing.[128] Additionally, heart rate shows modest correlations with dyspnea severity in both Campbell's original RDOS work and our current study.[127] Tidal volume and minute ventilation were included as biomarkers in our study but are not included in the RDOS. Interestingly, tidal volume had the largest predictive value in our study, which supports work by many others demonstrating the large independent impact of tidal volume on dyspnea in ventilated patients, with low-tidal volume and permissive hypercapnia often favored to prevent lung injury but leading to increased patient discomfort.[24,129] While each of these single biomarkers provide predictive value, more complex models which

capture nonlinear trends and multivariate relationships between biomarkers can provide improved predictive value across a variety of pathologies.

Dyspnea is accurately predicted using machine learning:

We show that dyspnea can be accurately identified using machine learning models and that this approach may produce more accurate estimations of self-reported dyspnea than human estimates via visual observation. Beyond the benefit of high recall and thus reducing false negative estimates, this model can provide continuous monitoring and notify healthcare providers when patients require intervention, particularly in-between routine check-ins when self-reported dyspnea can be obtained.

In recent years, several groups have found that other subjective sensations such as pain can be predicted using a variety of input variables.[60–62] Our findings align with this prior work, further suggesting that subjective sensations can be monitored or predicted using quantifiable inputs. These predictions are robust even given their relationship with psychological factors such as anxiety. We hypothesize that this is because anxiety modulates the input biomarkers in a predictable way and that underlying effects of anxiety on dyspnea are therefore captured.[130,131] Robust, reliable prediction of subjective sensations such as pain and dyspnea across a variety of patients and pathologies can improve patient outcomes and reduce suffering, particularly in patients with communication barriers.

Healthcare professionals under-estimate dyspnea severity:

Despite the variety of self-reported cut-offs and RDOS thresholds tested, performance metrics for visual estimates of dyspnea were less accurate than our predictive model at distinguishing significant dyspnea. Precision performance between healthcare providers and our model were remarkably similar. However, the healthcare provider observational estimate recall was consistently lower. This indicates great certainty in the positive results from using the RDOS, but a general underestimation of patient dyspnea, and a large proportion of false negative estimates. In these cases, patients with less severe dyspnea, and those who show less obvious signs, may be left with unmanaged dyspnea. Lowering the threshold of the RDOS from scores of three to two dramatically increases recall (**Table 6**) with minimal loss of precision, leading to F1 and accuracy increases. This indicates that RDOS may be more beneficial for detecting any presence of dyspnea rather than a specific threshold to indicate moderate dyspnea or other varied intensities. This supports recent work by Aikawa et al. (2024) who demonstrate that the RDOS, IC-RDOS, and MV-RDOS can predict the presence of dyspnea with moderate accuracy, but is limited in its ability to discriminate severity, although work by Zhuang et al. (2018) show the RDOS can perform fairly well in discriminating moderate to severe dyspnea in palliative care patients.[44,132] Aikawa et al. also demonstrated that lowering the cut off point for the RDOS was required to increase its performance, supporting our findings.

Limitations

It is important to note that our current model was trained and tested with data from young participants without significant cardiovascular or pulmonary disease. Our dataset also includes only hypercapnia and hypoxia-induced dyspnea stimuli. Therefore, further studies must be done to include data across additional dimensions of dyspnea such as fixed ventilation patterns, airflow resistance, and check wall tightness. There may also be time-dependent impacts as our dataset includes 4-minutes of dyspnea stimuli so the effects of inspiratory muscle fatigue are not considered. Further studies should also verify the application of predictive multi-biomarker models for diverse patient populations exhibiting heightened airway resistance, chest wall restrictions, and other limitations and medical interventions which may modulate dyspnea severity (e.g. sedation and neuromuscular blockade).

One other limitation of our study was the inability to score nasal flaring in video recordings due to the use of opaque oronasal face masks. While the probability that this feature alone would have significantly impacted performance of observational estimates, and many adaptations of the RDOS exclude nasal flaring as a grading criterion, our findings should be interpreted in the context of this limitation.

Conclusion

Machine learning is an excellent solution for the monitoring of subjective symptoms which manifest in measurable physiological biomarkers. Predictive models such as ours

can be extracted and used as a lightweight addition to existing monitoring software or as standalone with a small, low power computer. Machine learning methods allow for the use of many variables to be considered simultaneously in a way that is difficult or impossible to do for unassisted humans. The application of machine learning to monitoring technologies such as those for identifying dyspnea also allows continuous monitoring between in-person patient visits. Future work will prioritize extending the current predictive model to include additional dimensions of dyspnea and validation in diverse clinical populations.

Chapter 6: Concluding Remarks

In summary, dyspnea is a subjective and multivariate symptom prevalent in the ICU and other healthcare settings. While it is common for patients with pulmonary pathologies, it is present in a wide variety of pathologies and conditions, both chronic and acute. It poses a major risk to the physical and psychological well-being of patients. Those who have experienced severe dyspnea during a hospital stay frequently remember it as one of the most negative aspects and can develop PTSD-like symptoms due to the lasting mark it leaves. It increases the likelihood of a ventilated patient to fail weaning off the ventilator, increases risk of hospital re-admission for COPD patients, and increases chances of death in the ICU. All this highlights that due to the negative impact dyspnea has on patient outcomes, proper identification is critical. Large efforts have been made to generate a standardized method for the assessment of dyspnea by healthcare professionals, which is critical for patients who are not able to directly communicate their discomfort themselves. The Respiratory Distress Observation Scale allows healthcare professionals to quickly assess the level of breathing discomfort of their patients and has been shown to be a valuable tool for clinicians. From the work of others, as well as the data presented in this dissertation, it is clear the RDOS can work well for identifying dyspnea but has shortcomings which can lead to some patients' needs being unaddressed. Namely, it struggles with the variety of ways dyspnea can present, including in sedated patients or those with limited neuro-muscular activity, since many of the visual signs of dyspnea are masked in these cases.

In this dissertation, I investigated demographic, physiological and psychological variables' relationships with dyspnea severity. I found that while some of these variables do have independent relationships with dyspnea severity, they serve better as small pieces in a larger, multivariate model. Using machine learning algorithms to classify the data, I was able to achieve high levels of accuracy for discerning between no/low dyspnea and moderate/severe, providing a good intensity at which to seek intervention. The algorithm was able to significantly outperform physicians and nurses who assessed the participants from the same dataset, albeit with a slight limitation. I also showed that healthcare providers using the RDOS can perform nearly as well as these algorithms when the threshold for a positive dyspnea score is decreased, meaning the RDOS functioned better (in this dataset) as a detector of moderate and above dyspnea when any signs of dyspnea were noticed by the healthcare provider, rather than multiple. Based on my findings, using a lower threshold in the clinical setting should improve patient outcomes while minimizing risks due to the lower risk of harm associated with giving a patient who may be identified as a false positive additional care, while dramatically increasing the identification of dyspneic patients. Furthermore, these findings also highlight that it may be possible to create a dyspnea observational scale which incorporates subjective measures (such as look of fear) but relies more on the physiological state of the patient, allowing for healthcare providers who do not have access to a monitoring system running an algorithm to rapidly assess whether their patient is in respiratory discomfort. It is entirely possible that a slightly modified version of the RDOS as described above could function for the same purpose. It is important to once again note that these findings were

based on a relatively healthy and young participant pool. Further validation in the hospital setting and with patients experiencing a variety of pathologies and health disparities is needed before a machine learning method such as this can be touted as an excellent tool for monitoring dyspnea. However, as mentioned in my dedication at the beginning of this dissertation, it is within the essence of every scientist to sculpt reality through the pursuit of knowledge. I suppose now that I have finished writing, and you have finished reading, it is time to get back to work.

Bibliography:

1. Dyspnea. *Am J Respir Crit Care Med*. 1999;159(1):321-340. doi:10.1164/ajrccm.159.1.ats898

2. Parshall MB, Schwartzstein RM, Adams L, et al. An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea. *Am J Respir Crit Care Med*. 2012;185(4):435-452. doi:10.1164/rccm.201111-2042ST

3. Stevens JP, Dechen T, Schwartzstein RM, O'Donnell CR, Baker K, Banzett RB. Association of dyspnoea, mortality and resource use in hospitalised patients. *Eur Respir J*. 2021;58(3). doi:10.1183/13993003.02107-2019

4. Herigstad M, Hayen A, Wiech K, Pattinson KTS. Dyspnoea and the brain. *Respir Med*. 2011;105(6):809-817. doi:10.1016/j.rmed.2010.12.022

5. Burki NK, Lee LY. Mechanisms of Dyspnea. *Chest*. 2010;138(5):1196-1201. doi:10.1378/chest.10-0534

6. Stevenson NJ, Walker PP, Costello RW, Calverley PMA. Lung Mechanics and Dyspnea during Exacerbations of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2005;172(12):1510-1516. doi:10.1164/rccm.200504-595OC

7. Crisafulli E, Clini EM. Measures of dyspnea in pulmonary rehabilitation. *Multidiscip Respir Med*. 2010;5(3):202. doi:10.1186/2049-6958-5-3-202

8. Laveneziana P. Qualitative aspects of exertional dyspnea in patients with restrictive lung disease. *Multidiscip Respir Med*. 2010;5(3):211-215. doi:10.1186/2049-6958-5-3-211

9. Berliner D, Schneider N, Welte T, Bauersachs J. The Differential Diagnosis of Dyspnea. *Dtsch Ärztebl Int*. 2016;113(49):834-845. doi:10.3238/arztebl.2016.0834

10. Hui D, Bohlke K, Bao T, et al. Management of Dyspnea in Advanced Cancer: ASCO Guideline. *J Clin Oncol Off J Am Soc Clin Oncol*. 2021;39(12):1389-1411. doi:10.1200/JCO.20.03465

11. Vogt S, Schreiber S, Kollewe K, et al. Dyspnea in amyotrophic lateral sclerosis: The Dyspnea-ALS-Scale (DALS-15) essentially contributes to the diagnosis of respiratory impairment. *Respir Med*. 2019;154:116-121. doi:10.1016/j.rmed.2019.06.014

12. Pesola GR, Ahsan H. Dyspnea as an Independent Predictor of Mortality. *Clin Respir J*. 2016;10(2):142-152. doi:10.1111/crj.12191

13. Dupuis-Lozeron E, Soccal PM, Janssens JP, Similowski T, Adler D. Severe Dyspnea Is an Independent Predictor of Readmission or Death in COPD Patients Surviving Acute Hypercapnic Respiratory Failure in the ICU. *Front Med*. 2018;5:163. doi:10.3389/fmed.2018.00163

14. Campbell ML, Templin T, Walch J. A Respiratory Distress Observation Scale for Patients Unable To Self-Report Dyspnea. *J Palliat Med*. 2010;13(3):285-290. doi:10.1089/jpm.2009.0229

15. Fukushi I, Pokorski M, Okada Y. Mechanisms underlying the sensation of dyspnea. *Respir Investig*. 2021;59(1):66-80. doi:10.1016/j.resinv.2020.10.007

16. Gigliotti F. Mechanisms of dyspnea in healthy subjects. *Multidiscip Respir Med*. 2010;5(3):195-201. doi:10.1186/2049-6958-5-3-195

17. Schwartzstein RM, Manning HL, Weiss JW, Weinberger SE. Dyspnea: A sensory experience. *Lung*. 1990;168(1):185-199. doi:10.1007/BF02719692

18. Godfrey S. Breath-holding and the sensations due to chemical and mechanical stimuli to breathing. *Br J Dis Chest*. 1969;63(4):177-192. doi:10.1016/S0007-0971(69)80018-5

19. Godfrey S, Campbell EJM. Mechanical and Chemical Control of Breath Holding. *Q J Exp Physiol Cogn Med Sci*. 1969;54(2):117-128. doi:10.1113/expphysiol.1969.sp002011

20. Manning HL, Schwartzstein RM. Pathophysiology of Dyspnea. *N Engl J Med*. 1995;333(23):1547-1553. doi:10.1056/NEJM199512073332307

21. Banzett RB, Lansing RW, Binks AP. Air Hunger: A Primal Sensation and a Primary Element of Dyspnea. *Compr Physiol*. 2021;11(2):1449-1483. doi:10.1002/cphy.c200001

22. Banzett RB, Lansing RW, Brown R, et al. 'Air hunger' from increased PCO2 persists after complete neuromuscular block in humans. *Respir Physiol*. 1990;81(1):1-17. doi:10.1016/0034-5687(90)90065-7

23. Effects of voluntary constraining of thoracic displacement during hypercapnia. doi:10.1152/jappl.1987.63.5.1822

24. 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. doi:10.1016/0034-5687(92)90131-f

25. Evans KC, Banzett RB, Adams L, McKay L, Frackowiak RSJ, Corfield DR. BOLD fMRI Identifies Limbic, Paralimbic, and Cerebellar Activation During Air Hunger. *J Neurophysiol*. 2002;88(3):1500-1511. doi:10.1152/jn.2002.88.3.1500

26. Banzett RB, Pedersen SH, Schwartzstein RM, Lansing RW. The Affective Dimension of Laboratory Dyspnea. *Am J Respir Crit Care Med*. 2008;177(12):1384-1390. doi:10.1164/rccm.200711-1675OC

27. Lansing RW, Gracely RH, Banzett RB. THE MULTIPLE DIMENSIONS OF DYSPNEA: REVIEW AND HYPOTHESES. *Respir Physiol Neurobiol*. 2009;167(1):53-60. doi:10.1016/j.resp.2008.07.012

28. Grazzini M, Stendardi L, Gigliotti F, Scano G. Pathophysiology of exercise dyspnea in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD). *Respir Med*. 2005;99(11):1403-1412. doi:10.1016/j.rmed.2005.03.005

29. Duiverman ML, de Boer EWJ, van Eykern LA, et al. Respiratory muscle activity and dyspnea during exercise in chronic obstructive pulmonary disease. *Respir Physiol Neurobiol*. 2009;167(2):195-200. doi:10.1016/j.resp.2009.04.018

30. Buchanan GF, Richerson GB. Role of chemoreceptors in mediating dyspnea. *Respir Physiol Neurobiol*. 2009;167(1):9-19. doi:10.1016/j.resp.2008.12.002

31. Ortega-Sáenz P, Moreno-Domínguez A, Gao L, López-Barneo J. Molecular Mechanisms of Acute Oxygen Sensing by Arterial Chemoreceptor Cells. Role of Hif2α. *Front Physiol*. 2020;11:614893. doi:10.3389/fphys.2020.614893

32. Guyenet PG, Bayliss DA. Central respiratory chemoreception. *Handb Clin Neurol*. 2022;188:37-72. doi:10.1016/B978-0-323-91534-2.00007-2

33. Hayen A, Herigstad M, Pattinson KTS. Understanding dyspnea as a complex individual experience. *Maturitas*. 2013;76(1):45-50. doi:10.1016/j.maturitas.2013.06.005

34. Stoeckel MC, Esser RW, Gamer M, Büchel C, von Leupoldt A. Brain mechanisms of short-term habituation and sensitization toward dyspnea. *Front Psychol*. 2015;6:748. doi:10.3389/fpsyg.2015.00748

35. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T. A Comparison of the Level of Dyspnea vs Disease Severity in Indicating the Health-Related Quality of

Life of Patients With COPD. *Chest*. 1999;116(6):1632-1637. doi:10.1378/chest.116.6.1632

36. Borges-Santos E, Wada JT, da Silva CM, et al. Anxiety and depression are related to dyspnea and clinical control but not with thoracoabdominal mechanics in patients with COPD. *Respir Physiol Neurobiol*. 2015;210:1-6. doi:10.1016/j.resp.2015.01.011

37. Banzett RB, Schwartzstein RM. Dyspnea: Don't Just Look, Ask! *Am J Respir Crit Care Med*. 2015;192(12):1404-1406. doi:10.1164/rccm.201508-1637ED

38. Worsham CM, Banzett RB, Schwartzstein RM. Dyspnea, Acute Respiratory Failure, Psychological Trauma, and Post-ICU Mental Health. *Chest*. 2021;159(2):749-756. doi:10.1016/j.chest.2020.09.251

39. Yohannes AM, Willgoss TG, Baldwin RC, Connolly MJ. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. *Int J Geriatr Psychiatry*. 2010;25(12):1209-1221. doi:10.1002/gps.2463

40. Simms LJ, Prisciandaro JJ, Krueger RF, Goldberg DP. The structure of depression, anxiety and somatic symptoms in primary care. *Psychol Med*. 2012;42(1):15-28. doi:10.1017/S0033291711000985

41. Demoule A, Decavele M, Antonelli M, et al. Dyspnoea in acutely ill mechanically ventilated adult patients: an ERS/ESICM statement. *Intensive Care Med*. 2024;50(2):159-180. doi:10.1007/s00134-023-07246-x

42. Banzett RB, Lansing RW, Evans KC, Shea SA. Stimulus-response characteristics of CO2-induced air hunger in normal subjects. *Respir Physiol*. 1996;103(1):19-31. doi:10.1016/0034-5687(95)00050-X

43. Scano G, Gigliotti F, Stendardi L, Gagliardi E. Dyspnea and emotional states in health and disease. *Respir Med*. 2013;107(5):649-655. doi:10.1016/j.rmed.2012.12.018

44. Aikawa G, Imanaka R, Sakuramoto H, Hatozaki C, Unoki T, Okamoto S. Assessment of Dyspnea in Critically Ill Patients: A Comparative Analysis of Evaluation Scales. *Cureus*. 16(1):e52751. doi:10.7759/cureus.52751

45. Dangers L, Montlahuc C, Kouatchet A, et al. Dyspnoea in patients receiving noninvasive ventilation for acute respiratory failure: prevalence, risk factors and prognostic impact: A prospective observational study. *Eur Respir J*. 2018;52(2). doi:10.1183/13993003.02637-2017

46. Schmidt M, Banzett RB, Raux M, et al. Unrecognized suffering in the ICU: Addressing dyspnea in mechanically ventilated patients. *Intensive Care Med*. 2013;40(1):1. doi:10.1007/s00134-013-3117-3

47. Branson RD, Blakeman TC, Robinson BR. Asynchrony and Dyspnea. *Respir Care*. 2013;58(6):973-989. doi:10.4187/respcare.02507

48. Schwartzstein RM, Campbell ML. Dyspnea and Mechanical Ventilation: The Emperor Has No Clothes. *Am J Respir Crit Care Med*. 205(8):864-865. doi:10.1164/rccm.202201-0078ED

49. Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. *Am J Respir Crit Care Med*. 1997;155(6):1940-1948. doi:10.1164/ajrccm.155.6.9196100

50. Schmidt M, Demoule A, Polito A, et al. Dyspnea in mechanically ventilated critically ill patients*. *Crit Care Med*. 2011;39(9):2059. doi:10.1097/CCM.0b013e31821e8779

51. Dres M, Similowski T, Goligher EC, et al. Dyspnoea and respiratory muscle ultrasound to predict extubation failure. *Eur Respir J*. 2021;58(5). doi:10.1183/13993003.00002-2021

52. Puntillo K, Nelson JE, Weissman D, et al. Palliative care in the ICU: relief of pain, dyspnea, and thirst--a report from the IPAL-ICU Advisory Board. *Intensive Care Med*. 2014;40(2):235-248. doi:10.1007/s00134-013-3153-z

53. Mularski RA, Campbell ML, Asch SM, et al. A Review of Quality of Care Evaluation for the Palliation of Dyspnea. *Am J Respir Crit Care Med*. 2010;181(6):534-538. doi:10.1164/rccm.200903-0462PP

54. Zhuang Q, Yang GM, Neo SHS, Cheung YB. Validity, Reliability, and Diagnostic Accuracy of the Respiratory Distress Observation Scale for Assessment of Dyspnea in Adult Palliative Care Patients. *J Pain Symptom Manage*. 2019;57(2):304-310. doi:10.1016/j.jpainsymman.2018.10.506

55. Campbell ML, Yarandi HN. Effectiveness of an Algorithmic Approach to Ventilator Withdrawal at the End of Life: A Stepped Wedge Cluster Randomized Trial. *J Palliat Med*. 2024;27(2):185-191. doi:10.1089/jpm.2023.0128

56. Wong RX, Shirlynn H, Koh YS, Goh Seow Lin S, Quah D, Zhuang Q. Exploration and Development of a Simpler Respiratory Distress Observation Scale (modRDOS-4) as a Dyspnea Screening Tool: A Prospective Bedside Study. *Palliat Med Rep*. 2021;2(1):9-14. doi:10.1089/pmr.2020.0094

57. Decavèle M, Bureau C, Campion S, et al. Interventions Relieving Dyspnea in Intubated Patients Show Responsiveness of the Mechanical Ventilation–Respiratory Distress Observation Scale. *Am J Respir Crit Care Med*. 2023;208(1):39-48. doi:10.1164/rccm.202301-0188OC

58. Hui D, Morgado M, Vidal M, et al. Dyspnea in Hospitalized Advanced Cancer Patients: Subjective and Physiologic Correlates. *J Palliat Med*. 2013;16(3):274-280. doi:10.1089/jpm.2012.0364

59. Haugdahl HS, Storli SL, Meland B, Dybwik K, Romild U, Klepstad P. Underestimation of Patient Breathlessness by Nurses and Physicians during a Spontaneous Breathing Trial. *Am J Respir Crit Care Med*. 2015;192(12):1440-1448. doi:10.1164/rccm.201503-0419OC

60. Hsiao FJ, Chen WT, Pan LLH, et al. Machine learning–based prediction of heat pain sensitivity by using resting-state EEG. *Front Biosci-Landmark*. 2021;26(12):1537-1547. doi:10.52586/5047

61. Lötsch J, Ultsch A. Machine learning in pain research. *Pain*. 2018;159(4):623-630. doi:10.1097/j.pain.0000000000001118

62. Lee J, Mawla I, Kim J, et al. Machine learning-based prediction of clinical pain using multimodal neuroimaging and autonomic metrics. *Pain*. 2019;160(3):550-560. doi:10.1097/j.pain.0000000000001417

63. McKee PC, Budnick CJ, Walters KS, Antonios I. College student Fear of Missing Out (FoMO) and maladaptive behavior: Traditional statistical modeling and predictive analysis using machine learning. *PLoS ONE*. 2022;17(10):e0274698. doi:10.1371/journal.pone.0274698

64. Schumann P, Trentzsch K, Stölzer-Hutsch H, et al. Using machine learning algorithms to detect fear of falling in people with multiple sclerosis in standardized gait analysis. *Mult Scler Relat Disord*. 2024;88. doi:10.1016/j.msard.2024.105721

65. Baggio T, Grecucci A, Meconi F, Messina I. Anxious Brains: A Combined Data Fusion Machine Learning Approach to Predict Trait Anxiety from Morphometric Features. *Sensors*. 2023;23(2):610. doi:10.3390/s23020610

66. Demiris G, Corey Magan KL, Parker Oliver D, et al. Spoken words as biomarkers: using machine learning to gain insight into communication as a predictor of anxiety. *J Am Med Inform Assoc JAMIA*. 2020;27(6):929-933. doi:10.1093/jamia/ocaa049

67. Horwitz A, McCarthy K, House SL, et al. Intensive Longitudinal Assessment Following Index Trauma to Predict Development of PTSD using Machine Learning. *J Anxiety Disord*. 2024;104:102876. doi:10.1016/j.janxdis.2024.102876

68. Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS ONE*. 2012;7(11):e48230. doi:10.1371/journal.pone.0048230

69. Skapinakis P. Spielberger State-Trait Anxiety Inventory. In: Michalos AC, ed. *Encyclopedia of Quality of Life and Well-Being Research*. Springer Netherlands; 2014:6261-6264. doi:10.1007/978-94-007-0753-5_2825

70. Heinrich EC, Orr JE, Gilbertson D, et al. Relationships Between Chemoreflex Responses, Sleep Quality, and Hematocrit in Andean Men and Women. *Front Physiol*. 2020;11. doi:10.3389/fphys.2020.00437

71. google random number generator - Google Search. Accessed November 8, 2025. https://www.google.com/search?si=AMgyJEs8WU70xyfCuhMkrqzGp4HefxknVKm6TPquCK_BQRA-wceq0541UUMXyYh9I4dB8EUgTGGk44OWrSWO_t0CS1RiuRDNNE1fsrel2conyMQAaLCXtxTIOoNY7-1buRMOeZkaV2hvSlD8uxo7yCzGqBJpryWIFTgSoWFwqrtudHoMBBntputn82zQtqic5p280gGneGSB4tK43E8iHjKddx0RUYteW85SfY5RcRoxskPemaU-2HTHV4NZTNMl392LzPsJUdSJhsPQ4g_Qdj_zV18Zx5avOl2d-VsFeep6iB7WKxGSxdA6v0b56fT0hzBm1PcXSyjs_FDY2CMpP65Y9HPFmJKQMyeekm1cZ7VipKCZzQL8xuvkFrDV9nCX0MAHlWPqqzeJGVRKWX7tj7Wwnt7R-zOb7enKu9wX00mn_lyn9SCuS3oO0g2vMmcdtiBtdOoUnwsjA35juiHDsFciv3ctiYobD2o9QN-WlgrWRB0z2IKBnx7M5s-mm9FkdNhoK-XJ9Mj1gp1aO37VzR6dq_wtQWOJK49EyQ4XeY9rzDYCv1SKQxm7X9GKYP1LdsBFZrFZ0DRIm5uxGiofeOJNRpgCRXMYSJV9gI9fiLAXGAJzZO_McfEHhcwa82zjEy8XnRmwzbh_-8O1dTLm_jnd21mYqEn5Diyfw6-5foKAEayjl7YYv0hnNWFSySJgIEv-yr97TR_hFhQ7NbgxXSA1OpsnjLkLdQ%3D%3D&hl=en-US&shndl=21&source=sh/x/fbx/m1/1&kgs=e985e1639744211b&shem=shrtsdl&utm_source=shrtsdl,sh/x/fbx/m1/1&sei=NBsPaaHKLvqgkPIPgN2K4QY

72. Louie A, Feiner JR, Bickler PE, Rhodes L, Bernstein M, Lucero J. Four Types of Pulse Oximeters Accurately Detect Hypoxia during Low Perfusion and Motion. *Anesthesiology*. 2018;128(3):520. doi:10.1097/ALN.0000000000002002

73. McKinney W. Data Structures for Statistical Computing in Python. In: 2010:56-61. doi:10.25080/Majora-92bf1922-00a

74. Harris CR, Millman KJ, van der Walt SJ, et al. Array programming with NumPy. *Nature*. 2020;585(7825):357-362. doi:10.1038/s41586-020-2649-2

75. Seabold S, Perktold J. Statsmodels: Econometric and Statistical Modeling with Python. *Proc 9th Python Sci Conf*. 2010;2010.

76. Hunter JD. Matplotlib: A 2D Graphics Environment. *Comput Sci Eng*. 2007;9(3):90-95. doi:10.1109/MCSE.2007.55

77. Waskom ML. seaborn: statistical data visualization. *J Open Source Softw*. 2021;6(60):3021. doi:10.21105/joss.03021

78. Centrum Wiskunde & Informatica: Python tutorial. Accessed November 17, 2025. https://ir.cwi.nl/pub/5007

79. Pedregosa F, Pedregosa F, Varoquaux G, et al. Scikit-learn: Machine Learning in Python. *Mach Learn PYTHON*.

80. Cover T, Hart P. Nearest neighbor pattern classification. *IEEE Trans Inf Theory*. 1967;13(1):21-27. doi:10.1109/TIT.1967.1053964

81. Chen T, Guestrin C. XGBoost: A Scalable Tree Boosting System. In: *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*. 2016:785-794. doi:10.1145/2939672.2939785

82. Cortes C, Vapnik V. Support-vector networks. *Mach Learn*. 1995;20(3):273-297. doi:10.1007/BF00994018

83. Breiman L. Random Forests. *Mach Learn*. 2001;45(1):5-32. doi:10.1023/A:1010933404324

84. Cox DR. The Regression Analysis of Binary Sequences. *J R Stat Soc Ser B Methodol*. 1958;20(2):215-242.

85. Webb G. Naïve Bayes. In: 2016:1-2. doi:10.1007/978-1-4899-7502-7_581-1

86. Ting SL, Ip WH, Tsang A. Is Naïve Bayes a Good Classifier for Document Classification? *Int J Softw Eng Its Appl*. 2011;5.

87. Reuben DB, Mor V. Dyspnea in Terminally Ill Cancer Patients. *Chest*. 1986;89(2):234-236. doi:10.1378/chest.89.2.234

88. Baille G, Chenivesse C, Perez T, et al. Dyspnea: An underestimated symptom in Parkinson's disease. *Parkinsonism Relat Disord*. 2019;60:162-166. doi:10.1016/j.parkreldis.2018.09.001

89. Chonan T, Mulholland MB, Leitner J, Altose MD, Cherniack NS. Sensation of dyspnea during hypercapnia, exercise, and voluntary hyperventilation. *J Appl Physiol Bethesda Md 1985*. 1990;68(5):2100-2106. doi:10.1152/jappl.1990.68.5.2100

90. 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):141-154. doi:10.1152/japplphysiol.00594.2002

91. Ramalho SHR, Santos M, Claggett B, et al. Association of Undifferentiated Dyspnea in Late Life With Cardiovascular and Noncardiovascular Dysfunction. *JAMA Netw Open*. 2019;2(6):e195321. doi:10.1001/jamanetworkopen.2019.5321

92. O'Donnell DE, Banzett RB, Carrieri-Kohlman V, et al. Pathophysiology of Dyspnea in Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc*. 2007;4(2):145-168. doi:10.1513/pats.200611-159CC

93. Chua TP, Harrington D, Ponikowski P, Webb-Peploe K, Poole-Wilson PA, Coats AJS. Effects of Dihydrocodeine on Chemosensitivity and Exercise Tolerance in Patients With Chronic Heart Failure. *JACC*. 1997;29(1):147-152. doi:10.1016/S0735-1097(96)00446-9

94. Onodera H, Okabe S, Kikuchi Y, Tsuda T, Itoyama Y. Impaired chemosensitivity and perception of dyspnoea in Parkinson's disease. *The Lancet*. 2000;356(9231):739-740. doi:10.1016/S0140-6736(00)02638-6

95. Grønseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnea prevalence: Results from the BOLD study. *Eur Respir J*. 2014;43(6):1610-1620. doi:10.1183/09031936.00036813

96. Milne KM, Mitchell RA, Ferguson ON, Hind AS, Guenette JA. Sex-differences in COPD: from biological mechanisms to therapeutic considerations. *Front Med*. 2024;11:1289259. doi:10.3389/fmed.2024.1289259

97. Cory JM, Schaeffer MR, Wilkie SS, et al. Sex differences in the intensity and qualitative dimensions of exertional dyspnea in physically active young adults. *J Appl Physiol*. 2015;119(9):998-1006. doi:10.1152/japplphysiol.00520.2015

98. Gut-Gobert C, Cavaillès A, Dixmier A, et al. Women and COPD: do we need more evidence? *Eur Respir Rev*. 2019;28(151):180055. doi:10.1183/16000617.0055-2018

99. Sin DD, Jones RL, Man SFP. Obesity Is a Risk Factor for Dyspnea but Not for Airflow Obstruction. *Arch Intern Med*. 2002;162(13):1477-1481. doi:10.1001/archinte.162.13.1477

100. Sahebjami H. Dyspnea in Obese Healthy Men. *Chest*. 1998;114(5):1373-1377. doi:10.1378/chest.114.5.1373

101. Ora J, Laveneziana P, Ofir D, Deesomchok A, Webb KA, O'Donnell DE. Combined Effects of Obesity and Chronic Obstructive Pulmonary Disease on

Dyspnea and Exercise Tolerance. *Am J Respir Crit Care Med*. 2009;180(10):964-971. doi:10.1164/rccm.200904-0530OC

102. Oeung B, Pham K, Olfert IM, et al. The normal distribution of the hypoxic ventilatory response and methodological impacts: a meta-analysis and computational investigation. *J Physiol*. 2023;601(19):4423-4440. doi:10.1113/JP284767

103. Simonson TS, Baker TL, Banzett RB, et al. Silent hypoxaemia in COVID-19 patients. *J Physiol*. 2021;599(4):1057-1065. doi:10.1113/JP280769

104. Binks AP, Vovk A, Ferrigno M, Banzett RB. THE AIR HUNGER RESPONSE OF FOUR ELITE BREATH-HOLD DIVERS. *Respir Physiol Neurobiol*. 2007;159(2):171-177. doi:10.1016/j.resp.2007.06.014

105. Nakano T, Iwazaki M, Sasao G, et al. Hypobaric hypoxia is not a direct dyspnogenic factor in healthy individuals at rest. *Respir Physiol Neurobiol*. 2015;218:28-31. doi:10.1016/j.resp.2015.07.009

106. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging*. 2006;1(3):253-260. doi:10.2147/ciia.2006.1.3.253

107. Molgat-Seon Y, Dominelli PB, Ramsook AH, et al. The effects of age and sex on mechanical ventilatory constraint and dyspnea during exercise in healthy humans. *J Appl Physiol*. 2018;124(4):1092-1106. doi:10.1152/japplphysiol.00608.2017

108. von Leupoldt A, Sommer T, Kegat S, et al. The Unpleasantness of Perceived Dyspnea Is Processed in the Anterior Insula and Amygdala. *Am J Respir Crit Care Med*. 2008;177(9):1026-1032. doi:10.1164/rccm.200712-1821OC

109. Wolkove N, Dajczman E, Colacone A, Kreisman H. The Relationship Between Pulmonary Function and Dyspnea in Obstructive Lung Disease. *Chest*. 1989;96(6):1247-1251. doi:10.1378/chest.96.6.1247

110. Bruera E, Schmitz B, Pither J, Neumann CM, Hanson J. The Frequency and Correlates of Dyspnea in Patients with Advanced Cancer. *J Pain Symptom Manage*. 2000;19(5):357-362. doi:10.1016/S0885-3924(00)00126-3

111. Herigstad M, Hayen A, Evans E, et al. Dyspnea-Related Cues Engage the Prefrontal Cortex: Evidence From Functional Brain Imaging in COPD. *Chest*. 2015;148(4):953-961. doi:10.1378/chest.15-0416

112. Chan PYS, von Leupoldt A, Liu CY, Hsu SC. Respiratory perception measured by cortical neural activations in individuals with generalized anxiety disorder. *Respir Physiol Neurobiol*. 2014;204:36-40. doi:10.1016/j.resp.2014.09.009

113. Janssens T, De Peuter S, Stans L, et al. Dyspnea Perception in COPD: Association Between Anxiety, Dyspnea-Related Fear, and Dyspnea in a Pulmonary Rehabilitation Program. *Chest*. 2011;140(3):618-625. doi:10.1378/chest.10-3257

114. JULIAN LJ. Measures of Anxiety. *Arthritis Care Res*. 2011;63(0 11):10.1002/acr.20561. doi:10.1002/acr.20561

115. 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):1009-1014. doi:10.1164/ajrccm/142.5.1009

116. Cammarota G, Simonte R, De Robertis E. Comfort During Non-invasive Ventilation. *Front Med*. 2022;9:874250. doi:10.3389/fmed.2022.874250

117. von Leupoldt A, Dahme B. Psychological aspects in the perception of dyspnea in obstructive pulmonary diseases. *Respir Med*. 2007;101(3):411-422. doi:10.1016/j.rmed.2006.06.011

118. Frese T, Sobeck C, Herrmann K, Sandholzer H. Dyspnea as the Reason for Encounter in General Practice. *J Clin Med Res*. 2011;3(5):239-246. doi:10.4021/jocmr642w

119. Adams L, Lane R, Shea SA, Cockcroft A, Guz A. Breathlessness during different forms of ventilatory stimulation: a study of mechanisms in normal subjects and respiratory patients. *Clin Sci Lond Engl 1979*. 1985;69(6):663-672. doi:10.1042/cs0690663

120. Baker KM, DeSanto-Madeya S, Banzett RB. Routine dyspnea assessment and documentation: Nurses' experience yields wide acceptance. *BMC Nurs*. 2017;16:3. doi:10.1186/s12912-016-0196-9

121. Mkrtchyan K, Lohn B, Qazi A, Ma S, Heinrich E. Addressing Disparities Between Physician Rated and Self-Reported Dyspnea Using Machine Learning. *Physiology*. 2024;39(S1):2192. doi:10.1152/physiol.2024.39.S1.2192

122. Mkrtchyan K g., Lohn B, Qazi A, Heinrich E, Ma S. Non-invasive Prediction of Dyspnea Severity Using Machine Learning. In: *B80-2. ABNORMALITIES IN STRUCTURE AND FUNCTION IN COPD*. American Thoracic Society International Conference Abstracts. American Thoracic Society; 2024:A4545-A4545. doi:10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A4545

123. Palliative Care Benchmarks from Academic Medical Centers. doi:10.1089/jpm.2006.0048

124. Wysham NG, Miriovsky BJ, Currow DC, et al. Practical Dyspnea Assessment: Relationship Between the 0–10 Numerical Rating Scale and the Four-Level Categorical Verbal Descriptor Scale of Dyspnea Intensity. *J Pain Symptom Manage*. 2015;50(4):480-487. doi:10.1016/j.jpainsymman.2015.04.015

125. Campbell ML, Templin TN. Intensity cut-points for the Respiratory Distress Observation Scale. *Palliat Med*. 2015;29(5):436-442. doi:10.1177/0269216314564238

126. Decavèle M, Rozenberg E, Niérat MC, et al. Respiratory distress observation scales to predict weaning outcome. *Crit Care*. 2022;26:162. doi:10.1186/s13054-022-04028-7

127. Campbell ML. Psychometric Testing of a Respiratory Distress Observation Scale. *J Palliat Med*. 2008;11(1):44-50. doi:10.1089/jpm.2007.0090

128. Izumizaki M, Masaoka Y, Homma I. Coupling of dyspnea perception and tachypneic breathing during hypercapnia. *Respir Physiol Neurobiol*. 2011;179(2-3):276-286. doi:10.1016/j.resp.2011.09.007

129. Banzett RB, Lansing RW, Binks AP. Air Hunger: A Primal Sensation and a Primary Element of Dyspnea. *Compr Physiol*. 2021;11(2):1449-1483. doi:10.1002/j.2040-4603.2021.tb00156.x

130. Ritsert F, Elgendi M, Galli V, Menon C. Heart and Breathing Rate Variations as Biomarkers for Anxiety Detection. *Bioengineering*. 2022;9(11):711. doi:10.3390/bioengineering9110711

131. Tipton MJ, Harper A, Paton JFR, Costello JT. The human ventilatory response to stress: rate or depth? *J Physiol*. 2017;595(17):5729-5752. doi:10.1113/JP274596

132. Zhuang Q, Yang GM, Neo SHS, Cheung YB. Validity, Reliability, and Diagnostic Accuracy of the Respiratory Distress Observation Scale for Assessment of Dyspnea in Adult Palliative Care Patients. *J Pain Symptom Manage*. 2019;57(2):304-310. doi:10.1016/j.jpainsymman.2018.10.506