Review

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The occurrence mechanism, assessment, and non-pharmacological treatment of dyspnea

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Abstract: Dyspnea is a subjective sensation often described as a feeling of respiratory effort, tightness, or air hunger. The underlying mechanisms of this symptom are multifaceted and involve factors such as respiratory centers, cardiovascular system, airways, neuromuscular components, and metabolic factors, although not fully elucidated. The classical theory of imbalance between inspiratory neural drive (IND) and the simultaneous dynamic responses of the respiratory system posits that the disruption of a normal and harmonious relationship fundamentally shapes the expression of respiratory discomfort. Assessment and comprehensive treatment of dyspnea are crucial for patient rehabilitation, including subjective self-reporting and objective clinical measurements. Non-pharmacological interventions, such as pulmonary rehabilitation, fan therapy, exercise, chest wall vibration, virtual reality technology, traditional Chinese medicine (acupuncture and acupressure), and yoga, have shown promise in alleviating dyspnea symptoms. Additionally, oxygen therapy, has demonstrated short-term benefits for patients with pre-hospital respiratory distress and hypoxemia. This review provides a comprehensive overview of dyspnea, emphasizing the importance of a multifaceted approach for its assessment and management, with a focus on non-pharmacological interventions that contribute to enhanced patient outcomes and quality of life.

Keywords: dyspnea; assessment; interventions

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Introduction

Definition of dyspnea

The American Thoracic Society (ATS) defines dyspnea in its official statement as a subjective experience of breathing discomfort, consisting of qualitative sensations of varying intensity. It arises from various physiological, psychological, social, and environmental factors and may elicit secondary physiological and behavioral responses [1]. Dyspnea is one of the most common and distressing symptoms affecting critically ill patients in the late stages, often compounded by other associated symptoms such as fatigue, anxiety, and depression. This leads to functional limitations, reduced quality of life, and increased family burden [2]. As a predictive factor for all-cause mortality, dyspnea is considered a symptom [3]. The prevalence of dyspnea in the general adult population is estimated at 10 % (7 %–15 %, 95 % CI), with high heterogeneity across studies. The most commonly reported risk factors include increasing age, female gender, elevated BMI, and respiratory or cardiac diseases [4]. Additionally, recent research suggests a correlation between personality traits and lung function, as well as dyspnea [5].

The subjective sensations of dyspnea mainly include three types: a sense of effortful breathing, tightness, and a feeling of air hunger/unsatisfying inspiration. Speech descriptions associated with each dimension of dyspnea are summarized in Figure 1 [6]. Specifically, air hunger serves as an initial homeostatic warning signal for inadequate alveolar ventilation, potentially inducing fear and anxiety, and significantly affecting the lives of cardiorespiratory, neuromuscular, psychological, and end-stage disease patients. Thus, dyspnea is a subjective experience and verbal description may not be sufficient for differential diagnosis (Figure 2). The sense of effortful breathing informs the body of the need to increase respiratory muscle activity and warns of potential respiratory impediments. The most common chest tightness associated with bronchoconstriction may warn of airway inflammation and constriction by activating airway sensory nerves [7]. The ATS statement emphasizes that (1) different sensations, such as effort, tightness, and air lack/insufficient inspiration, are associated with different mechanisms and afferent pathways; (2) different sensations are usually not independently occurring; (3) various sensations of dyspnea differ in their unpleasantness, as well as emotional and behavioral expressions [1].

The physiological processes of respiration

The respiratory process is completed through three interconnected and simultaneous stages, including pulmonary ventilation, gas exchange in the lungs, and the exchange of gases between blood and tissue cells. Each respiratory cycle begins with inhalation and ends with exhalation. During inhalation, the diaphragm and external intercostal muscles contract, causing an enlargement of the chest cavity. The intrathoracic pressure decreases, leading to a reduction in alveolar pressure, which forces the lungs to expand, allowing air to enter. Due to the elastic properties of the lungs, expiration occurs passively when the diaphragm relaxes. Respiration is a complex process that relies on the coordinated action of respiratory muscles and the central control centers of the brain [8].

The primary function of the lungs is to facilitate the exchange of gases between inhaled air and the circulatory system. This process aids in delivering oxygen to the bloodstream and removing carbon dioxide from the body. The control and perception of respiration depend on the intricate interaction of signals generated within the central nervous system. This complex interplay of physiological processes ensures the vital function of respiration, allowing the body to maintain homeostasis by adapting to varying oxygen and carbon dioxide levels. Crucial receptors in this information transmission include central nervous system (medulla, cortex, and limbic system), metabolic (carotid/aortic bodies, medullary chemoreceptors), and respiratory sensors (pulmonary stretch receptors, J receptors, airway C-fibers, upper airway receptors, muscle spindles and tendon organs, chest wall joint receptors) [9]. Various sensory pathways convey information from mechanical, neural, and metabolic sensors, including:

a. Respiratory center: The respiratory center, located in the brainstem, is the primary regulatory center for breathing, including the medullary respiratory control center. This center senses changes in oxygen and carbon dioxide levels in the body and controls the activity of respiratory muscles through neural regulation.
b. Chemoreceptors: The carotid bodies and aortic bodies in the aortic arch serve as chemoreceptors, detecting changes in oxygen and carbon dioxide levels in the blood. When the body requires more oxygen or needs to eliminate carbon dioxide, these receptors send signals prompting the respiratory center to increase respiratory effort.
c. Neurotransmitters: Various neurotransmitters, such as acetylcholine, dopamine, and serotonin, play a role in respiratory regulation. Additionally, activation of the pontine respiratory group in the pons and the adrenal medulla's catecholamines (epinephrine and norepinephrine) can increase respiratory and cardiac responses, transmitting signals between neurons to regulate the excitability and inhibition of the respiratory center or induce compensatory responses [10].
d. Sensory systems: Associated with brain regions like the cerebral cortex, thalamus, and cerebellum, these areas receive information from sensory neurons, including gas concentrations, mechanical changes in the lungs, and chest cavity. This information helps regulate the amplitude and frequency of respiratory efforts.
e. Motor system: Respiratory effort involves the coordinated activity of respiratory muscles, primarily the diaphragm and intercostal muscles. Neural commands from the brain to the spinal cord transmit to these muscles, coordinating their synchronized contraction and relaxation to achieve breathing.

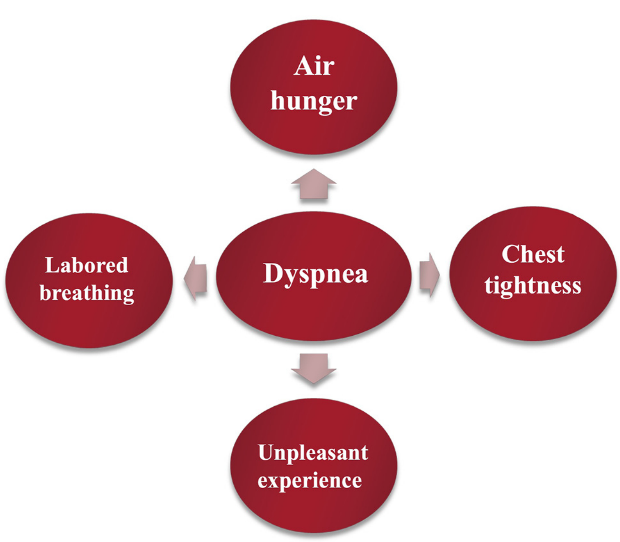

Figure 1: The most common description of dyspnea.

Pathophysiological processes of dyspnea

For most patients, difficulty in breathing typically originates from physiological injury. When these signals are transmitted to the cerebral cortex, they generate feelings of discomfort or unpleasantness [11]. These unpleasant subjective sensations often occur simultaneously and may involve different underlying pathophysiological processes [12].

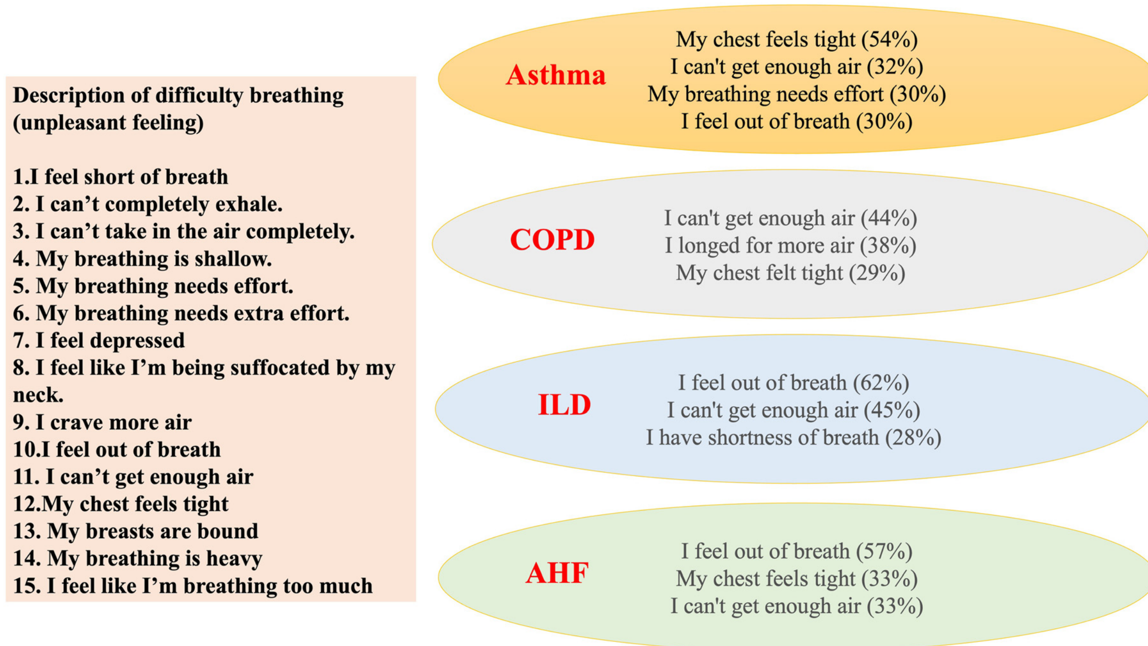

Figure 2: The subjective experience and verbal description of dyspnea.

The sensation of "air hunger" may result from increased stimulation of the brainstem respiratory center by metabolic factors, such as hypercapnia or hypoxia, leading to an increased stimulus that mismatches the appropriate ventilatory response. The sensation of "effort" is perceived through respiratory muscle afferents (speed, shortening, pressure, and frequency) [13]. How this information matches the effort level of a given workload (such as exercise) or metabolic demand is processed through awareness of efferent voluntary motor commands [14] (Figure 3).

Chest tightness is commonly experienced by asthma patients. In volunteers with asthma undergoing non-invasive mechanical ventilation and monitoring during spontaneous breathing, the degree of chest tightness experienced is related to acetylcholine-induced bronchoconstriction, independent of the degree of overinflation or respiratory muscle activity. Tension primarily arises from stimulation of airway receptor receptors such as rapidly adapting receptors (RARs) and C-fiber receptors, which can sense airway muscle contraction or airway irritation/inflammation [15]. Therefore, even with normal lung parenchyma, breathing difficulty may be triggered and should not be confused with hypoxia [16] (Figure 4).

Two theories on the genesis of respiratory distress

The Motor Command Theory suggests that respiratory distress and effort are mediated by the same mechanism, namely the central motor commands from the respiratory center to the motor neurons of the respiratory muscles. The motor output can be consciously identified as a "sense of

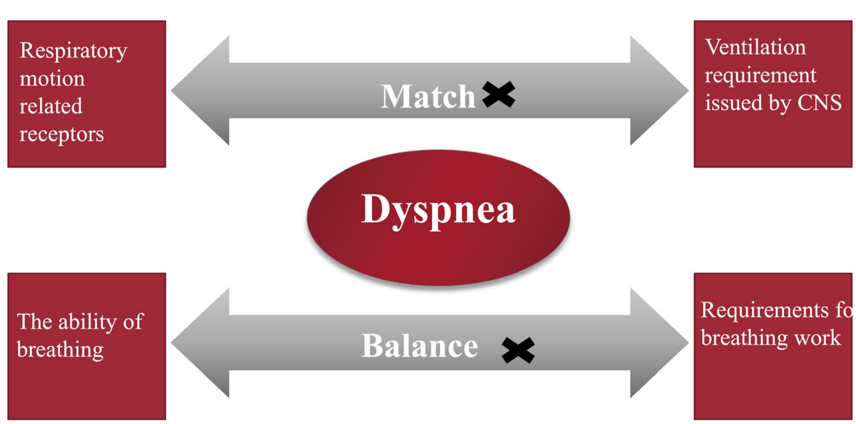

Figure 3: The processes of dyspnea.

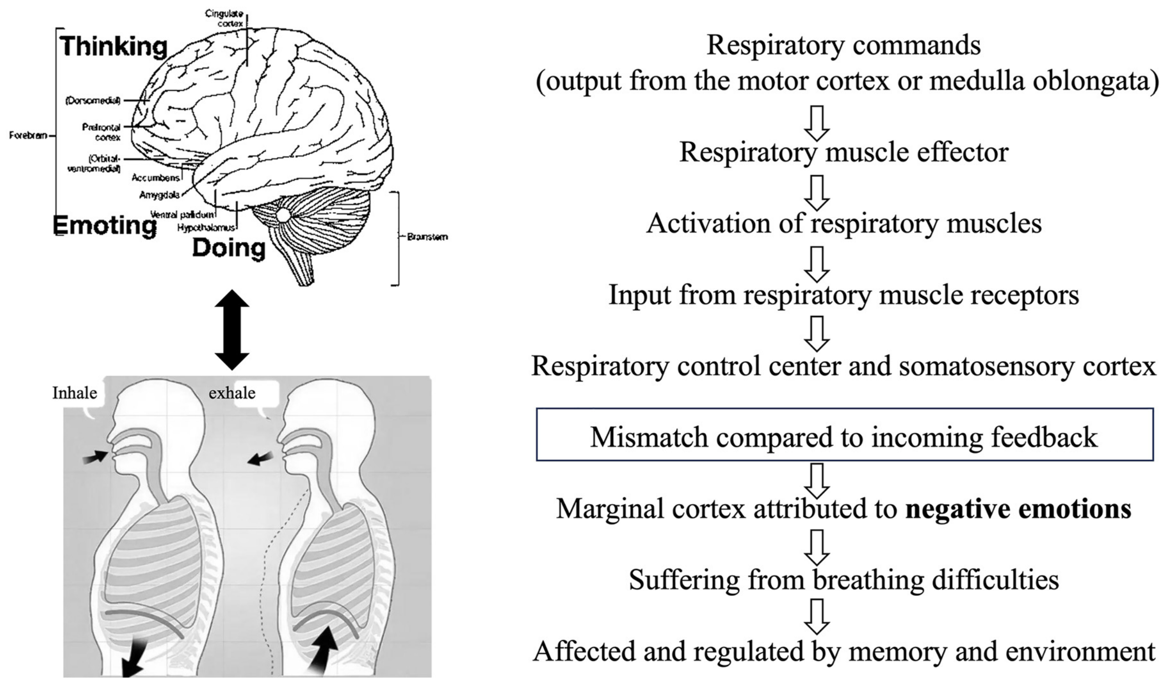

Figure 4: The trajectory of dyspnea.

effort" and is the result of efferent motor commands originating from the respiratory center and ascending to the sensory cortex (Figure 2).

The Mismatch Theory of breathlessness posits that respiratory distress arises from a disconnection between the signals conveying respiratory movement sensations to the brain (input signals) and the output respiratory motor commands [17]. This disconnection is attributed to the separation between lung capacity (length) and the pressure generated by respiratory muscles (tension). In chronic obstructive pulmonary disease (COPD) patients, the theoretical framework for the origin of activity-related breathlessness generally supports the classical Demand-Capacity Imbalance theory. The disruption of the normal and harmonious relationship between inspiratory neural drive (IND) and the dynamic response of the respiratory system fundamentally shapes the expression of breathlessness in COPD [18] (Figure 3).

Neurophysiological processes of dyspnea

According to the Mismatch Theory, dyspnea results from a dissociation or mismatch between the anticipated respiratory motor output set by the lower brainstem respiratory neuronal network and the completed respiratory output. The mechanism by which neural signals of dyspnea are transmitted to higher sensory brain centers remains unclear. Additionally, information from central and peripheral chemoreceptors controlling fluid homeostasis is aggregated in higher brain centers, altering the perception of dyspnea. Furthermore, the mental state can influence the sensitivity and threshold for perceiving dyspnea [19].

Incoming information from peripheral sensors is transmitted to the brain through the thalamus, including the limbic system and somatosensory cortex. Signals from vagal C fibers and peripheral chemoreceptors are conveyed to the nucleus tractus solitarius (NTS) in the medulla, then forwarded to the thalamus, cingulate gyrus, insula, and other higher brain regions. The activation of the thalamus occurs through input from the vagus nerve. Stimulation of the vagus nerve in the neck region activates the somatosensory cortex and insular cortex (Figure 5).

Scale assessments

a. Medical Research Council (MRC) Dyspnea Scale and Modified Medical Research Council (mMRC) Dyspnea Scale: MRC and mMRC are globally utilized dyspnea scales due to their simplicity, ease of use, and good reliability and validity. The MRC scale ranges from 0 to 4, primarily assessing patients with significant clinical symptom changes, being less sensitive to mild symptom variations. The mMRC Dyspnea Questionnaire correlates positively with the severity of airflow limitation

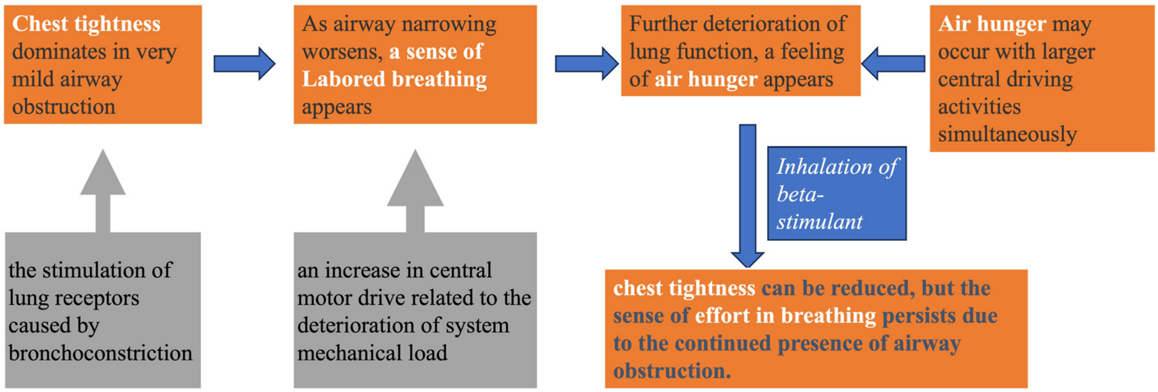

Figure 5: The occurrence of dyspnea affects the advanced brain center and psychological effects.

and lung function impairment, with ratings from 0 to 5. An mMRC rating of ≥ 2 serves as the boundary between "mild" and "severe" dyspnea [20, 21].

b. Visual Analog Scale (VAS): The VAS uses a 100 mm line for patients to indicate the degree of dyspnea, with one end representing "no difficulty breathing at all" and the other end indicating "extreme difficulty breathing". This scale has demonstrated reliability and validity [22, 23].

c. Edmonton Dyspnea Inventory (EDI): The EDI requires assessment with a dyspnea measurement device, evaluating the level of dyspnea during patients' activities of daily living (ADL), exercise, and rest. Scores range from 0 (no dyspnea) to 10 (extreme dyspnea) and are commonly used in clinical assessments of idiopathic pulmonary fibrosis [24].

d. Respiratory Distress Observation Scale (RDOS): RDOS is applicable to patients with speech loss, cognitive impairment, and those nearing death. With eight assessment items, it evaluates the presence and intensity of respiratory distress, standing out as the sole dyspnea symptom assessment tool with good reliability and validity [25, 26].

e. Borg Scale: Frequently used to assess the impact of physical activity on dyspnea, the Borg Scale has established reliability and validity in both the general population and COPD patients [27].

f. Multidimensional Dyspnea Profile (MDP): Widely used, reliable, effective, and responsive across various chronic diseases, environments, and languages. It is considered a standard tool for measuring dyspnea dimensions in international trials. MDP is a recent tool dividing the existence and intensity of the sensory dimension (SQ), unpleasantness of the emotional dimension (A1), and emotional response (A2), based on a mature pain perception concept model [28].

g. Dyspnea-12 Scale (D-12): A multiple-choice survey designed to understand an individual's perception of dyspnea at specific time points. The scale typically comprises 12 questions, covering various aspects of dyspnea during activities such as sitting, walking, and climbing stairs [29].

h. Baseline/Transition Dyspnea Index (BDI/TDI): Assesses daily activity impairment, effort required for activities, and the intensity of activities causing dyspnea. This tool is sensitive to treatment effects but less sensitive for inactive or low-activity patients [30].

i. Shortness of Breath Questionnaire (SOBQ): Evaluates improvement in dyspnea over the past week, demonstrating good reliability [27].

j. Chronic Respiratory Disease Questionnaire (CRQ): Widely used to measure the quality of life in COPD patients, CRQ divides patients' dyspnea severity into 0–7 levels, showing sensitivity to pulmonary rehabilitation and drug treatment effects [31].

k. St. George's Respiratory Questionnaire (SGRQ): Invented in 1991 by Jones et al. [32], currently applied in clinical and research work.

l. Pulmonary Functional Status Scale (PFSS): A self-assessment scale for evaluating the functional status of patients with pulmonary diseases [33].

m. Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ): Also a self-assessment scale, measures post-activity dyspnea in COPD patients. A revised version (PFSDQ-M) has been simplified and both versions show good reliability, validity, and responsiveness [34].

n. Activities of Daily Living Research on the Multidimensional Nature of Dyspnea: Examines the multidimensional aspects of dyspnea symptoms and their impact on ADL in patients with heart and lung diseases and cancer, requiring effective measures. Eight assessment scales have been identified. During the review, three multidimensional assessment scales were available to assess dyspnea symptoms, and five multidimensional scales were available to examine the impact of dyspnea on ADL [35].

o. Dyspnea-Induced Limitations (DYSLIM): Considers 18 activities (from eating to climbing stairs), each with five modes: slow completion of the task, rest, seeking help, changing habits, and avoiding activity. Scores for each mode range from five (never) to one (often). The DYSLIM questionnaire is expected to assess limitations caused by dyspnea in chronic respiratory system diseases and appears suitable for use in various situations [36].

Differential diagnosis of dyspnea

Dyspnea is one of the most common symptoms in primary healthcare units, and potential threatening diseases, especially acute heart failure and its causes, pneumonia, pleural effusion, pulmonary embolism, and pneumothorax, must be promptly ruled out, with initial risk stratification [37]. In addition, emergency and critical care physicians often encounter patients with dyspnea. Recognizing acute critical illness with dyspnea as the primary symptom is a crucial part of the assessment. Detailed symptom history and clinical examinations are essential for accurate diagnosis [38]. On the other hand, in patients with chronic dyspnea (lasting more than 1 month), comprehensive history collection and physical examinations are necessary. Staged testing is recommended, including complete blood cell count, biochemical results, electrocardiography, chest radiography, respiratory measurements, and pulse oxygen saturation. If the cause of dyspnea is not identified, non-invasive tests such as echocardiography, cardiac pressure testing, pulmonary function testing, and computed tomography of the lungs are suggested. Invasive tests, in collaboration with specialized assistance, may be considered as a final option.

a. Ultrasound Technology: The diagnosis of pulmonary diseases primarily relies on imaging techniques and pulmonary function tests [39]. Imaging assessments play a relatively crucial role, such as chest radiography to assess the presence of fluid, consolidation, malignant inflation, pneumothorax, and cardiac enlargement in the lungs or pleura. CT provides more detailed imaging of the cardiorespiratory system with better sensitivity and specificity but comes with higher radiation exposure. The advantage of ultrasound is its radiation-free nature, rapid feasibility for bedside testing, and suitability for evaluating unstable patients [40]. In recent years, Point-of-Care Ultrasound (PoCUS) has been widely researched and applied in patients with dyspnea. In cases of dyspnea in emergency situations, the use of PoCUS aids in early diagnosis and better outcomes [41]. PoCUS can narrow down the range of differential diagnoses, providing faster and more feasible diagnostics in pre-hospital emergency environments compared to other available diagnostic methods [42]. PoCUS helps improve the accuracy of dyspnea diagnosis [43, 44]. Studies have found that continuous ultrasound-guided treatment with Inferior Vena Cava Collapse Index (IVC-CI) and Lung Ultrasound (LUS) B-lines can reduce the mortality, readmission, and length of hospital stay (LOS) in acutely dyspneic patients. B-lines and IVC-CI are dynamic variables that change over time and with treatment. A single ultrasound measurement can influence prognostic outcomes [45]. The current specific applications suggests that PoCUS can provide useful information in the initial assessment of patients with acute dyspnea, rapidly assessing for pleural effusion or other abnormalities, and assisting in guiding non-invasive respiratory support modes [46].

b. Pulmonary Function Assessment: In most patients with dyspnea, chronic inflammation in small airways and lung parenchyma often leads to conditions like obstructive bronchiolitis, lung parenchymal damage, and emphysema. Common manifestations include pulmonary ventilation disorders, reduced ventilatory reserve, increased oxygen consumption, and gas exchange disorders such as decreased oxygen pressure and increased carbon dioxide pressure [47, 48].

c. Cardiopulmonary Exercise Testing (CPET): In CPET, patients undergo progressively challenging exercises such as cycling or running while physiological parameters are monitored. CPET uniquely allows the comprehensive assessment of respiratory, cardiovascular, metabolic, peripheral muscle, and neurosensory system abnormalities during periods of increased physiological stress. CPET assesses maximal effort, peak oxygen consumption, respiratory requirements, pulmonary gas exchange, respiratory reserve, pulmonary operative volume, and exertional dyspnea during patients with symptoms of dyspnea. CPET greatly facilitates the diagnosis of unexplained dyspnea, with common causes including bronchiectasis, emphysema, recent pneumonia, diffuse interstitial pneumonia, variable functional impairment, excessive tension reaction, rhythm or repolarization disorders [49, 50].

d. Invasive Cardiopulmonary Exercise Testing: This usually involves inserting measuring devices, such as catheters or probes, internally to directly measure heart and lung function. This includes Right Heart Catheterization, which directly measures heart blood flow, pressure, and oxygenation by inserting a catheter into the major vessels in the neck or legs. This aids in evaluating heart valve function, heart disease, and other cardiovascular issues. Oximetry measures the difference in oxygen levels between arteries and veins to understand oxygen exchange in the lungs and tissues. Pulmonary Artery Catheterization involves inserting a catheter into the pulmonary artery to measure pulmonary artery pressure, a useful tool for assessing heart and lung function in identifying the causes of unexplained dyspnea. It helps in early identification and prediction of heart failure patients with preserved ejection fraction and pulmonary arterial hypertension. It has also been proven beneficial in constructing a multidisciplinary approach to treating chronic respiratory distress [51].

e. New Assessment Models: Recent research has improved the understanding of the mechanisms of dyspnea, emphasizing the need for threefold assessments. These three key aspects correspond to the "Respiration, Thought, Function" clinical model, proposing a multidimensional approach to respiration, emotion, and function. Before initiating treatment, each specific case must be assessed for several reasons. This involves determining the type of dyspnea affecting the patient, evaluating the impact of shortness of breath, and estimating the effectiveness of the applied treatment [52].

Characteristics of dyspnea symptoms in various diseases

COPD

Dyspnea is the most common symptom in patients with COPD. Despite the wide range of available treatments, as many as 50–91 % of patients with COPD continue to experience significant dyspnea with daily activities [53, 54]. Dyspnea often worsens with exertion and may become chronic and progressive. Patients may describe a sensation of air hunger, chest tightness, or difficulty breathing out. Dyspnea may be accompanied by coughing and sputum production, especially during exacerbations.

In mild COPD, the persistent disruption of gas exchange and the development of "restrictive" dynamic mechanics collectively result in exercise intolerance. The inspiratory neural drive of the respiratory control center needs compensatory increases to maintain ventilation matching the increased metabolic demands. The ultimate clinical consequence of this heightened inspiratory neural drive is the early appearance of severe respiratory mechanical constraints and an increased perception of respiratory discomfort at relatively lower levels of physical activity. Additionally, to avoid exertional dyspnea, many patients adopt a sedentary lifestyle, predictably leading to widespread skeletal muscle imbalance, social isolation, and negative psychological implications [18]. The importance of accurately assessing dyspnea in patients with COPD, emphasizing effective interventions that can delay or reverse the decline in lung function, cannot be overstated [55]. Therefore, non-pharmacological interventions mainly focus on three aspects: (1) reducing dynamic intrinsic positive end-expiratory pressure (IND) without affecting alveolar ventilation (VA); (2) improving respiratory mechanics and related muscle function; (3) intervening in the emotional dimension. In a series of therapeutic interventions (drug treatment, exercise training, oxygen therapy, inspiratory muscle training), a common final pathway to alleviate dyspnea and improve exercise tolerance is to reduce the neuromechanical dissociation of the respiratory system. These interventions, either alone or in combination, partially restore the harmony between the excessive IND and the achieved respiratory machine output. A combined intervention and a structured multidisciplinary approach are needed, carefully tailored to meet individual needs [56].

Asthma

Dyspnea tends to occur episodically and is often associated with wheezing, coughing, and chest tightness. The incidence of dyspnea in asthma was reported 42 % [57]. Dyspnea in asthma is a result of the complex interplay between airway inflammation, bronchoconstriction, increased mucus production, and airflow limitation. In detail, the combination of airway inflammation, bronchoconstriction, and mucus production results in reduced airflow through the airways. As a result, individuals with asthma experience difficulty breathing, often described as dyspnea. Dyspnea in asthma can be triggered by various factors, including exposure to allergens, exercise, cold air, respiratory infections, or exposure to irritants such as smoke or strong odors. These triggers can exacerbate airway inflammation and bronchoconstriction, leading to worsening dyspnea. Symptoms can vary in severity and may be triggered by allergens, exercise, or environmental factors, and may respond well to bronchodilator medications. In breathless asthmatics, dyspnea is also differentially modulated by hyperventilation symptoms and anxiety [58].

Acute heart failure/respiratory failure

Acute heart failure (AHF)

In hospitalized patients with AHF, the most common symptom is dyspnea. AHF typically involves left ventricular dysfunction, leading to congestive heart failure. Over 90 % of patients with AHF have dyspnea [59]. Dyspnea is often described as orthopnea (difficulty breathing while lying flat) or paroxysmal nocturnal dyspnea (sudden onset of dyspnea during sleep). Patients may experience dyspnea during exertion or even at rest in severe cases. Dyspnea may be accompanied by other symptoms such as edema, fatigue, and palpitations.

When the left ventricle cannot efficiently pump blood to the body, pulmonary veins become congested, resulting in pulmonary edema. Pulmonary edema fills the alveoli with fluid, hindering gas exchange and causing dyspnea. Currently, a comprehensive assessment of the clinical effectiveness of potential therapies for treating respiratory distress in AHF patients is lacking [60]. There is a need for a more universally applicable measurement tool established on a unified single-dimensional scale.

Acute respiratory failure (ARF)

Dyspnea is one of the key symptoms of ARF. The prevalence of moderate-to-severe dyspnea was 55 % at the time of ICU admission and 39 % after the first non-invasive ventilation session [61]. Patients with ARF may experience the most distressing form of dyspnea, namely air hunger. Air hunger activates brain pathways known to be involved in post-traumatic stress disorder (PTSD), anxiety, and depression [62]. This is more likely to occur, especially during mechanical ventilation when tidal volume is restricted, a condition often associated with Acute Respiratory Distress Syndrome (ARDS), a common cause of ARF. Post-intensive care syndrome is more prevalent in ARDS patients. Maintaining low tidal volume is a cornerstone of modern ARDS treatment and can still lead to air hunger in patients, even with sedation. Adjunct neuromuscular blockade does not prevent or alleviate air hunger and may contribute to the development of PTSD [62]. Currently, there is a lack of mechanical ventilation strategies aimed at reducing the incidence of respiratory distress.

Dyspnea and Dyspnea-Related Anxiety (DAA) often occur in the ICU patient population. Dyspnea is commonly associated with anxiety, prolonged mechanical ventilation, and worsening post-ICU quality of life. It also increases the risk of PTSD after ICU discharge and is considered part of post-intensive care syndrome [63].

Idiopathic pulmonary fibrosis, pulmonary hypertension, and pulmonary embolism

Idiopathic Pulmonary Fibrosis (IPF) is a progressive disease associated with severe dyspnea and limited exercise capacity, has a dyspnea prevalence of 90 % at diagnosis [64]. It carries a high symptom burden and reports of low health-related quality of life [64]. Dyspnea is often progressive and may be chronic, with a gradual onset over time. Patients may experience dyspnea during exertion and may have a non-productive cough. Dyspnea may be associated with other symptoms such as weight loss, fatigue, and clubbing of the fingers.

Patients with pulmonary embolism (PE) had substantially higher prevalences of both exertional dyspnea (53.0 % vs. 17.3 %) and wake-up dyspnea (12.0 % vs. 1.7 %) compared to control subjects [65]. Dyspnea is often progressive and may be chronic, with a gradual onset over time. Patients may experience dyspnea during exertion and may have a non-productive cough. Dyspnea may be associated with other symptoms such as weight loss, fatigue, and clubbing of the fingers.

Patients with Pulmonary Hypertension (PH) often experience dyspnea during exertion [66], their symptoms were dyspnea (87 %), compared to fatigue (42 %), and lower extremity edema (21 %) [67]. Long-term dyspnea and exercise intolerance are also common clinical issues after acute PE [68]. The potential reasons for exertional dyspnea in these patients include the following factors influenced by the respiratory system during exercise: Respiratory Center Activity, Actual Ventilation, and Respiratory Demand. During exercise, the metabolic curve shifts upward excessively due to the production of carbon dioxide, reaching anaerobic threshold early, hypoxemia, and abnormal exercise response due to the dead space-to-tidal volume ratio. This population has higher respiratory demands. Simultaneously, dynamic hyperinflation and respiratory muscle weakness reduce the actual ventilation for a given respiratory center activity, causing a dissociation between demand and ventilation. Consequently, respiratory demand and respiratory center activity gradually increase during exercise. Despite relatively low ventilation, the high activity of the respiratory center's cortical projection leads to exertional dyspnea [69]. Based on this, the respiratory system is the primary determinant of exertional dyspnea in patients with PH, while the cardiovascular system is an indirect contributor [69].

COVID-19

The pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) rapidly swept across the world and continues to evolve at a significant pace. Infections with SARS-CoV-2 can lead to viral sepsis, pneumonia, and hypoxic respiratory failure collectively known as COVID-19 [70].

One hundred and 15 patients (51 %) reported persistent dyspnea five months after hospitalization [71]. It is noteworthy that some studies have found severe hypoxemia in COVID-19 often occurs without respiratory distress and difficulty breathing. The term "silent hypoxemia" is preferred to describe a notable lack of distress when hypoxemia is present. This phenomenon can be explained by physiological mechanisms involving the control of respiration, respiratory perception, and cardiovascular compensation. It may involve hypotheses related to central and peripheral nervous system viral infection, presenting new challenges to clinicians regarding the physiological mechanisms of respiratory control and regulation [72, 73].

Scientists speculate that SARS-CoV-2 might affect the medullary respiratory center in the brainstem, potentially playing a role in causing neurogenic ARF. On the other hand, respiratory distress, shortness of breath, and chest pain are common symptoms of Post-Acute Sequelae of SARS-CoV-2 infection (PASC), with a broad overlap in symptoms with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Dyspnea is reported in approximately 60 % of PASC [74]. One of the initial stimuli for breathing during exercise is metabolic feedback conveyed through skeletal muscles. Exaggerated respiratory responses exacerbate breathing difficulties, not only restricting exercise capacity but also further impairing muscle energy status [75].

Late-stage cancer

Dyspnea in cancer patients is a common yet complex clinical issue, representing one of the most frequent and distressing symptoms in advanced cancer cases. It is also a predictor of poor prognosis. Research has summarized the incidence, intensity, distress, and impact of dyspnea in cancer patients, with a weighted average incidence of 58.0 % in advanced cancer patients [76]. Dyspnea in these patients may arise from various factors related to the site, type, progression, and treatment of the tumor. Therefore, routine screening is recommended for all cancer patients.

Diseases associated with dyspnea

Palpitations are a primary symptom of atrial fibrillation (AF), but up to two-thirds of patients also complain of self-reported dyspnea. The pathophysiological mechanisms of dyspnea related to AF attacks include central hemodynamics, peripheral muscle oxygen consumption, neural involvement (reflexes), respiratory mechanisms, and impaired ventilation efficiency, along with the impact of negative emotions. Treatment aims to maximize the relief of dyspnea, but there is currently a lack of guidelines specifically addressing the assessment and management of dyspnea in AF patients [77].

In Parkinson's disease patients, reported dyspnea reaches up to 40 %, and despite its high frequency, research on this symptom is relatively scarce, making it a less-known aspect of the disease. Dyspnea leads to limitations in physical abilities and decreased quality of life in Parkinson's disease patients [78]. Currently, there is limited understanding of the pathophysiology of dyspnea and respiratory dysfunction in Parkinson's disease, leading to some patients being labeled with "unexplained dyspnea". Recent studies have highlighted the importance of considering the role of brainstem parenchyma and the pontine respiratory control center in Parkinson's disease [79].

Dyspnea is one of the most common symptoms associated with chronic kidney disease (CKD). It profoundly affects the quality of life for CKD patients, and its root causes are often related to adverse outcomes. However, there is limited knowledge of its pathophysiology. While blood dialysis can address fluid overload issues, it often fails to significantly improve dyspnea. Mechanisms contributing to CKD-related dyspnea include systemic inflammation-induced endothelial dysfunction, pulmonary fibrosis, anemia, malnutrition, and muscle atrophy [80].

Upper Airway Dysfunction (UAD) refers to dyspnea symptoms caused by structural or functional abnormalities in the upper respiratory tract, including the nasal cavity, pharynx, and larynx. Problems affecting these areas can lead to upper airway respiratory difficulties. In a study, most patients with UAD showed no abnormal vocal cord movement during laryngoscopy [81].

Dyspnea is a crucial symptom after a stroke, and it is associated with limitations in activity and reduced community engagement [82]. Early detection and appropriate treatment of dyspnea in stroke patients are strongly recommended as it may improve activity and social participation.

In hypermobile Ehlers-Danlos syndrome (hEDS) and generalized hypermobility spectrum disorder (G-HSD) patients, dyspnea is a common symptom [81].

Non-pharmacological treatment for dyspnea

Inspiratory muscle training

Inspiratory Muscle Training (IMT) is a simple and well-tolerated physical therapy that induces adaptive changes in respiratory muscle structure by increasing the strength or endurance of inspiratory muscles and other respiratory support muscles, helping to alleviate dyspnea. The frequency of IMT sessions refers to how often the training sessions are performed per week. Typical frequencies range from three to seven sessions per week [83–85]. However, the optimal frequency may vary based on individual needs and training goals. The intensity of IMT refers to the resistance or load applied to the inspiratory muscles during training. It can be adjusted using devices that provide resistance to inhalation, such as handheld devices or specialized IMT equipment. The intensity may be prescribed as a percentage of the individual's maximum inspiratory pressure (MIP) or based on subjective perception of effort during training. Intensity levels can range from low to high resistance, depending on the individual's capabilities and training goals. The duration of IMT sessions refers to the length of time spent performing the training exercises during each session. Sessions typically range from 10 to 30 min [83–85], with shorter durations for beginners or those with limited respiratory capacity, and longer durations for more experienced individuals or those training for specific goals. The duration may also depend on the number of repetitions or sets performed during each session. IMT protocols often incorporate progressive overload principles, where the frequency, intensity, or duration of training is gradually increased over time to continually challenge the inspiratory muscles and promote adaptation. Progression may involve increasing the resistance level, adding more sets or repetitions, or increasing the frequency or duration of training sessions. Rest periods between sets or exercises may also be included in IMT protocols to allow for recovery and prevent overexertion of the respiratory muscles. The length of rest periods can vary based on individual fitness levels and training intensity. Some IMT programs may incorporate periodization, which involves dividing the training program into specific phases or cycles, each with different emphasis on intensity, volume, or recovery. Periodization allows for systematic progression and adaptation while minimizing the risk of overtraining and injury [86].

COPD: A meta-analysis shows that IMT can enhance inspiratory muscle strength, endurance, and the degree of dyspnea in COPD patients [87]. However, on the other hand, some researchers argue that although IMT seems beneficial for improving dyspnea, its efficacy seems less significant. In a single-blind randomized controlled trial, researchers found that combining 4 weeks of IMT with pulmonary rehabilitation significantly reduced dyspnea severity after the 6 min walk test in patients with severe and very severe COPD compared to the control group receiving only pulmonary rehabilitation, but there was no statistically significant difference between the two groups [88].

Asthma: A systematic review on the impact of respiratory muscle training on asthma suggests that IMT plans are effective interventions for improving inspiratory muscle strength in asthma patients and may positively affect exertional dyspnea [89].

PH: A meta-analysis suggests that based on the current limited evidence, IMT is an effective physical therapy for improving respiratory muscle function and exercise capacity in patients with PH, but its impact on dyspnea in PH patients is still lacking evidence [90].

Cancer: Current research consistently confirms the benefits of IMT in improving dyspnea. Sakai et al. [91] found that IMT significantly improved dyspnea symptoms in advanced lung cancer patients at rest and during exercise, with a higher adherence rate in the late-stage cancer patient population unable to undergo high-intensity exercise, indicating potential clinical significance.

Invasively mechanically ventilated: Bissett et al. [92] conducted a clinical randomized controlled trial to observe the improvement in dyspnea symptoms in mechanically ventilated patients after 48 h of weaning following 2 weeks of IMT. The results showed effective improvement in inspiratory strength in the training group, but there was no statistically significant difference in improving dyspnea compared to the control group.

In summary, IMT can improve the degree of dyspnea to some extent, providing more options for clinical treatment of dyspnea. However, more evidence is needed to prove its effectiveness, and whether it can be a promising intervention in the future remains uncertain. Further exploration is needed to investigate the impact of different IMT training protocols (frequency, intensity, and duration) on outcomes and to determine the extent to which IMT-related changes can translate into clinically significant improvements in adults with dyspnea.

Fan therapy

Fan therapy, also known as pan therapy, refers to a physical therapy method where air is blown onto the patient's face using a handheld or electric fan. Each treatment session typically lasts for 5 mins [93]. The mechanism by which fan therapy alleviates respiratory difficulties is not yet clear. It may be primarily related to the airflow's ability to cool and/or stimulate the skin and mucous membranes governed by the second and third branches of the trigeminal nerve, along with attention diversion and increased self-efficacy [94].

Terminal Cancer: Several research studies have confirmed the effectiveness of fan therapy in reducing dyspnea caused by various diseases, with significant short-term effects. It is advantageous due to its high safety, simplicity of operation, and cost-effectiveness, making it a viable option among non-pharmacological treatments [95, 96]. No adverse events or worsening of blood pressure, pulse rate, respiratory rate, or SpO_2 levels have been reported [97]. However, the current evidence level for this therapy is relatively low [98]. After three weeks of using a small fan at home to blow air onto their faces, there was no significant difference observed in dyspnea and physical activity levels (PAL) among subjects (outpatients with dyspnea caused by chronic respiratory failure) [99]. Future high-quality randomized controlled trials are needed to validate these results and explore the application of fan therapy in treating dyspnea in more diverse populations and settings.

In addition, there are other studies suggesting that Fan therapy is effective to reduce dyspnea in COPD, heart failure, and other types of lung diseases, but they are all observational and qualitative studies, and there are no prospective randomized controlled trials yet [100–102].

Exercise

COPD: Research results indicate that exercise training reduces the symptoms of dyspnea in COPD patients and may be related to a decrease in respiratory demand and enhanced symptom tolerance [103]. Studies have found that in moderate to severe COPD patients, especially males, respiratory muscle and limb muscle training can improve dyspnea during exercise and daily life [104]. Rehabilitation programs, include lower limb endurance training, reduce dyspnea, health-related quality of life (HRQoL), and exercise capacity in stable COPD patients [105]. However, there is currently no unified standard for the specific exercise regimen (such as type and intensity) [106]. Compared to aerobic exercise on land, aerobic exercise in water (including swimming, water aerobics, etc.) has a significantly additional effect on improving endurance in COPD patients [107]. Cooper et al. [108] found that exercise training reduced dyspnea in COPD patients during walking tests but did not benefit dyspnea during incremental exercise, suggesting that attention should be paid to the choice of exercise type when designing training programs for patients. Regarding whether patients should always receive exercise guidance, research by Carrieri-Kohlman et al. [109] found that guided exercise training was not more effective than standalone exercise training, providing a possibility for home-based rehabilitation for patients. Home-based pulmonary rehabilitation (HBPR) reduced the level of dyspnea, increased the distance covered in the six-minute walk test, improved HRQoL, and reduced the impact of the disease on COPD patients in home-based pulmonary rehabilitation [110]. However, for patients with severe dyspnea, more limiting factors should be considered when developing exercise plans. Patients with severe dyspnea may not tolerate high-intensity, continuous exercise, so respiratory support (such as mechanical ventilation, mixed gas supplementation, etc.) can be provided to patients during exercise, and intermittent exercise can be used instead of continuous exercise when necessary [111].

Idiopathic Pulmonary Fibrosis: Pulmonary rehabilitation aims to improve exercise capacity, dyspnea, and health-related quality of life in IPF patients. A multicenter randomized controlled trial study found that patients receiving rehabilitation therapy had better exercise capacity at follow-up than those receiving routine care, particularly in patients experiencing persistent dyspnea after pulmonary embolism [68]. Rehabilitation therapy is recommended for patients with exertional dyspnea, and further research is needed to demonstrate the long-term clinical benefits of palliative care for these individuals [112].

COVID-19: Pulmonary rehabilitation is safe and beneficial for improving respiratory difficulties, exercise capacity, lung function, and fatigue in both acute and chronic COVID-19 patients [113].

Obese: The official statement from the American Thoracic Society indicates that exercise (including aerobic and resistance exercise) as a major component of pulmonary rehabilitation can effectively improve patients' level of dyspnea [1]. Bernhardt et al. [114] confirmed that 120 min of aerobic exercise training per week effectively improved the exertional dyspnea of obese women. Clinical research results also showed that obese patients experienced a significant reduction in self-perceived dyspnea after subthreshold aerobic exercise [115].

Cancer: Koelwyn et al. [116] suggested that exercise therapy as a supplementary strategy has great potential in treating dyspnea in cancer patients.

In conclusion, when developing exercise plans for patients with dyspnea, the individual differences among patients should be fully considered to ensure the effectiveness and safety of the plans.

Chest wall vibration

Chest wall vibration refers to a non-pharmacological treatment method that involves using a vibrator to induce vibrations in the inspiratory or expiratory muscles, thereby achieving airway clearance or alleviating respiratory difficulties, changing with the patient's respiratory phase [117]. The reduce in dyspnea may be related to a reduction in respiratory effort, the stimulation of intercostal muscles by the vibrator, which may influence the higher brain centers, or the reflex inhibition of the brainstem respiratory output.

COPD: Relevant research evidence shows that in-phase chest wall vibration is beneficial for relieving resting dyspnea in patients with chronic respiratory system diseases and for COPD patients during constant load exercise below the anaerobic threshold [118]. However, the results of a single-blind randomized controlled clinical trial showed that continuous chest wall vibration on the basis of a standard pulmonary rehabilitation program did not affect the dyspnea of COPD patients [119]. Cristiano et al. [120] found that in-phase chest wall vibration reduce dyspnea in COPD patients in a hypercapnic state but was not beneficial during exercise. This suggests that chest wall vibration may be less effective in reducing dyspnea in COPD patients in certain situations. In a randomized, single-blind, placebo-controlled trial, continuous chest wall vibration, in addition to a standard pulmonary rehabilitation program, and simultaneous aerobic training, may improve functional exercise capacity but does not affect dyspnea, respiratory muscle function, or quality of life in COPD patients [119]. Therefore, the specific definition of the therapeutic window for chest wall vibration treatment requires further research to determine its applicability in a clinical setting.

Virtual reality technology

With the continuous advancement of science and technology in recent years, virtual reality (VR) technology has gradually been applied to neurological and musculoskeletal rehabilitation, providing patients with a realistic three-dimensional experience and creating a new therapeutic environment, thereby enhancing patient compliance to some extent.

COVID-19: Some current studies are attempting to use VR to reduce dyspnea symptoms in COVID-19 patients [121–123]. Stavrou et al. [121] found that COVID-19 patients who exercised using a VR system had lower dyspnea scores than the control group. A randomized double-blind trial suggested that VR can alleviate dyspnea, reduce fatigue, and anxiety in hospitalized COVID-19 patients [122]. In contrast, Rutkowski et al. [123] believe that although VR is attractive, its use in addition to a conventional rehabilitation program does not significantly affect dyspnea in COVID-19 patients.

ICU patients: Merliot-Gailhoustet et al. [124] found through a randomized controlled trial, that VR with computer-generated images was most effective in reducing physiological stress responses (dyspnea, pain, etc.) in non-delirious ICU patients.

Traditional Chinese medicine

Traditional Chinese Medicine have advantages such as fewer side effects and simplicity of operation. In addition, acupuncture produces therapeutic effects on dyspnea by promoting the release of endogenous opioid peptides and regulating the autonomic nervous system, amygdala, and hypothalamus-pituitary-adrenal axis [125]. In the treatment of dyspnea, acupuncture regulates the central response area, similar to the region affected by acupuncture analgesia. The results of a randomized controlled trial showed that traditional acupuncture significantly improved the subjective rating of dyspnea in patients compared to the control group, while the objective indicators of lung function in both groups remained unchanged [126].

COPD: On the other hand, research results show that acupressure can reduce sympathetic nerve stimulation, dyspnea, and anxiety symptoms in COPD patients, including those using mechanical ventilation for a long time [127, 128].

Asthma: Maa et al. [129] found that both acupuncture and acupressure are beneficial for dyspnea in patients with chronic obstructive asthma. More high-quality research is needed to explore the long-term benefits and potential risks of these methods.

Late-stage diseases: According to the ESMO Clinical Practice Guidelines, acupuncture and acupressure are beneficial in the short term for reducing dyspnea symptoms in cancer patients [130]. A meta-analysis confirmed that acupuncture significantly reduced the severity of dyspnea in the treatment of late-stage diseases [131]. However, in a single-blind randomized crossover study, standardized acupuncture techniques did not show specific effectiveness in relieving disabling dyspnea [132].

Yoga

Yoga, as an ancient practice of Hinduism, represents perfect control of the body, senses, and mind. Yoga includes breathing, relaxation, meditation, and posture exercises. As a mind-body therapy, yoga has gradually attracted the attention of researchers in complementary and alternative medicine [133].

COPD: The results of Özer et al.'s [134] study showed a significant reduction in the severity of dyspnea in chronic respiratory disease patients (mainly asthma and COPD patients) who participated in yoga training. Donesky-Cuenco et al. [135] confirmed that yoga can reduce the level of breathlessness during exercise in elderly COPD patients. A meta-analysis showed that breath-based yoga intervention has a positive effect on dyspnea in COPD patients [136].

Lung resection surgery: In addition, research results indicate that simple yoga breathing exercises can alleviate dyspnea in patients undergoing perioperative lung resection surgery, improving rehabilitation outcomes [133].

The above research results indicate that both simple yoga breathing training and multi-form yoga training, including breathing and posture exercises, have good therapeutic effects on patients with dyspnea and are worthy of promotion in clinical treatment.

Oxygen therapy supplemental

Oxygen is widely used to alleviate respiratory distress associated with hypoxemia; High-Flow Nasal Cannula (HFNC) is a high-flow oxygen therapy technique designed to provide warm, humidified, and high-concentration oxygen to patients. For patients experiencing respiratory distress and hypoxemia before hospitalization, the short-term benefits of HFNC are undeniable. HFNC is superior to Conventional Oxygen Therapy (COT) in reducing the risk of requiring advanced ventilation and experiencing respiratory distress. Even before a diagnosis of respiratory distress is confirmed, HFNC may be considered a frontline therapy [137].

AHF: In terms of treatment, controlling the underlying disease is undoubtedly crucial for symptom improvement. Currently, high-flow nasal cannula oxygen therapy is generally considered superior to traditional oxygen therapy, but its efficacy in reducing intubation rates for hypoxia and respiratory distress due to AHF is superior to non-invasive mechanical ventilation [138]. Non-invasive ventilation combined with Bi-level Positive Airway Pressure (BiPAP) is applied to heart failure patients and proves beneficial for their exercise tolerance and respiratory distress [139]. It is safe, well-tolerated by heart failure patients, and should be considered for inclusion in rehabilitation plans. For patients without hypoxemia, the precise role and effectiveness of supplemental oxygen in treating respiratory distress remain undetermined.

Advanced progressive diseases: A meta-analysis result does not support supplemental oxygen therapy for alleviating respiratory distress in patients with advanced progressive diseases, while controlling symptoms through medication, exercise, behavioral therapy, treating associated anxiety, and using fans may be more effective and cost-effective than oxygen therapy [140]. Another systematic review discovered that, compared to the control group, supplemental oxygen during exercise could improve respiratory distress in patients without resting hypoxemia [141].

Light therapy

Stellate ganglion irradiation can significantly alleviate dyspnea caused by external inspiratory loads in healthy adults. In some cases, stellate ganglion irradiation may be an option for treating dyspnea [142]. Further research is needed to study individuals with different types of dyspnea and clinical environments.

Multicomponent interventions

Late-Stage Cancer: As breathlessness experienced by loved ones at the end of life can be overwhelming and lead to clinically unjustifiable emergency hospitalizations, personalized palliative care is needed to reduce suffering or even panic, enabling continued home life – a practice model experts advocate for widespread adoption [143]. In terms of personalized treatment, the first step involves identifying potential reversible causes. Multicomponent interventions including behavioral and psychoeducational, activity and rehabilitation, and integrative medicine interventions, and were found to be associated with improved breathlessness compared with usual care or control interventions by a systematic review [144]. For patients with an expected lifespan of a few days, referral for palliative care and continuous palliative care are the ultimate measures to relieve symptoms and alleviate caregiver distress [42].

Table 1: Summary of prevalence of dyspnea in common diseases, description of dyspnea, and recommended nonpharmacological treatments.

Common disease	Incidence of dyspnea	Descriptors of breathlessness in Mahler et al.'s study [143]	Descriptors of breathlessness in Wilcock et al.'s study [6]	Non-pharmacological treatment recommended according to this review
Chronic obstructive pulmonary disease	50 %–91 %	My breathing requires effort. (51 %)	I cannot get enough air. (44 %)	Inspiratory muscle training, exercise, chest wall vibration, traditional Chinese medicine, yoga
Asthma	42 %	I cannot get enough air. (50 %)	My chest feels tight. (54 %)	Inspiratory muscle training, traditional Chinese medicine
Acute heart failure	Over 90 %	My breathing requires effort. (47 %)	I feel out of breath. (57 %)	Oxygen therapy supplemental
Idiopathic pulmonary fibrosis	90 %	I feel out of breath. (54 %)	I feel out of breath. (62 %)	Inspiratory muscle training, exercise
Late-stage cancer	58 %	/	I feel out of breath. (43 %)	Fan therapy, traditional Chinese medicine, oxygen therapy supplemental, palliative care

Conclusions

In conclusion, the study delves into the intricate facets of dyspnea, shedding light on its occurrence mechanisms, assessment methodologies, and the application of non-pharmacological treatments. Dyspnea, as a distressing symptom, arises from a complex interplay of physiological, psychological, and environmental factors, making its assessment and management a challenging yet crucial aspect of patient care. Assessment strategies encompass a spectrum from subjective self-reporting, capturing the patient's experience, to objective clinical measurements, providing a more comprehensive understanding of dyspnea's nuances. The various non-pharmacological interventions explored in this study present promising avenues for alleviating dyspnea symptoms, each with its unique mechanisms and benefits. Pulmonary rehabilitation, fan therapy, exercise, chest wall vibration, virtual reality technology, traditional Chinese medicine, and yoga offer diverse options catering to the individualized needs of patients (Table 1). Furthermore, oxygen therapy, notably through High-Flow Nasal Cannula (HFNC), emerges as a valuable short-term intervention for individuals facing pre-hospital respiratory distress and hypoxemia. However, the study underscores the need for further research to solidify the evidence supporting the efficacy of these interventions across diverse patient populations.

In summary, the multifaceted nature of dyspnea necessitates a holistic approach, combining subjective and objective assessments along with tailored non-pharmacological interventions. This comprehensive understanding of dyspnea's occurrence and management contributes to improved patient outcomes and enhanced quality of life. The exploration of non-pharmacological treatments opens avenues for personalized and effective strategies in the care of individuals experiencing dyspnea across various medical conditions.

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