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Series on dyspnea. Part 2. Analysis of its mechanisms as the years go by

Series en disnea. Parte 2. Análisis de sus mecanismos según pasan los años

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ABSTRACT

This article is devoted to a detailed analysis of the mechanisms of dyspnea. Chemical control of breathing, neural reflexes, breathing mechanics, the cost of oxygen to breathe, and the mismatch between tension and muscle fiber length will be discussed. In general, the different explanations were associated with the development of devices and study methodologies in pulmonary laboratories. All the theories had defenders and detractors and, interestingly, with the development of sophisticated neurophysiological techniques and functional imaging, it has been possible to prioritize each of the mechanisms. All have survived the passage of time and none can singularly explain dyspnea in all clinical situations, showing the complex and multifactorial nature of the phenomenon.

Key words: Dyspnea; Physiology; Physiopathology; Breathing mechanics

RESUMEN

Este artículo está dedicado al análisis detallado de los mecanismos de disnea. Se tratarán el control químico de la respiración, los reflejos neurales, la mecánica respiratoria, el costo de oxígeno para respirar y la inadecuación entre tensión y longitud de la fibra muscular. En general, las diferentes explicaciones estuvieron asociadas al desarrollo de aparatos y metodologías de estudio de los laboratorios pulmonares. Todas las teorías tuvieron defensores y detractores e, interesantemente, con el desarrollo de sofisticadas técnicas neurofisiológicas y de imágenes funcionales ha sido posible jerarquizar cada uno de los mecanismos. Todas han sobrevivido al paso del tiempo y ninguna puede explicar de manera unicista la disnea en todas las situaciones clínicas, lo cual habla de la naturaleza compleja y multifactorial del fenómeno.

Palabras clave: Disnea; Fisiología; Fisiopatología; Mecánica respiratoria

INTRODUCTION

The first part of this series analyzes the evolution of the definitions of the term "dyspnea" and the proposed mechanisms for its generation. It was also mentioned that the experience of dyspnea is beginning to be seen as a **multidimensional phenomenon** that should be centered on what the patient feels. This fact cannot be overlooked, not even in the presence of the exciting complex-

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ity of the physiopathological mechanisms we will analyze.

The physiopathological mechanisms that explain dyspnea, unlike pain, are complex and can coexist; but depending on the clinical condition, some may be more relevant than others. However, there are common denominators, and there is one dyspnea-producing mechanism that is accepted as predominant. The experience of dyspnea involves both **sensory** components (intensity and quality) and **affective** components (discomfort, distress) that generally impact or impose a burden on an individual's ability to perform activities of daily living (**quality of life**).[1]

DYSPNEA AND CHEMICAL CONTROL (HYPOXEMIA, HYPERCAPNIA, ACIDOSIS)

In 1868, Pfluger observed that hypoxemia and hypercapnia produced dyspnea, but considered hypoxemia to be of greater importance. Eight years later, Haldane and Smith found that while breathing in a closed circuit with increasing levels of CO_2 up to 3% (23 mmHg), the individuals experienced dyspnea, but not until the O_2 concentration had dropped to 14%. In 1910, Winterstein introduced the concept of the H^+ ion as a stimulant of ventilation and a producer of dyspnea.[2]

These experiments were revisited in light of the possibility of more reliable gasometric determinations.[3] The concept of the H^+ ion as a stimulant was retained, but something that now seems quite obvious was defined: dyspnea is very intense with hypercapnic hypoxia, less intense with hypercapnia and hyperoxia, and moderate with hypocapnic hypoxia.[3]

This period finished with Jonathan Meakins' article in 1923 where he stated that "dyspnea is usually produced by two causes: the need for oxygen and the retention of carbon dioxide, relative or absolute".[3] Meakins' description deserves to be reproduced: "The use of oxygen, of course, does not eliminate the need to adopt all other means to treat heart failure, and by no means are physical and mental rest less important [...]. It is remarkable how patients improve with good nursing care and general comfort". It is appealing to speculate that with these words, Meakins anticipated the multidimensional concept of dyspnea by several decades.

This conceptual framework by Meakins justified certain clinical observations regarding the acute effects of inhaling CO_2 in normal subjects or patients:

1. Healthy individuals engaged in physical activity are capable of identifying hypercapnia due to CO_2 inhalation if they are instructed how to maintain ventilation proportional to their physical activity (the addition of hypercapnia to exercise would increase ventilation, and not doing so would lead to more dyspnea).
2. Various studies showed that patients with chronic poliomyelitis and respiratory failure reported ventilatory discomfort when the PCO_2 increased by about 10-20 mmHg.
3. Patients with high cervical spinal cord injuries who were chronically ventilated were able to detect increases in PCO_2 with a sensation described as "air hunger."

However, in patients with chronic obstructive pulmonary disease (COPD) or neuromuscular disorders (NMDs) with chronic CO_2 retention, it wasn't clear to what extent hypercapnia was related to dyspnea:

1. Patients with COPD or NMDs and chronic hypercapnia may experience little dyspnea at rest.
2. In other clinical conditions (such as bronchial asthma), dyspnea can be present with eucapnia or even hypocapnia.
3. Similarly, there are many patients with hypoxemia who do not experience dyspnea, and vice versa. Furthermore, some patients show slight improvement when oxygen administration corrects hypoxemia.

Clearly, there were many aspects to clarify during those times, and it wasn't until the early 21st century that it was understood that if the information from chemoreceptors (hypoxia) and mechanoreceptors indicates inability to adequately respond to the efferent impulse to the respiratory muscles, dyspnea is produced. Indirect evidence suggests that hypoxia leads to dyspnea through corollary discharge to higher centers, if ventilation and PCO_2 are limited to normal levels.[4, 5]

DYSPNEA AND REFLEXES (INTRAVASCULAR AND MUSCULAR RECEPTORS, VAGUS NERVE)

In 1931, basing on clinical observations, Cullen et al questioned the explanation that blood chemical changes were the cause of dyspnea. It was already evident that dyspnea often had little or nothing to do with impaired gas exchange. Arterial blood gases could be completely normal and have at the same time considerable dyspnea. These queries led to the search for new mechanisms. This was the onset of the neural reflex era.[6]

In 1932, Harrison et al demonstrated that breathing is stimulated by reflexes mediated by the vagus nerve, originating from the large central vessels (due to increased pressure from heart failure) and from muscular movements.[7]

Years later, in 1935, the studies conducted by Gessel and Moyer defined the role of reflexes in the control of ventilation and dyspnea.[8] It was considered that the effects of various combinations of afferent impulses (physical and chemical) could largely lead to the rhythmic discharge of respiratory centers originating from reflex mechanisms. However, on the other hand, the existence of an automatic discharge center under the influence of chemical and physical changes of nerve impulses wasn't ruled out.[9]

In 1938, Christie[2] summarized the knowledge of this period by stating the following: "although the conditions under which dyspnea occurs are diverse, giving the impression of being complex, the main causes are few and relatively simple. They consist of chemical and reflex disturbances. Chemical disturbances appear to be the least important. Dyspnea is usually of reflex origin". This was undoubtedly a reckless attempt to simplify the issue.

DYSPNEA AND BREATHING MECHANICS

At the beginning of this period, the relationship between relative ventilation and ventilatory capacity and its connection with dyspnea were recognized.[8] If ventilation is expressed as a percentage of the maximum ventilatory capacity (MVC), ventilation should reflect the intensity of effort and of dyspnea. Decades later, the ventilatory index (VE/MVC) would become a synonym of dyspnea.[10]

In 1946, Rahn and Otis were able to measure the impedance and forces involved in the act of breathing in healthy subjects.[10, 11] Their article has been significant in understanding the breathing mechanics. Patients with heart failure or emphysema had 2 to 4 times greater respiratory work than controls. In 1954, Marshall et al suggested that dyspnea in patients with mitral stenosis and emphysema was related to transpulmonary pressure rather than respiratory work.[12]

In his classic experiment of 1954, Fowler demonstrated that the discomfort associated with voluntary apnea could be relieved if the subject was allowed to take a few breaths from a bag containing gases with the same composition as alveolar air. Surprisingly, even though the levels of hypoxia and hypercapnia wouldn't change, the maneuver allowed the apnea to be maintained for an additional period of time[13] (Figure 1). The implication of this study was that chemoreceptor activity (hypoxia and hypercapnia) didn't seem to be the direct source of the sensation that compelled the end of the apnea. Other observations in line with this idea:

1. Hypercapnia produced by adding CO_2 to inspired air causes less dyspnea if the respiratory pattern consists of large thoracic movements.
2. Conversely, dyspnea increases if thoracic movements are voluntarily restricted below those corresponding to a free pattern.

An interesting observation made by Fowler[13] in his study was that "towards the end of voluntary apnea, strong involuntary contractions of the respiratory muscles occur, and a significant voluntary effort is required to prolong the apnea. The subjective relief occurs immediately upon breaking the apnea, though less strongly after the second and third periods of voluntary apnea".

These observations led to the understanding that the **dissociation** between the chemical drive to breathe and the absence of thoracic movements during voluntary apnea intensifies the sensation of dyspnea. During this period, it wasn't possible to reach a consensus on the most relevant mechanical factor causing dyspnea, but the concept that breathing mechanics are important in the sensation of dyspnea is now widely accepted.

DYSPNEA AND OXYGEN COST OF BREATHING

Due to the ease of obtaining reliable and relatively quick measurements of oxygen consumption (VO_2), the focus shifted to understanding the relationship

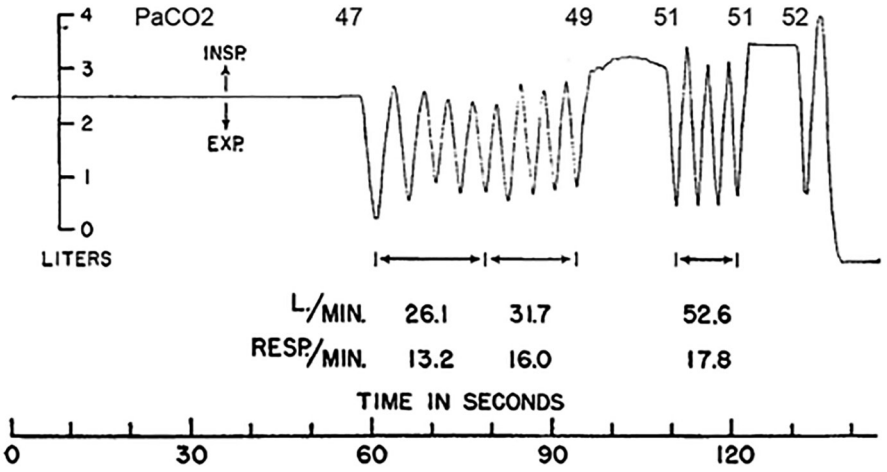

Figure 1. Ventilatory recording of successive periods of voluntary inspiratory apnea while inhaling a mixture of 8.2% O_2 and 7.5% (57 mmHg) CO_2. The relief of dyspnea was immediate after breaking the apnea, despite the fact that no changes occurred in the gases (adapted from Fowler[13]).

between dyspnea and the oxygen cost of breathing (VO_{2resp}).

VO_{2resp}, which represents the oxygen consumed by the respiratory muscles (and other movements associated with breathing), serves as an index of the energy required for ventilation. Therefore, it was initially determined that VO_{2resp} increases when ventilation and impedance to the action of respiratory muscles increase.[8, 14] In fact, since the diaphragm and most likely other respiratory muscles obtain their energy almost totally through oxidative metabolism across a wide range of respiratory work, changes in their energy requirements can closely approximate the total VO_2.[15]

In 1958, Mc Ilroy concluded this first stage by stating: "All conditions in which dyspnea occurs, except respiratory paralysis, share two common features: 1) a reduction in maximum oxygen uptake; and/or 2) an increase in VO_{2resp} […]. VO_{2resp} can increase due to abnormal lung or chest compliance or resistance, or due to abnormally high ventilation during exercise […]. Dyspnea may result from inadequate supply of oxygenated blood to the respiratory muscles".[16]

During this stage, the relationship between dyspnea and VO_{2resp}, was developed, but it wasn't possible to conduct an isolated analysis of these variables.[17] Recognizing this fact led to the current concept that the analysis should consider measurements of events related to metabolism, circulation, and breathing, along with associated sensory events.[18] This new approach was shaped by the works of O'Donnell, Mahler, Killian, Jones, and others.[2, 18-20]

DYSPNEA AND INADEQUACY BETWEEN TENSION AND LENGTH

The effort of respiratory muscles and the magnitude of ventilation required for common tasks like walking and climbing stairs give rise to sensations that are recognized as adequate. It's possible to accurately classify the magnitude of tidal volume (VT), flow rate, respiratory pressure, added resistance, or elasticity. However, one rarely becomes conscious of breathing until changes in the interplay of effort, tension, length, and speed lead to the conscious sensation of **inadequacy**.[10]

The foundations of this hypothesis were present since Fowler's time, but it was Campbell and Howell who suggested that "an imbalance in the relationship between tension and displacement of respiratory muscles could be the central mechanism for developing dyspnea".[21] According to this hypothesis, dyspnea occurs when there is **imbalance** between the **planned** change in length and the **achieved** length. In other words, dyspnea arises when the **achieved** displacement is less than the **expected** displacement.[21-23]

As will be seen later, this theory has been refined since then in order to include the general concept

of a mismatch between outgoing motor signals (efferents) to the respiratory muscles and incoming information (afferent). The conscious recognition of inadequacy is omnipresent across all sensory systems.[10] For this reason, there are certain clinical observations that are worth highlighting:

1. The sensation of dyspnea in normal subjects can be evoked by breathing through a narrow tube or attempting deep breaths while someone applies pressure to the abdomen. In other words, an attempt is made to move the chest and lungs, but there is an obstruction preventing the respiratory muscles from shortening to achieve the expected displacement.
2. The concept of inadequacy seems to hold true even in the absence of mechanical load. When the respiratory centers in the central nervous system are stimulated, increasing the drive to breathe, dyspnea appears to worsen when chest wall movement is reduced. This suggests that the lack of correspondence between efferent signals originating from the brain and afferent signals returning from the chest wall results in a sensation of breathlessness.
3. The immediate relief of dyspnea that allows for chest movements after breaking voluntary apnea,13 without improving the blood gas status, is also consistent with the concept of inadequacy or dissociation.

Which are the receptors for this inadequacy? Although by the end of the 19th century it was recognized that Golgi tendon organs mediated the sensation of tension, while joint receptors did so for displacement (position and movement), muscle spindles were not acknowledged as mediators of the sensation of displacement until the 1960s.[12] These are abundant in the intercostal muscles, and their afferent projections form spinal and supraspinal reflexes. The diaphragm contains tendon organs that detect tension and exert inhibitory influences on central respiratory activity.[24] This finding allowed for the refinement of the inadequacy theory by appealing to the gamma system (intrafusal fibers).[10] **If the shortening program is not fulfilled (inadequacy), this information reaches sensory areas and dyspnea appears.**

The concept of mismatch between tension and length, along with all its derivations, stood the test of time. It also allowed for the explanation of dyspnea caused by momentary suppression of breathing during speech and swallowing, as well as the discomfort caused by inadequate patient-respirator interaction.[25] Its foundation would be further supported in the coming decades with the introduction of the concept of "efferent copy" or "corollary discharge," along with brain mapping through functional neuroimaging.

DYSPNEA IN DIFFERENT DISEASES AND CONDITIONS

The mechanisms of dyspnea have been extensively studied in chronic obstructive pulmonary disease (COPD).[19, 21-23, 26, 28] Regarding the limits of tolerance, patients with moderate to severe disease consistently report that the intensity of respiratory discomfort is severe and that **each inhalation feels unrewarded (unsatisfied inspiration).**[2] Neurophysiological constructs invoking a demand-capacity imbalance or a neuromechanical dissociation provide a reasonable theoretical basis for this dominant qualitative descriptor of effort-related dyspnea in COPD.

As the severity of COPD increases, there is a progressive decrease in the resting inspiratory capacity (IC) as a result of lung hyperinflation. During exercise, ventilation increases in response to higher metabolic demand, but the baseline state of hyperinflation limits the increase in tidal volume. Respiratory rate increases to attempt to maintain the VE, but this results in a shorter expiratory time and thus greater hyperinflation, further limiting the VE (Figure 2).

Dyspnea occurs as a consequence of neuromechanical uncoupling (high ventilatory drive with low effective ventilation) and the stimulation of stretch receptors in the lung parenchyma and chest wall due to hyperinflation. In patients with lower resting IC, the mechanical limit can be reached earlier, and dyspnea becomes intolerable at the start of exercise. The corollary is that even small increases in resting IC following an intervention such as bronchodilator therapy or surgical/endoscopic volume reduction procedures delay the onset of critical neuromechanical uncoupling and the resulting intolerable dyspnea.[2, 28, 29]

In response to increased metabolic demand, ventilation increases through an increase in VT at the expense of the inspiratory reserve volume (IRV) (to a greater extent) and expiratory reserve volume (ERV). When VT reaches significant

values (usually around 60% of the forced vital capacity, FVC), further increases in ventilation occur through an elevated respiratory rate (RR). In COPD patients, the basal IRV is reduced due to air trapping, which limits the ability to increase VT. This is compensated by a significant increase in RR, resulting in shorter expiratory time and more air trapping.

In patients with thoracic restrictive disease, a higher elasticity of the thoracic-pulmonary system limits the increase in VT. Ventilatory increase is primarily achieved through an elevated RR.

Panel A of Figure 3 illustrates the relationship between dyspnea and incremental exercise ventilation in COPD patients, grouped into four severity levels (Q1 to Q4) based on FEV_1 values. It can be observed that similar ventilation levels produce more dyspnea as COPD worsens (based on FEV_1). However, when the VT is normalized (panel B) according to the IC (VT/IC%), there is a turning point (70%-80%) common to all severity levels, beyond which dyspnea notably increases.[30]

In **bronchial asthma**, various factors influencing dyspnea have been identified, such as the rate of airway obstruction development, use of medication, psychological profile, and the level of severity. But, differences in the intensity and quality of the symptoms, both intra-individual and inter-individual, can be largely attributed to dynamic lung hyperinflation and its mechanical consequences, including inspiratory threshold loading, reduced dynamic compliance and IC, muscle weakness, and critical mechanical limitations in chest expansion, all leading to the resulting neuromechanical dissociation of the ventilatory system.

The mechanisms underlying dyspnea in **interstitial lung disease** (ILD) are not fully understood and have not been extensively studied.[29-31] However, abnormalities in ventilatory mechanics, along with an increased demand relative to capacity, contribute significantly to the intensity and quality of dyspnea in these patients. As a result, interventions that decrease ventilatory demand, improve ventilatory capacity, reduce mechani-

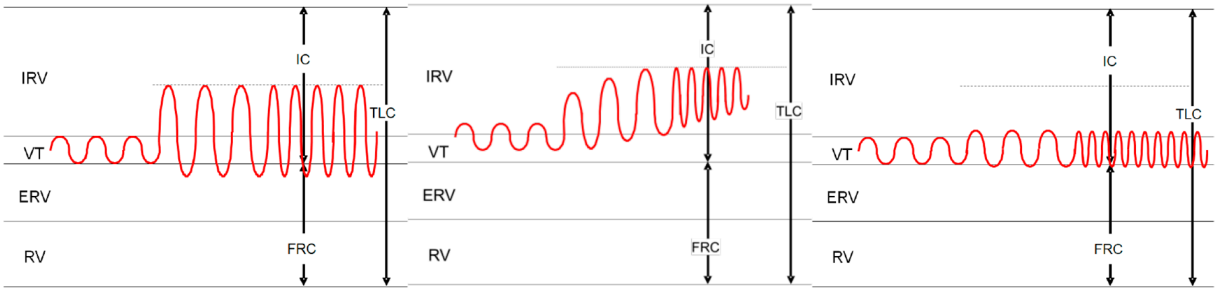

Figure 2. Patterns of ventilation increase in normal subjects, COPD patients, and patients with thoracic restrictive disease during exercise. Ventilatory increase during exercise in normal subjects (left panel), in patients with obstructive disease (center panel), and in patients with restrictive disease (right panel).

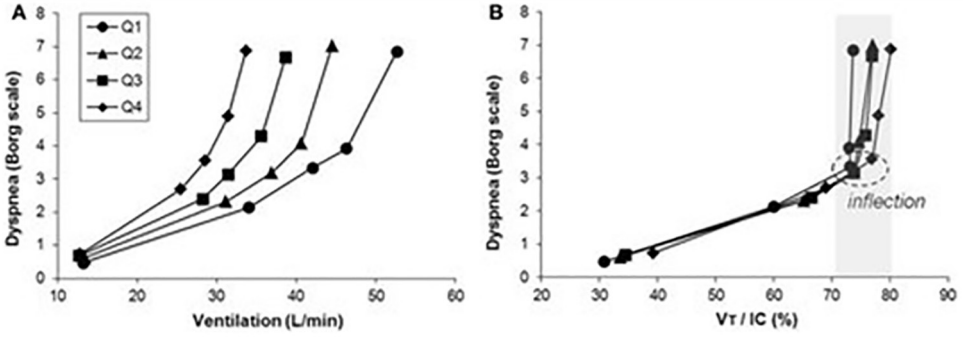

Figure 3. Dyspnea and breathing mechanics in COPD patients. Relationship between ventilation and dyspnea based on severity levels (FEV_1) and in relation to the VT/IC ratio (%).

cal load, or enhance respiratory muscle capacity should alleviate dyspnea.[24, 25] The concept of neuromechanical dissociation is highly relevant in these conditions.

Despite their obvious differences, **pregnancy** and **obesity** share ventilatory and perceptual responses to the physiological stress of exercise.[31-34] Over 70% of pregnant women and obese adults (otherwise healthy) report dyspnea during daily physical activities (for example, climbing stairs). Studies in obese individuals and pregnant women support the following conclusions:

1. Mechanical/muscular respiratory factors are not a major source of activity-related dyspnea during pregnancy.
2. Gestational dyspnea reflects awareness of increased VE and respiratory muscle effort accompanying the rise in neural motor drive (detected by increased central corollary discharge to sensory areas of the brain).
3. However, the increase in dyspnea during physical activity in pregnant women cannot be easily explained by mechanical/muscular respiratory factors or an increase in the central chemoreflex response, and presumably also peripheral response.

The higher perception of activity-related dyspnea experienced by many pregnant and obese individuals likely reflects the awareness of an increase in the neural respiratory motor drive needed to tolerate the greater ventilatory demands of exercise in these specific populations.[32, 33]

CONCLUSIONS

All the theories had defenders and detractors and, interestingly, with the development of sophisticated neurophysiological techniques and functional imaging it has been possible to prioritize each of the mechanisms. All have survived the passage of time and none can singularly explain dyspnea in all clinical situations, showing the complex and multifactorial nature of the phenomenon.

It isn't possible to overlook the fact that patients with COPD and ILD, in addition to experiencing dyspnea during exercise or at rest, often suffer from other symptoms such as general fatigue, weight loss, depression, anxiety, loss of appetite, nausea, dry mouth, and insomnia.[34] Therefore, these patients require a broader approach to their general symptoms that can further deteriorate their quality of life.

KEY POINTS

1. Unlike pain, the physiopathological mechanisms explaining dyspnea are complex and can coexist. Depending on the clinical condition, one mechanism can be more relevant than others. However, there are common denominators.
2. The explanation involving neural reflexes was developed to account for the presence of dyspnea in the absence of gasometric alterations, but it wasn't sufficiently convincing, so the role of altered breathing mechanics and the oxygen cost of breathing were suggested.
3. Based on our current knowledge, dyspnea occurs when there is imbalance between the demand for breathing (central neural drive) and the capacity to breathe (respiratory muscle function): tension-length inadequacy. This explanation gained acceptance, in part because it integrated other mechanisms and was strengthened by additional neurophysiological and imaging techniques.

Conflict of interest

Authors have no conflicts of interest to declare.

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