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# Depression, anxiety and chronic pain in patients with chronic obstructive pulmonary disease: the influence of breath

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## Abstract

Chronic obstructive pulmonary disease (COPD) is a major public health problems, causing significant mortality and morbidity in the world. It is a complex and progressive disease, characterized by chronic inflammation and dysfunction of the respiratory airways. The article reviews the available information on the potential role of the diaphragm in this disease. The purpose is to identify a potential correlation between symptoms such as depression, anxiety and chronic pain, frequently observed in COPD, with the activity of the diaphragm. The morphology and metabolism of the diaphragm are usually modified in the presence of COPD: a correlation between this symptoms and a pathological adaptation of breathing can be hypothesized. The management of these conditions should always be multidisciplinary, in order to have a global vision of the patient.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by chronic inflammation and dysfunction of the upper airways [1,2]. The WHO estimates a current mortality rate of around 64 million people; it has been estimated that, in 2030, COPD will represent the third cause of mortality in the world [1]. Currently, the relation between comorbidities and the presence and evolution of COPD is still unclear [2]. Comorbidities such as depression, anxiety and chronic pain are commonly observed [3]. The focus of the present article is to discuss the potential correlation between the above mentioned comorbidities, COPD and the diaphragmatic innervation and functionality. In this article the authors hypothesize that the dysfunction of the diaphragm detectable in this chronic conditions can have a role in the occurrence of these comorbidities.

## Adaptation of the diaphragm in patients affected by COPD

The progressive limitation of the airflow in COPD patients causes a pathological adaptation of the diaphragm, although the reasons for these changes are not fully clear. The dome of the diaphragm is lowered, in inspiratory position [4]. The contractile force is decreased, with electrical and metabolic alterations. The muscle thickness is increased, especially on the left side, with decreased mechanical excursion, probably due to fibers' shortening [5,6]. There is a decrease of anaerobic type fibers (type II) and an increase in aerobic fibers (type I); this process progressively increases with the pathology worsening [6]. The increase in the oxidative process, however, does not correspond to an improvement of diaphragmatic function. The rate of detectable myosin decreases, resulting in altered sarcomeric organization and further decreasing of the contractile strength [6]. The phrenic activity is abnormal, presumably due to the nerve stretching caused by the chronic lowering of the diaphragm, resulting in such a neuropathy [7]. The exercise intolerance in patients with COPD does not correlate with the common functional index (forced expiratory volume in 1 second - FEV1); rather it is the peripheral muscle adaptation, including that of the diaphragm, to have a heavy influence on the symptomatic scenario [8,9] (Figures 1 and 2).

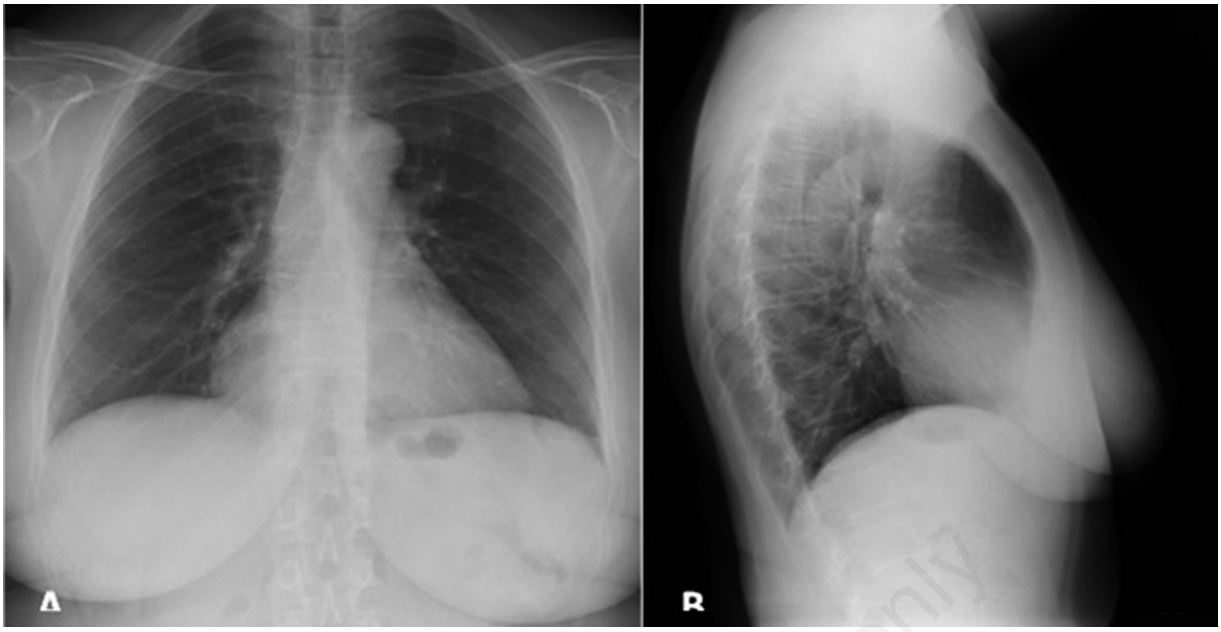


Figure 1. The chest radiograph performed in inspiration, in two projections. A) posteroanterior; B) Lateral. Under normal conditions the right hemidiaphragm is slightly higher than the left, as well as the front portions are higher than that of the side and rear.

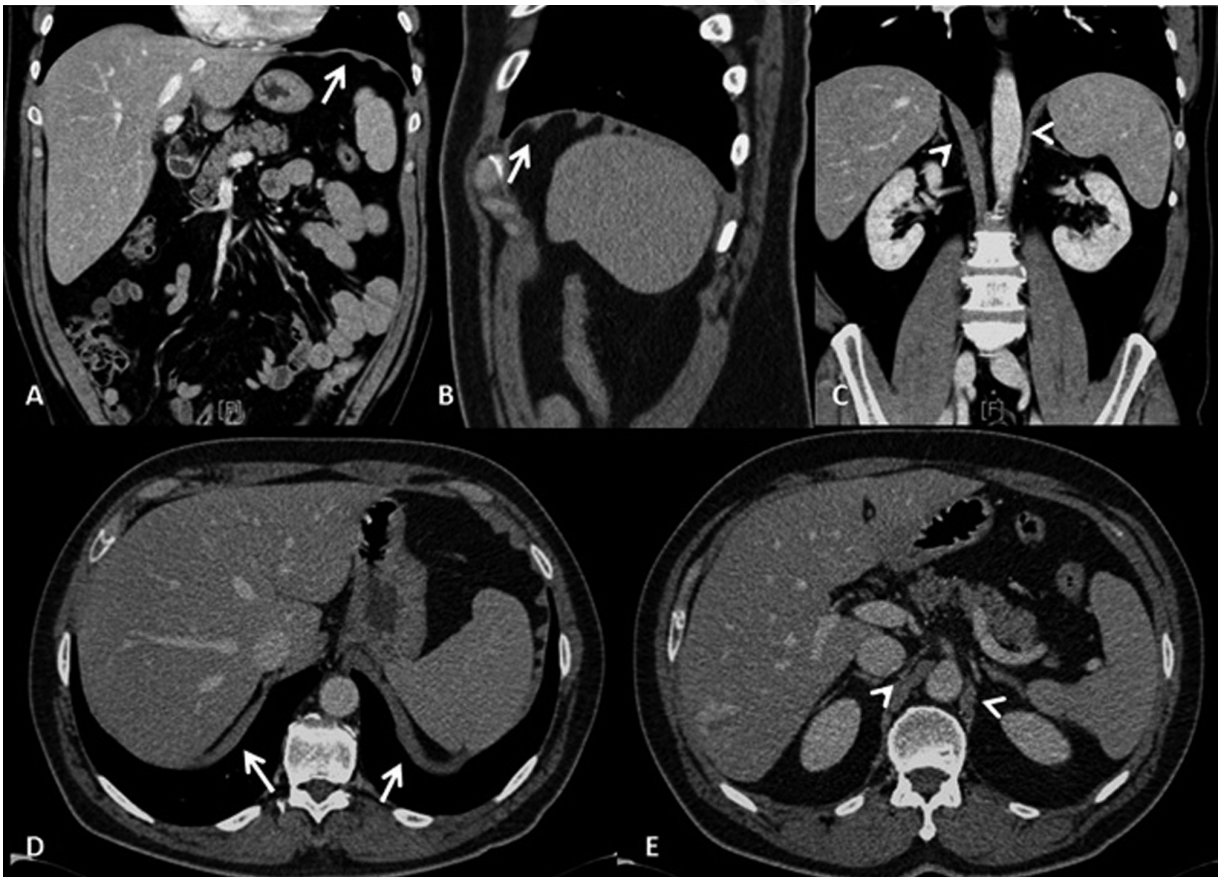


Figure 2. Computed tomography (CT). The CT images in the coronal and axial plane allow the visualization of the diaphragm as a hyperdense linear band interposed between the chest and the abdominal cavity (respectively A and D, see arrows). Sagittal images highlight a sort of "corrugated" morphology that shows the orientation of the muscle bundles (B, see arrows), which may appear more or less pronounced in wellness or pathological conditions, such as chronic obstructive pulmonary disease. Clearly visible also appear diaphragmatic pillars both the coronal plane (C) that the axial plane (E) (arrow heads).

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## Depression, anxiety and chronic pain in COPD

Psychiatric disorders such as depression and anxiety, and chronic pain, are symptomatic scenarios often observed in patients with COPD.3 These co-morbidities complicate the therapeutic approach and increase hospitalizations and mortality rate [10,11].

In patients with COPD the incidence of depression varies from 8% to 80%, according to different studies [2]. Depression may be considered a predictor of mortality during hospitalization for acute respiratory events [12]. Depression and anxiety negatively affect the re-hospitalization, but only 33% of patients are treated with a pharmacological process taking into account these psychiatric symptoms [12]. Currently, there is no gold standard therapy and not even a psychological approach considered the most appropriate. Depression affects the physical status of the patient, with a worsening in the test of Cooper (12 minutes-run) and an increased mortality rate [12]. Anyway, there are not enough data exhaustively explaining this correlation [12]. The co-presence of depression and anxiety in patients with COPD increases the mortality rate (of 83% according to some authors) [1,13]. The incidence of depression/anxiety increases with COPD worsening [2,13]. Even in this case, the exact mechanisms leading to this correlation are unclear. Probably, many causes are present alone or in combination: the presence of dyspnea; systemic inflammation; severity of disease; female sex; lower body-mass index; low socioeconomic status; reduced physical performance; persistent smoking; long-term oxygen therapy or oxygen dependence [2,10]. Again, increased number of comorbidities, marital status (widowed, divorced, never married), living alone are risk factors for anxiety and depression [2,10]. The relationship of anxiety and depression to the acute exacerbation of COPD is significant, but it is also complex, multifaceted, and concerns many interrelated factors. Anyway, pulmonary rehabilitation has been shown to reduce dyspnea, fatigue, symptoms of anxiety and depression; this is despite poor adherence from patients with concurrent anxiety and depression [2].

Chronic pain in patients with COPD can be observed in 45-95% of the patients, mainly involving the chest, the spinal areas and upper/lower limb; pain severity increases with the presence of dyspnea [14]. Patients reported 2.5 times more pain and 3.7 times more interference of pain with daily activities, compared to healthy people [15]. Higher pain intensity in COPD is associated with poorer life quality, poorer sleep quality, less physical activity and an increased pain-related fear of movement [14]. The perceived pain has a negative impact on depression and anxiety; there is not a real relationship between the severity of the disease and the pain level [14]. The lack of relationship between pain intensity and lung function, suggest that other factors may influence pain experience [14]. There are not available data on the factors leading to pain onset [14]. One of the current hypotheses is the systemic inflammation usually present in these patients, which activates cytokines, may cause chronic and neuropathic pain [15]. Musculoskeletal disorders, inactivity, age-related comorbidities (osteoporosis, osteoarthritis) are also considered possible causes of pain in patient with COPD [15].The literature on the effects of intervention aimed at reducing pain in patients with COPD is lacking [15].

## The diaphragm influences the pain perception and the emotional status

The diaphragm is innervated by the phrenic nerve and the vagus nerve (in the portion which constitutes the esophageal hiatus) [16].

The phrenic nerve (C3-C5) receives pulses from groups of medullary neurons of the pre-Bötzinger complex and parafacial retrotrapezoid complex, connected in turn to the retroambiguous nucleus of the medulla, although these mechanisms are not completely clear [17]. It is a mixed nerve, sending efferent fibers and receiving sensitive afferents; it provides motor innervation to the diaphragm, and receives afferent information from vena cava, pericardium, pleura, Glisson capsule and from the infra-diaphragmatic peritoneal spaces clear [18]. In the sub-diaphragmatic portion, the right phrenic nerve forms one or more phrenic ganglia, which are connected to the celiac ganglion and to the adrenal gland, and in some subjects even with the sympathetic superior mesenteric ganglion; the left one forms a phrenic ganglion, which can be connected to the sympathetic ganglia and to the adrenal gland clear [19]. In these phrenic ganglia there are some neural sympathetic elements, which are involved in an information retrograde system affecting the diaphragmatic behavior through the phrenic nerve clear [19]. The phrenic nerve forms many anastomoses, in different way depending on the variable presence of some phrenic accessory nerves: vagus nerve, subclavian nerve, ansa cervicalis, stellate ganglion, cranial nerves XII and XI, supraclavicular nerve and sternohyoid nerve clear [20].

The vagus nerve (cranial nerve X) is the longest cranial nerve. The vagus nerve is mixed, with motor tasks (20% of efferent fibers) and sensitive tasks (80% of afferent fibers clear) [21]. The vagus nerve arises from the ambiguous nucleus, the solitary nucleus and the dorsal motor nucleus of the brainstem, immediately caudal to the glossopharyngeal one. The parasympathetic efferent/afferent fibers provide for the viscera of the mediastinum, and then cross and innervate the cardial diaphragmatic area (where the esophagus also crosses the muscle); in the abdomen, the right nerve constitutes the posterior trunk, while the left nerve the anterior trunk [22]. The vagus nerve forms different anastomosis, including the sympathetic system in the cervical and abdominal region and the phrenic nerve [22,23]. The phrenic and vagus nerves are involved in the respiratory functions of the diaphragm, in perfect synergy.

The pain perception is reduced in inspiratory apnea, when the diaphragm is lowered [17]. This event suggests the intervention of baroreceptors. During this respiratory action, the systolic pressure increases with a decrease in the cardiac frequency [17]. We know that, when the baroreceptor located in the carotid body and in the area of the aortic arch (in the adventitia of the vessels) are stimulated by the cardiac cycle (in particular during the systolic phase), the nociceptive stimulus is attenuated by the activation of baroreceptors [17]. Chronic and acute pain can alter the functions of the baroreceptors and consequently damage the regulating function of the cardiovascular system, leading to an increased risk of mortality and morbidity [17]. The afferent fibers reach the nucleus of the solitary tract (NTS), which regulates the efferent activation to the vagal system and the sympathetic inhibitory efferents at the spinal level in the nucleus ambiguous, the dorsal motor nucleus and the rostral ventrolateral area of the medulla [17]. The baroreceptorial afferents influence different areas of the central nervous system, with a general inhibitory effect. The NTS is interconnected with the reticular formation, and then to the lateral, medial and prefrontal insula, and to the anterior cingulate cortex; also thalamus, hypothalamus and periaqueductal grey area receive baroreceptorial signals from NTS [17]. There is a close relationship between the emotions, the breath and the intervention of baroreceptors [17].

Emotional conditions such as anxiety and depression can negatively affect the baroreceptors' response, as well as they can produce an altered function on the diaphragm [17]. Changes in the emotional status can lead to an increased pain perception [17]. We can state that the diaphragm has an influence on baroreceptors, perception of pain and emotional state [24]. The action of the diaphragm is not only controlled by metabolic factors, but also by emotional states such as sadness, fear, anxiety, and anger. The interaction between the breath and the emotions involves a complex interaction between the brainstem and a few

brain centers like the limbic area and the cortex [17]. The amygdala, which is part of the limbic system, is connected in biunivocal way to the respiratory areas, such as medulla, and it is considered the most important area in managing the emotional breath [17]. The amygdala is stimulated by a dopaminergic production of the tegmental area of the midbrain, and recent studies on animal models suggest that the dopamine that reaches the amygdala regulates the emotional breath [17]. The efferents derived from the amygdala pass through the areas related to the breath, such as the NTS and other correlated structures [17].

The breath stimulates the mechanoreceptors of the diaphragm and the visceroceptors of the viscera moving during the respiration, which constitute the interoception mechanism. This is the awareness of the body condition based on the information derived directly from the body [17]. The afferent fibers of the interoception are connected with the autonomic and homeostatic centers of the spinal cord and of the brainstem, and then with the anterior cingulate cortex and with the dorsal posterior insula, through the thalamus-cortical tract [17]. The interoception can modulate the exteroceptive representation of the body, as well as the tolerance to pain; a dysregulation in the interoceptive pathways could cause a distortion of the body image, affecting the emotional condition. Anxiety can alter a few afferent pathways related to breathing, amplifying one or more receptor pathways related to the respiration (quickly and slowly adapting receptors, type C bronchial and lung receptors, A-delta type receptors, cough receptors and neuroepithelial receptors) [17] (Figure 3 and 4).

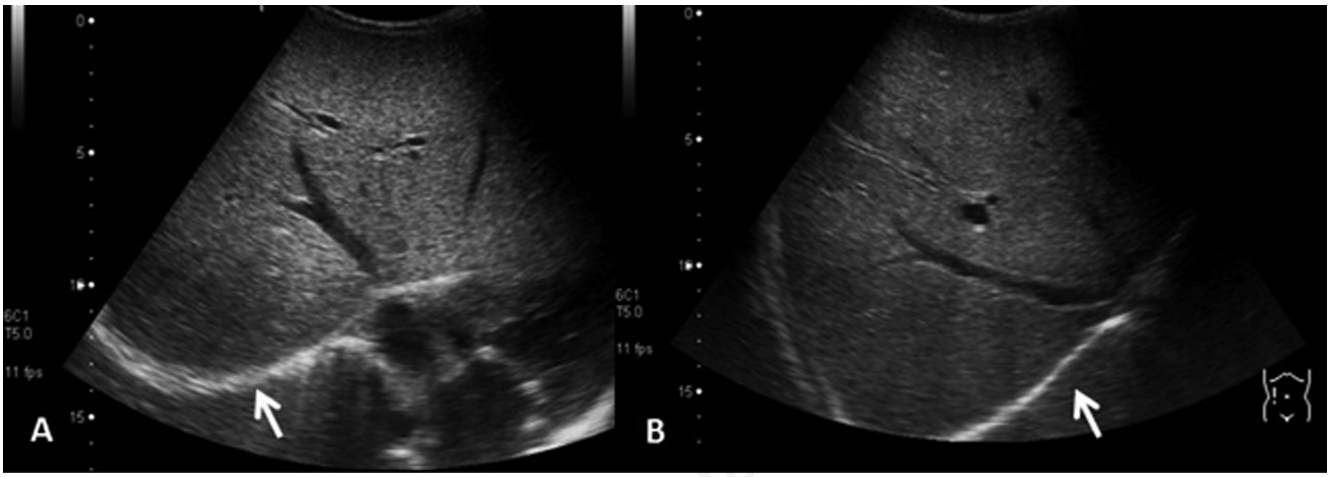


**Figure 3. Ultrasound. Ultrasound examination the diaphragm appears as a thin hyperechoic line, viewable in a better way on the right, in opposition of the adjacent homogeneous hypoechoic liver parenchyma. The echographic technique enables the evaluation "real time" of the excursion of the hemi-diaphragms and any paradoxes movements.**

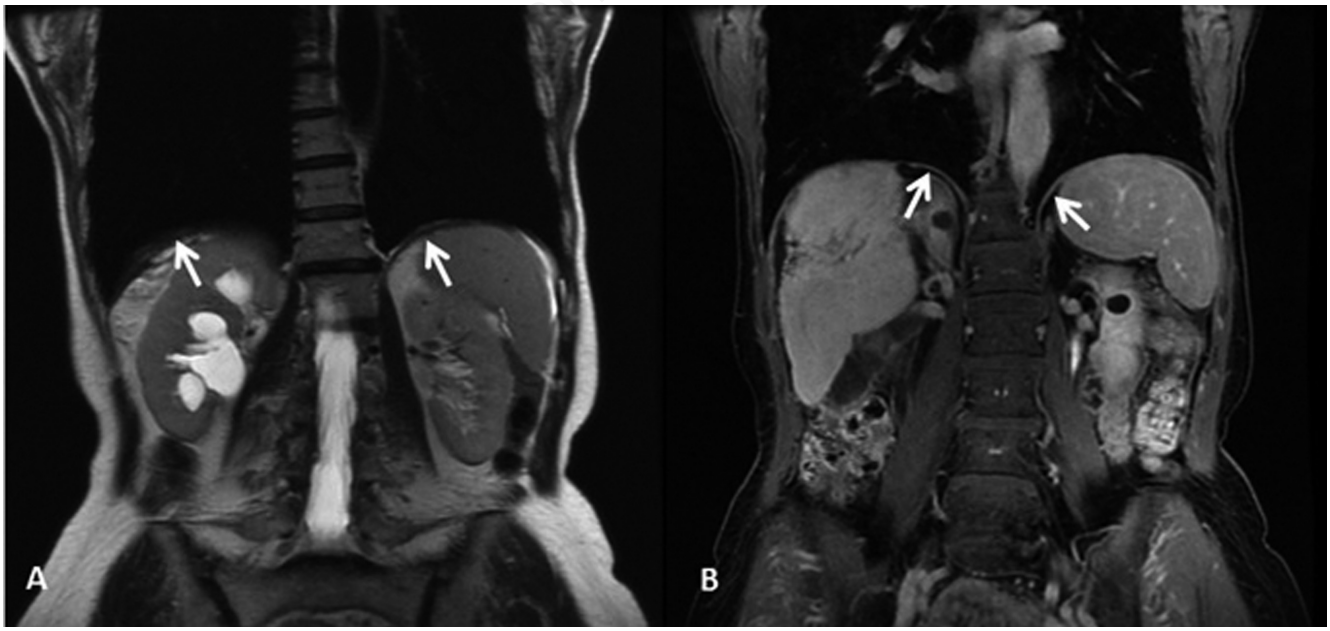


**Figure 4. Magnetic resonance imaging (MRI). Different MRI sequences for evaluating the diaphragm from a morphological point of view, better view of the structure in the coronal plane. The so-called "T2 weighted" sequences (A) allow visualization of the diaphragm as a hypointense streak (dark) interposed between two layers of adipose tissue (fat of the sub-pleural space and the sub-diaphragmatic) that are visible as hyperintense (clear). The sequences "T1-weighted after administration of the contrast" (B) use the opposite principle, i.e. they show a diaphragm as a linear structure hyperintense (or clear, as it is soaked by injected contrast) between two layers of adipose tissue hypointense (black, free of impregnation).**

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## New hypotheses and considerations on chronic pain and psychiatric status

The phrenic and vagus nerves provide visceral information. A current hypothesis is related to the solicitation of visceral nociceptors, sending continuous afferents in response to mechanical stress. This peripheral solicitation could lead to a central and spinal awareness, establishing a vicious circle between visceral information, emotional status and pain perception [25]. The visceral afferents, both interoceptive and nociceptive (small caliber A-delta and C afferents) reach the lamina I and II of the spinal cord, and are connected to some supraspinal centers, such as the ventromedial posterior nucleus of the thalamus and the limbic area [26,27]. The phrenic and vagus nerves could be stimulated and determine abnormal afferents, or being submitted to efferents derived from the supraspinal centers stimulated by the nociceptive information of the mediastinal viscera.

The peripheral nerve structure is subjected to a daily mechanical stress, as when a joint moves, with alternation of compression and stretching. The sliding of the fascial structures of the nerve and the nerve slippage between the various tissues is fundamental, so that the mechanical stress can communicate properly with the ability of adaptation and regeneration of the nerve. Abnormalities will lead to dysfunction and pathology. Where there is a nerve impingement, the rigidity of its fascial structures increases during articular or respiratory movements; the nerve may undergo a reduction in its diameter, defined as transverse contraction, with an increase in the pressure of the endoneural compartment. Repetitive elongations of nerves with reduced elasticity of the fascial properties will induce additional inability in the nerve's sliding, decreasing the blood flow and leading to potential ischemic processes. The fascial structures become more sensitive to mechanical stimuli and, after a few days of local inflammation, are able to generate an action potential similar to the initial stimulus causing the dysfunction; this potential can have an anterograde and retrograde propagation, causing inflammation at the extremities of the neural tract, such as in the spinal cord and in the innervated tissues. This mechanism is called ectopic electrogenesis [28]. In patients with COPD, the diaphragm muscle shows abnormalities, with changes in morphology and function, position and metabolism. The vagus and the phrenic nerves can undergo axonal alterations if the muscle movement is limited for such dysfunction, over time resulting in modified awareness schemes and allodynia [28,29].

The baroreceptor system, which influences the pain perception and emotional state, is altered in COPD patients [8,30]. Most likely, the pathological changes observed for the diaphragm negatively affect its innervation, causing a baroreceptor dysfunction. This could be a further cause for chronic pain and psychiatric conditions. We can still speculate that and altered function of the diaphragm may adversely influence the patient's emotional state, probably because the interoceptive mechanisms stimulated by breathing are handled as motivational information, since these are bidirectional pathways [17]. The breathing requested during physical exercise could cause strong emotional reactions in anxious people, worsening the respiratory function [17]. The interoception is also related to visceral movement during respiration; people more susceptible to visceral afferents usually show more intense emotions. A potential cause might be related to neurogenic neuroinflammation in the spinal cord, where different areas are more likely to respond to minimal stimuli, leading to higher levels of anxiety and pain [17]. This event could lead to a pleiotropic effect of functional impairment of the muscle tissue, further destabilizing the function of the diaphragm. The term of "emotional respiratory allodynia" can be used when the breath, stimulating the interoceptive afferent pathways, causes psychological symptoms [17].

The innervation of the diaphragm muscle may be directly responsible for the emotional state of the patient through the phrenic nerve, not only due to the interoceptive mechanism. The afferent stimulation to the NTS by the phrenic nerve could affect the emotional response, because NTS handles the visceral afferents and has a close relationship with the nerve [17]. These connections need to be confirmed. The phrenic nerve forms sub-diaphragmatic ganglia and is connected with the adrenal gland; anyway, further data even on these connections are currently needed. We know that the adrenal gland and the hypothalamus-pituitary axis (HPA) affect pain perception, and the intensity of the emotions [17]. It should be useful to further investigate the potential relation between the HPA axis, the phrenic nerve's activity, the emotional status and the pain perception. The vagus nerve affects the emotional spectrum and the respiratory rhythm, probably always through NTS. Anyway, reliable correlations are not known, neither if there are bi-directional mechanisms influencing the emotions and involving the diaphragm portions innervated by the vagus nerve [17].

There is a close relationship between vagus nerve and pain perception. The afferents of the vagus nerve are usually able to inhibit the activity of the second order nociceptive neurons of the spinal cord, through spinotalamic and spinoreticular tracts and in the trigeminal nuclei [31]. The vagus nerve has the ability to transmit painful information, particularly visceral pain, to the supraspinal centers [17]. This can happen thanks to a retrograde transport of biochemicals through the nerve [31]. The same nerve collaborates to the formation and maintenance of the central pain memory, modulating inhibitory descendant pathways to nociceptive areas in the spinal cord [31]. Complete information are not available on these ascendant mechanisms (probably involving NTS, parabrachial nuclei, periaqueductal grey area, hypothalamus, limbic area, magnum raphe, locus ceruleus), as well as on descendant ones, but we can state that the vagal tone has an important influence on pain perception [32]. A compression of the vagus nerve can alter its function, just as a dysfunction of a peripheral nerve, mimicking an entrapment syndrome [33]. An abnormal tension of the diaphragm in the region of the vagus nerve could cause a compression of the nerve, limiting its antinociceptive and anti-inflammatory ability, even though no scientific evidence currently confirm this hypothesis. The diaphragm has a phrenic center, consisting of connective tissue (in the shape of "V"), with a variable amount of contractile tissue [29]. The fascial system is richly innervated by proprioceptors, which can represent a source of painful afferents and become nociceptors [29]. The crural and connective area is populated by proprioceptors; we can assume that an alteration of the position and function of the diaphragm could lead to irritability of these proprioceptors and consequent occurrence of pain. We could also assume that, if the position of the diaphragm is abnormal, as in patients COPD, the phrenic and vagus nerves can be compressed or stimulated, causing nociceptive afferents, just as occurs in peripheral nerves [28].

To conclude, even a dysfunction of the sympathetic nervous system negatively affects the pain perception, and the emotions [34,35]. Patients with COPD have an altered sympathetic function [36,37]. The splanchnic nerves cross the diaphragm through small muscular spaces [38]. The sympathetic system, when activated, can amplify the pain severity, and record information related to pain perception [39]. We can assume that, if the sympathetic nerves are compressed in the region of the diaphragm, their function and morphology can change, negatively affecting the innervated tissues. The phrenic nerve has a close relationship with the sympathetic system,

not just below the diaphragm, but even in the region of the stellate ganglion, where post-ganglionic fibers arise and descend toward the diaphragm (particularly the right phrenic nerve) [40]. The vagus nerve also contains sympathetic fibers [23]. Therefore, conditions of abnormal phrenic and vagal function caused by over-stimulation of the sympathetic system can be hypothesized. Anyway, further studies are certainly needed on this topic.

## Conclusions

The close relationship between morphology and function of the diaphragm and the phrenic nerve, as described in ontogenetic processes, let us presume that pathologic conditions of the muscle could probably affect the phrenic function. At the same time, the connections between the vagus and the phrenic nerves, lead us to suggest that a dyssynergia between the two nerves could cause diaphragm pathological behavior.

The article discuss the potential scenarios in which a phrenic and vagal dysfunction could lead to non-respiratory symptoms (such as depression, anxiety and chronic pain), in patients with COPD. The diaphragm muscle shows changes in its morphology and metabolism in the presence of these chronic diseases, thus the pathological adaptation of breathing could have a potential role even in the occurrence of depression and chronic pain. The management, in these medical conditions, should always be multidisciplinary, in order to have a global vision of the patient.

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