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Series on Dyspnea. Part 1. Definitions, Mechanisms and Historical Perspective

Series en disnea. Parte 1. Definiciones, mecanismos y perspectiva histórica

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ABSTRACT

This article is the first in a series dedicated to that strange phenomenon of life caught halfway between consciousness and unconsciousness: dyspnea. The article provides information on the definitions of dyspnea over time and presents the evolution of ideas that led to the understanding of its mechanisms. The relevance of each of these mechanisms must be evaluated in the context of each specific clinical and pathophysiological situation. The experience of dyspnea begins to be seen as a *multidimensional phenomenon* that must be focused on what the patient perceives. Considering the complexity of the experience and its multiple dimensions, it is possible for new therapeutic options to be developed in future times.

Key words: Dyspnea; Respiratory Distress Syndrome; Definitions; Physiology; Physiopathology

RESUMEN

Este artículo es el primero de una serie dedicada a ese extraño fenómeno de la vida atrapado a medio camino entre lo consciente y lo inconsciente: la disnea. El artículo proporciona información sobre las definiciones a lo largo del tiempo y presenta la evolución de las ideas que hicieron a la comprensión de sus mecanismos. La relevancia de cada uno de ellos debe evaluarse en el contexto de cada situación clínica y fisiopatológica específica. La experiencia de la disnea comienza a ser vista como un *fenómeno multidimensional* que debe estar centrado en lo que percibe el paciente. Considerando la complejidad de la experiencia y su multidimensión, es posible que se desarrollen nuevas opciones terapéuticas en tiempos venideros.

Palabras clave: Síndrome de Dificultad Respiratoria; Disnea; Definición; Fisiología; Fisiopatología

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INTRODUCTION

The survival of our ancestors required strenuous physical activity. The respiratory discomfort experienced during that activity surely generated concern, but if it occurred at rest, the distress, fear, and uncertainty could have been unbearable. Due to his lack of understanding, the primitive man sought relief the best way he could, and attributed his symptoms to supernatural forces. Today we understand that, both yesterday and today, dyspnea is a primary experience associated with behaviors aimed at countering a threat to survival.

Undoubtedly, respiratory discomfort is one of the most distressing and frightening symptoms perceived by humans,[1] not only for those who suffer from it but also for their caregivers. Dyspnea is a symptom that can occur in very different respiratory and cardiovascular conditions, as well as in cancer, anemia, anxiety, and psychosomatic disorders, during exercise, or during respiratory loads in normal subjects.[2] This entity should be considered independently from other respiratory variables and physical sensations such as tachypnea, use of accessory muscles, hyperventilation or hyperpnea, and is different from the sensation of bodily effort and general fatigue or asthenia.

Physical activity, anxiety levels, onset speed, and experience can influence the perception and intensity of dyspnea.[3] Its prevalence varies according to the type of disorder and the progression stage. In the early stages of certain diseases, it may be circumstantial, reversible, and self-limiting, but it can become very difficult to alleviate as the disease progresses and, despite the best medical care, when it is difficult to control, it can deteriorate the quality of life of the patient and his/her close environment. Dyspnea is an independent predictor of mortality and is more related to quality of life than to lung function tests.[3, 4]

The possibility of improving the quality of care for patients with dyspnea depends on our ability to define the mechanisms involved, to break down all communication barriers between us and the patient, and to understand that dyspnea (similarly to pain) has physical, psychological, social, cultural, and spiritual components.[3]

Using the key word "dyspnea", the PubMed® database as of March 2022 yields just over 65,000 quotations.[5] There has been an increase in the number of publications since 1963, when *Grupo Campbell* proposed the lack of adjustment between tension and length as a central cause in its generation.[6, 7] Their highly influential work will be analyzed in the second part of this series.

This article provides information on the definitions and mechanisms of dyspnea from a historical perspective, and highlights the areas of interest for future research. While the earliest references to dyspnea date back to Hippocrates (406-360 BC), the history of the evolution of ideas about its mechanisms dates back to about 120 years.

Evolution of the definition of dyspnea

Most people have experienced shortness of breath and intuitively know what the term means, however, since the times of Cockroft and Guz, the need for an operational definition that allows for its quantification and the performance of experimental studies became evident. The semantics of breathlessness generated confusion. The terms "dyspnea" (dyspnoea in UK), breathlessness, and shortness of breath are often interchangeable. The expression "breathlessness", easily understandable for patients, is frequently used by them and their environment.[8]

History of the definitions of dyspnea and its components

In 1923, Jonathan Meakins defined dyspnea as the awareness of the need to increase the respiratory effort.[9] By the 1960s, Julius Comroe, in his legendary book, used the word dyspnea to connote a symptom, a sensory experience that, like pain, can only be perceived and judged by the patient.[10] In 1971, in the classic book by Bates, Macklem, and Christie, the authors defined dyspnea as the awareness of the respiratory effort.[8, 11] In the 1980s, Burky defined it as a pathological shortness of breath, as opposed to the shortness of breath that appears in situations where such difficulty could be expected, such as during exercise.[12] Campbell and Guz[13] defined dyspnea as a common sensation of uncomfortable breathing, whereas Killian and Jones[14] characterized it as the awareness of the motor effector command to the inspiratory muscles and later as a quantitative sensation without a threshold of the required motor effort of the respiratory muscles.[15] In the 1990s, Malher defined it as a medical term used to characterize a nonspecific sensation of shortness of breath.[16] More recently, Killian specified dyspnea as a term commonly used

to represent discomfort experienced in association with the act of breathing.[17]

There is general agreement that the discomfort of dyspnea comprises two main elements:

– An urge to breathe, commonly referred to as "air hunger".
– A sensation of excessive effort (inspiratory effort sensation) associated with breathing.[18]

Although the sensations of air hunger and effort usually increase together, they can be experimentally separated. Dyspnea in an individual patient can represent a combination of these sensations and can explain the different qualities (descriptors) of dyspnea.

Unlike localized sensations, such as touch and temperature, which mostly arise from the stimulation of a defined peripheral receptor, dyspnea is a vague visceral sensation, analogous to thirst or hunger. In addition, the different sensations of dyspnea do not usually occur in isolation. The sensation of dyspnea can vary both in the degree of discomfort and in its emotional and behavioral significance.[19, 20]

Pathological or physiological dyspnea?

It has been suggested that there is no accurate boundary between the "pathological" shortness of breath of the disease and the "physiological" dyspnea in normal individuals during intense exercise. Many patients report that the dyspnea they have now is qualitatively similar to the one they experienced during intense exercise, but now it occurs with light physical activity or even at rest.[21]

If we define dyspnea as the awareness of labored breathing or as air hunger, it implies an underlying pathological process. That is to say, the sensation must be experienced in association with a physical activity that should not be generating respiratory discomfort based on the individual's experience. However, it has been demonstrated that normal subjects have unpleasant respiratory sensations with exercise that can limit their performance and can be considered as dyspnea.

The emotional component of the sensory experience may vary if the dyspnea occurs *unexpectedly*, but whether the quality of the sensation is different or not, that is not so evident. A sound of 200 decibels will be bothersome whether or not the subject is expecting the sound, and most of us experience dyspnea when climbing 10 flights of stairs even when we expect to have shortness of breath.

Should this sensation be ignored or called something else simply because the individual has normal lungs and a normal cardiovascular system, and especially because the difficulty is expected for that physical activity?[22] The concept of a sensation that is *unexpected or inappropriate* for physical activity is not reasonable: *dyspnea is a primary experience associated with behaviors aimed at countering a threat to survival*.

General consensus of the definition of dyspnea

Trials of different definitions of dyspnea have resulted from advances in the knowledge of its mechanisms and multifactorial nature, leading to a consensus definition proposed by the American Thoracic Society (ATS) some years ago.[23]

"Term used to characterize a subjective experience of shortness of breath that consists of qualitatively different sensations that vary in intensity. The experience stems from interactions among multiple physiological, psychological, social, and environmental factors, and can induce secondary physiological and behavioral responses".

There are several aspects to highlight in this definition:

– The experience is *subjective* (only the patient can say he/she is experiencing dyspnea).
– Different *qualities* of sensations can be identified (expressed through a variety of descriptors).
– The *intensity* can vary (and can be evaluated using various scales).
– The emotional state, personality, experience, and cognitive function of an individual, as well as social factors, influence the experience and the way the patient reports such experience.

The last part of the definition is often not given enough consideration. However, the sensation of dyspnea has a psychological dimension, just like pain. It is widely recognized in clinical practice that anxiety and depression can increase the intensity of dyspnea beyond the alteration of the cardiopulmonary function and can contribute to the degree of disability associated with dyspnea.

The 2012 ATS Consensus Statement proposed that "*instruments or groups of instruments related to dyspnea should be classified as addressing the domains of sensory-perceptual experience, emotional distress, or symptom/disease impact and burden*."[19]

Sensory-perceptual measures include determination of *intensity* (real-time measures of dyspnea) and sensory *quality*. Emotional distress can refer

to both a perception of immediate unpleasantness as well as a cognitive evaluative response or judgment about the possible consequences of what is being perceived (e.g., "if this continues, I may suffocate"). Measures that evaluate the impact of dyspnea do not directly assess what breathing feels like.[19]

The ATS Consensus was categorical: any evaluation of dyspnea should attempt to measure both the *intensity* and *quality* of the sensation of respiratory discomfort, as well as the *emotional and behavioral response* to respiratory discomfort.[19,24] Therefore, dyspnea represents the sum of pathophysiological and psychological factors that together result in one of the most common symptoms for which patients seek medical assistance.

The therapeutic implication of this ATS definition recognizes and provides evidence that strategies to modulate the dyspnea symptom may involve other dimensions of the experience beyond the physiological domain. These are the cognitive, sensory, emotional, and behavioral dimensions.

Mechanisms of dyspnea, a historical perspective

Given the fact that dyspnea is a perception, studies on its mechanisms must be limited to human beings and are restricted by the difficulty of measuring a subjective experience to underlying neuronal activity. However, for the past two decades, there has been better understanding of the differences between the respiratory *sensation* (the neural activation resulting from the stimulation of a peripheral receptor) and *perception* (the individual's sensitive reaction to that sensation).

The pathways involved in the generation of conscious sensations are shown in Figure 1. The upper sequence outlines the neurophysiological pathway from stimulus to sensory impression, while the lower sequence allows for modulation of the intensity and quality of symptom perception and is unique to each individual.

The best understanding of the mechanisms of dyspnea is intimately related to knowledge in breathing control. In 1905, the ground-breaking work of Haldane concluded that CO_2, acting exclusively on the brain, was the dominant chemoreflex stimulus, and that hypoxia stimulates breathing by acidifying the brain. This was the vision during the first quarter of the 20th century, but in 1920, two key observations indicated that this scenario was incorrect. First, it was found that arterial pH does not decrease, but rather increases during hypoxia, indicating that something other than a hydrogen ion was driving the ventilatory response to hypoxia. It was also shown that during a voluntary suspension of respiratory movements, the respiratory oscillator in the brainstem stops, refuting the original concept that corticospinal projections were the dominant pathway by which the cortex influenced breathing. This established the importance of supratentorial influence on humans in breathing control.[25,26] The interaction of chemical stimuli and respiratory sensations was subsequently confirmed by Fowler and Remmers.[27,28] Despite that breakthrough, it was during the second half of the 20th century that the relationship between the control of ventilation and dyspnea began to be understood.[19,26,29-31]

Table 1 shows the evolution of ideas that led to the understanding of the mechanisms that generate dyspnea. The more recent ones do not necessarily discard the previous ones. Due to its complexity, the relevance of each mechanism

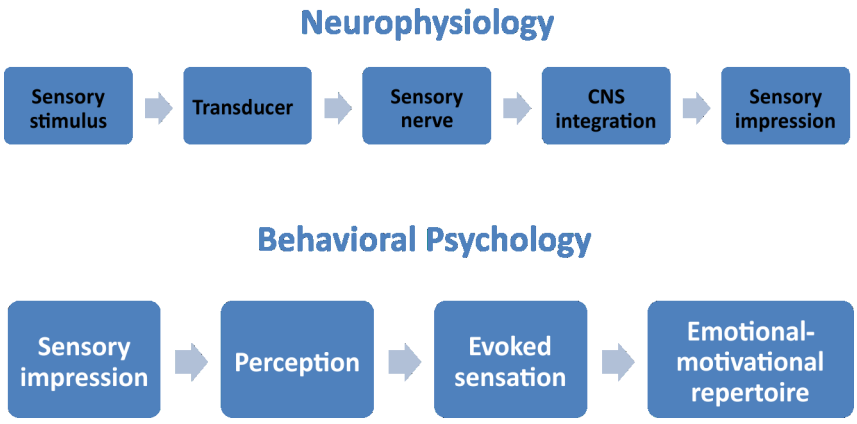

Figure 1. Sequential units used in the generation of conscious sensations.

TABLE 1. Guide to the timeline of topics addressed throughout the 20th and 21st centuries to understand dyspnea

Period	Most important topics under evaluation
1868-1923	Chemical control of breathing
1931-1938	Neural reflexes
1924-1954	Breathing mechanics
1954-1960	Cost of breathing oxygen
1962-1966	Inadequacy between tension and length
1978-2000	Corollary discharge or efference copy
1981-1995	Psychophysics of dyspnea
1990-2010	The language of dyspnea. Descriptors
1995-2005	Quality of life
2001-2012	Cortical substrate for the perception of dyspnea
2007-2022	Multidimensional approach of dyspnea

should be evaluated in the context of each specific clinical and pathophysiological situation. The time periods for each of the aspects under evaluation should be used for guidance purposes.

After almost 120 years, psychometric measurements and descriptors of dyspnea have been added to traditional pathophysiological hypotheses. In the last 30 years, certain neurophysiological aspects (efference copy-corollary discharge) have been refined. Only at the end of the 20th century did interest arise in the quality of life and suffering in the experience of dyspnea.[32,33] In the 21st century, brain areas that perceive dyspnea have begun to be identified, a modern analogue of Wilder Penfield's homunculus. The experience of dyspnea is beginning to be seen as a *multidimensional phenomenon* that must be centered on what the patient feels.

Integrated analysis of the dyspnea mechanisms

Although the precise mechanisms of dyspnea are not fully understood, it is possible to build a *neurobiological model* to describe our current understanding of the perception of dyspnea in parallel with breathing control (Figure 2). The simplified neurophysiological model describes both the control of breathing that regulates ventilation and the perception of dyspnea. With the activation of one or more sensory receptors (chemoreceptors, mechanoreceptors, and those located in respiratory muscles/chest wall), afferent impulses are transmitted to the central nervous system (CNS; brainstem, limbic system, and cerebral cortex) for integration and processing of information. Discriminative and affective pathways have been proposed. The CNS directs an outgoing motor command through the phrenic nerves to the respiratory muscles.

The different receptors inform the CNS to integrate the information. Dyspnea results in various elements (sensory, emotional, impact on daily activities).

CONCLUSIONS

In this first part, we have analyzed the evolution of the definitions of dyspnea and its mechanisms. Technological breakthrough has undoubtedly allowed for the exploration of mechanisms that were once inaccessible, and as in many other fields, the 20th century allowed us to ask questions and answer them like never before. It is noteworthy that after almost 90 years of studying dyspnea it was at the end of the 20th century that we started to consider that it could deteriorate the quality of life and could be measurable. At the beginning of the 21st century, dyspnea began to be seen as a *multidimensional phenomenon* that should be centered on what the patient perceives. The experience of dyspnea involves both *sensory* components (intensity and quality) and *emotional* components (discomfort, distress) that generally impact or impose a burden on an individual's ability to perform daily activities and on his/her *quality of life*.

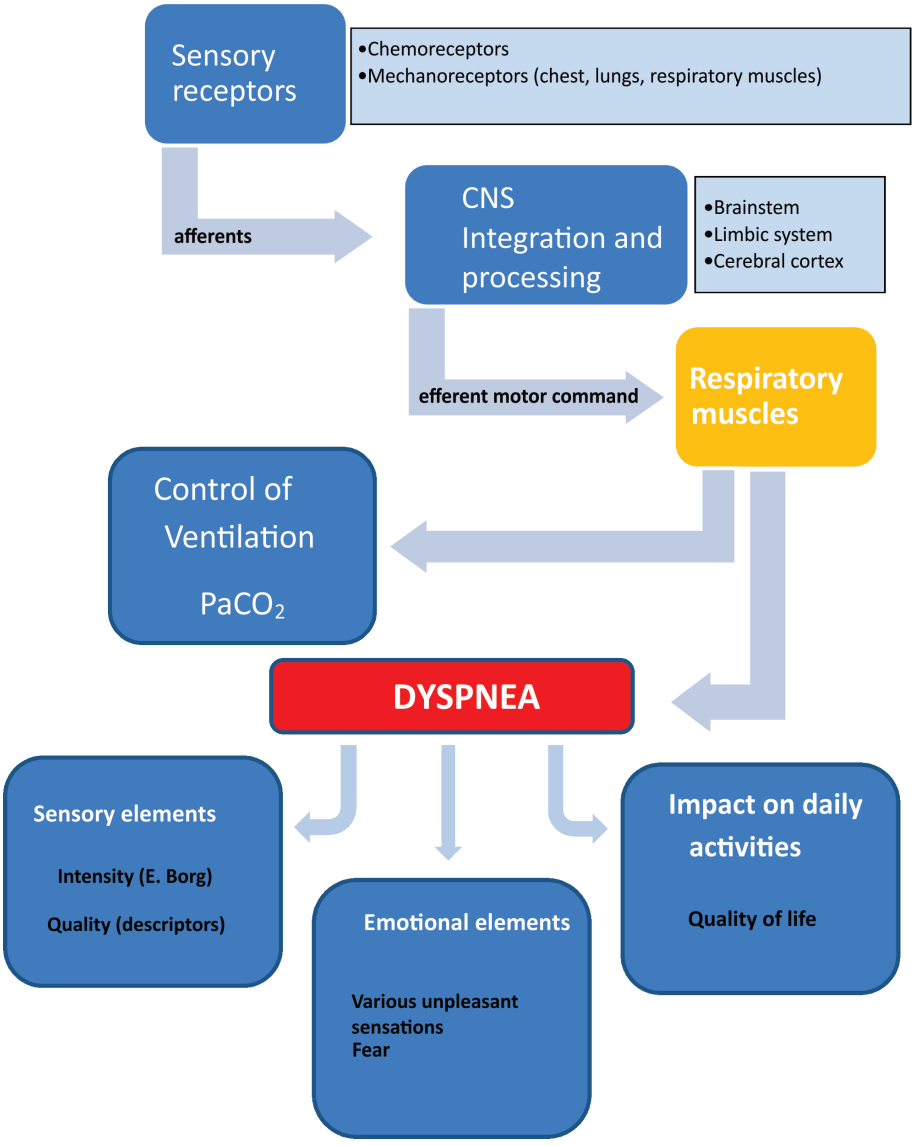

Figure 2. Simplified neurophysiological model: it describes the control of breathing regulating both ventilation and perception of dyspnea.

Considering the complexity of the dyspnea experience and its multiple dimensions, it is possible that new therapeutic options develop in the future. Making reference to Table 1, in the second part of this series we will detail the dyspnea production mechanisms.

Key points

- Without a doubt, the discomfort experienced in relation to the act of breathing - dyspnea - is one of the most distressing and frightening symptoms perceived by humans, and only the patient can report it.
- Dyspnea should not be ignored in individuals with normal lungs and a normal cardiovascular system only because the difficulty is the one expected for physical activity. We think the concepts unexpected or inappropriate sensation or physiological dyspnea aren't reasonable.
- We understand that dyspnea is a primary experience associated with behaviors intended to counteract a threat to survival.

- It is possible to identify different qualities of sensations; the intensity may vary, and an individual's emotional state, personality, experience, cognitive function, as well as social factors can influence the experience of dyspnea and the way the patient describes it.
- Therefore, any assessment of dyspnea should attempt to measure the intensity and quality of the respiratory discomfort sensation and the emotional and behavioral response to that respiratory discomfort.
- The possibility of improving the management of patients with dyspnea depends on our ability to define the mechanisms involved, break down all communication barriers between us and the patient, and understand that dyspnea (similarly to pain) has physical, psychological, social, cultural, and spiritual components.
- The experience of dyspnea is starting to be seen as a multidimensional phenomenon that should be centered on what the patient perceives.

Conflict of interest
The author has no conflict of interest to declare.

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