Review Article

Autonomic dysfunction in patients with chronic obstructive pulmonary disease (COPD)

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ABSTRACT It has been recognized that chronic obstructive pulmonary disease (COPD) is a systemic disease which has been shown to negatively affect the cardiovascular and autonomic nerve system. The complexity of the physiologic basis by which autonomic dysfunction occurs in patients with COPD is considerable and the knowledge in this field remains elementary. The purpose of this review is to provide an overview of important potential mechanisms which might affect the autonomic nervous system in patients with COPD. This review aims to summarize the basic research in the field of autonomic dysfunction in patients with COPD. In COPD patients the activity of sympathetic nerves may be affected by recurrent hypoxemia, hypercapnia, increased intrathoracic pressure swings due to airway obstruction, increased respiratory effort, systemic inflammation and the use of betasympathomimetics. Furthermore, experimental findings suggest that autonomic dysfunction characterized by a predominance of sympathetic activity can significantly modulate further inflammatory reactions. The exact relationship between autonomic dysfunction and health status in COPD remains to be elucidated. Treatment aimed to restore the sympathovagal balance towards a reduction of resting sympathetic activity may modulate the inflammatory state, and possibly contributes to improved health status in COPD.

Key Words: COPD; cardiac autonomic dysfunction; hypoxemia; hypercapnia; increased intrathoracic pressure swings; increased respiratory effort; systemic inflammation; betasympathomimetics

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Introduction

The autonomic nervous system (ANS) regulates multiple physiological processes. Amongst other factors it is responsible adjusting heart rate, blood pressure, gastrointestinal secretion, temperature regulation, vagally mediated reflex constriction of airway smooth muscle, secretion from submucosal glands, capillary permeability and blood flow in the bronchial circulation, cardiovascular responses to exercise and release of mediators from the mast cells and other inflammatory cells. Dysfunctions of the autonomic nervous system are recognized by the symptoms that result from failure of the sympathetic or parasympathetic components. Disruption of autonomic reflexes with increased sympathetic tone, loss of parasympathetic tone and altered baroreceptor sensitivity (BRS) have been shown to be major risk factors for cardiac morbidity and mortality (1-3).

Chronic obstructive pulmonary disease (COPD) is associated with abnormal inflammatory response of the lungs to chronic inhalational of noxious inhaled gases or particles causing obstruction of the airways which is often irreversible. There is increasing evidence, indicating that COPD is more complex and not only involving airflow obstruction. It has been recognized that COPD is a systemic disease which has been shown to negatively affect the cardiovascular and autonomic nerve system (4, 5).

The complexity of the physiologic basis by which autonomic dysfunction occurs in patients with COPD is considerable and the knowledge in this field remains elementary. The insight into

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sympathovagal imbalance as a pathological phenomenon in COPD may be important in understanding the pathophysiology of COPD and may have a potential clinically importance for improving risk stratification and treatment of patients with COPD. Therefore, the purpose of this review is to provide an overview of important potential mechanisms which might affect the autonomic nervous system in patients with COPD.

Cardiac autonomic dysfunction in COPD

Patients with COPD have functional alterations of cardiac autonomic modulation as reflected in elevated resting heart rate, reduced baroreflex sensitivity, reduced heart rate variability (HRV) (6, 7), reduced respiratory sinus arrhythmia (RSA) (8), a direct increase in muscle sympathetic nerve activity (9, 10) and abnormal heart rate recovery (HRR) following exercise (11). This phenomenon suggests that COPD patients have enhanced sympathetic tone at rest and are less able to respond to sympathetic and parasympathetic stimuli, in comparison with healthy persons. In addition, resting muscle sympathetic nerve activity is significantly higher in patients with COPD as compared to age- and sex-matched healthy control subjects (9). Enhanced sympathetic tone at rest and disruption of autonomic reflexes give rise to a self-perpetuating cycle that contributes to the pathogenesis of COPD and possibly play an important role regarding the mortality in these patients (1, 2).

Sensory receptors

COPD seems to induce a generalized attenuation of excitatory pathways regulating respiratory, cardiac autonomic and cardiovascular systems. In this context, mutual interference of these systems is likely to occur in response to alterations affecting only single parts, because these systems share identical control mechanisms (12). The abnormality of autonomic function in patients with COPD may affect stimulus reception, afferent nerve conduction, central processing, efferent nerve conduction, and neuromuscular response. The sensory receptors that might play a significant role in autonomic dysfunction in patients with COPD are arterial and cardiac baroreceptors, metabolic and pulmonary stretch receptors, bronchopulmonary C-fibres and arterial chemoreceptors.

Arterial chemoreceptors

Type II respiratory failure in COPD is defined by co-existing hypoxemia and hypercapnia. It is likely that these two conditions have different effects on the autonomic nervous system; hypoxia is acting mainly on peripheral chemoreceptors while hypercapnia is mainly stimulating central chemoreceptors. It has been demonstrated that acute hypoxemia increases sympathetic nerve activity by stimulation of arterial chemoreceptors in healthy humans (13, 14). Saito et al have demonstrated that the degree of hypoxia correlates with the degree of sympathetic muscle nerve activity (15). Furthermore, it has been demonstrated that short-term oxygen supplementation significantly and favorably improves cardiac autonomic modulation underlining the predominant role of hypoxemia in COPD patients with mild hypoxemia (16).

However, the overall role of hypoxia may be overestimated as impaired or altered autonomic regulation was observed in both hypoxemic and normoxemic patients with COPD (4, 6-7, 17), and daytime blood gases do not correlate with sympathetic activation (9). The effect of chronic hypoxemia on autonomic dysfunction however, is difficult to predict as the sensitivity of arterial chemoreceptors may change over time. Furthermore, an interaction between arterial baroreceptors and the chemoreceptor reflex has been demonstrated; an increase in baroreceptor activation causes an inhibition of the chemoreceptor reflex (22).

Conflicting evidence exists regarding the role of hypercapnia on autonomic dysfunction in patients with COPD. Several studies have suggested that hypercapnia leads to increased sympathetic tone (23) and that combined hypercapnia and hypoxia synergistically increase sympathetic activity through impaired baroreceptor-cardiac reflex control in healthy humans (22, 24). On the contrary, in other studies hypercapnia and respiratory acidosis were found to increase the parasympathetic modulation of HRV in healthy humans (25, 26).

Arterial and cardiac baroreceptors

Peripheral baroreceptors are located in the carotid and aortic vessels and are responsive to changes in systemic blood pressure. Under normal conditions, arterial blood pressure fluctuates throughout the respiratory cycle, falling with inspiration and rising with expiration. Large intrathoracic pressure changes, as occurring in chronic obstructive pulmonary disease, are transmitted to the heart and great vessels and can influence both peripheral baroreceptors and cardiac performance. Large pressure changes may cause fluctuations in cardiac performance, and therefore, in systemic blood pressure provoking finely modulated compensatory changes of the heart rate mediated by separate outputs of both intra- and extrathoracic baroreceptors (27). Furthermore, intrathoracic baroreceptors can be influenced high aortic transmural pressure gradients induced by abnormal breathing (28). Even in healthy subjects, resistive load breathing stimulates aortic baroreceptors and consecutively impacts on the autonomic nerve system (29, 30).

Furthermore, mechanical mechanisms linked to respiratory fluctuations in cardiac transmural pressure, atrial stretching

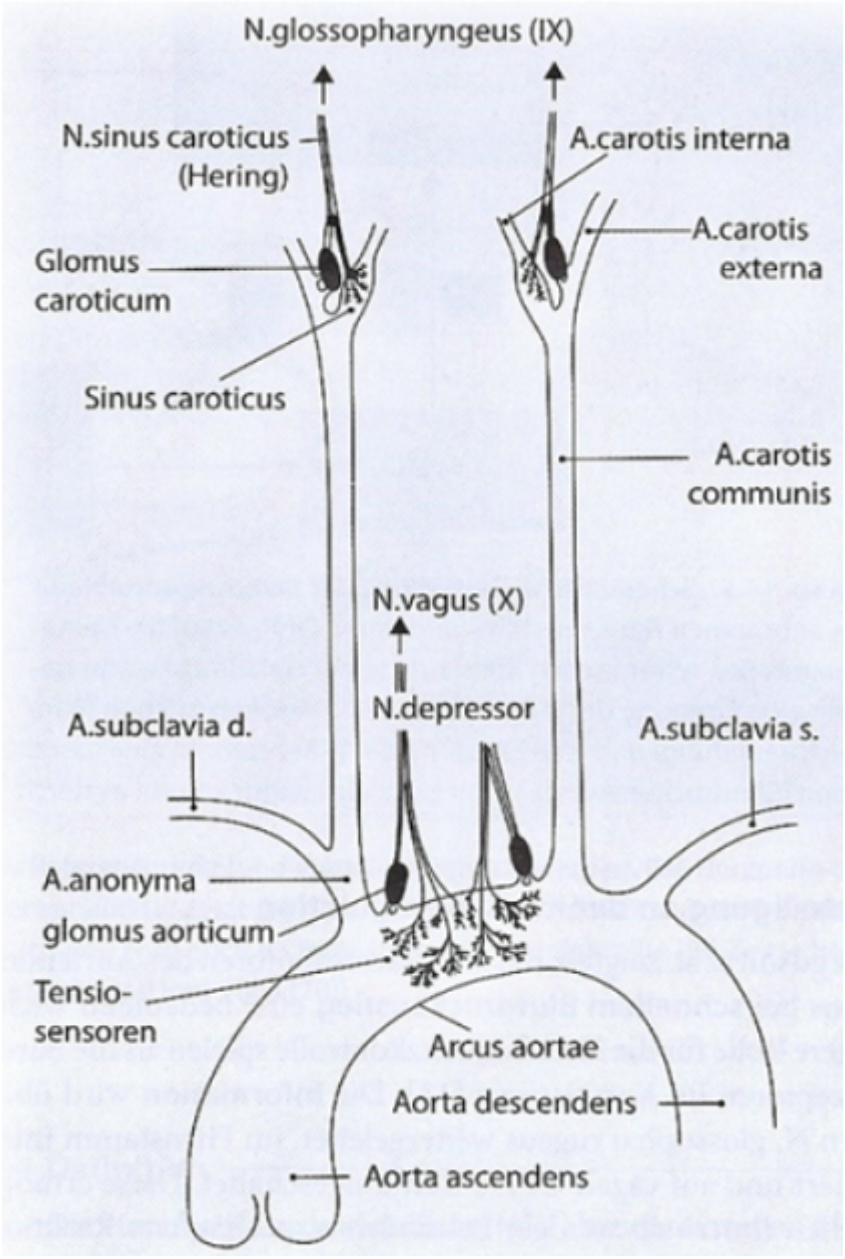

Fig 1. Overview of peripheral baroreceptors (tensiosensoren) located in the carotid and aortic vessels. Large intrathoracic pressure changes, as occurring in chronic obstructive pulmonary disease, are transmitted to the peripheral baroreceptors and may play a predominant role in autonomic dysfunction in these patients.

and venous return sensed by cardiac baroreceptors may also determine autonomic dysfunction in COPD (31, 32).

Patients with COPD have reduced baroreflex sensitivity to transient rise of blood pressure (BRS) (6, 7). It has been demonstrated, that impaired baroreflex sensitivity leads to an increase in sympathetic activity through inhibitory afferents (21, 18). Besides mechanical influences, other factors are discussed as possible causes of the reduced baroreflex sensitivity in patients with COPD. There is considerable evidence of interactions between peripheral chemoreceptor and arterial baroreceptor reflexes (19). Hypoxia, but not hypercapnia, alters the baroreflex sensitivity (20). Furthermore it has been demonstrated, that elevated pulmonary arterial pressure alters baroreflex sensitivity in patients with COPD (33).

Breathing pattern

Eckhart and colleagues found evidence that the respiratory pattern influences autonomic output by inhibiting the ability of baroreceptor inputs to modulate the activity of autonomic motoneurons (34). The influence of the respiratory pattern on cardiac autonomic modulation is well known: the magnitude of parasympathetic induced heart rate variability has been shown to depend on both the lung hyperinflation (tidal volume

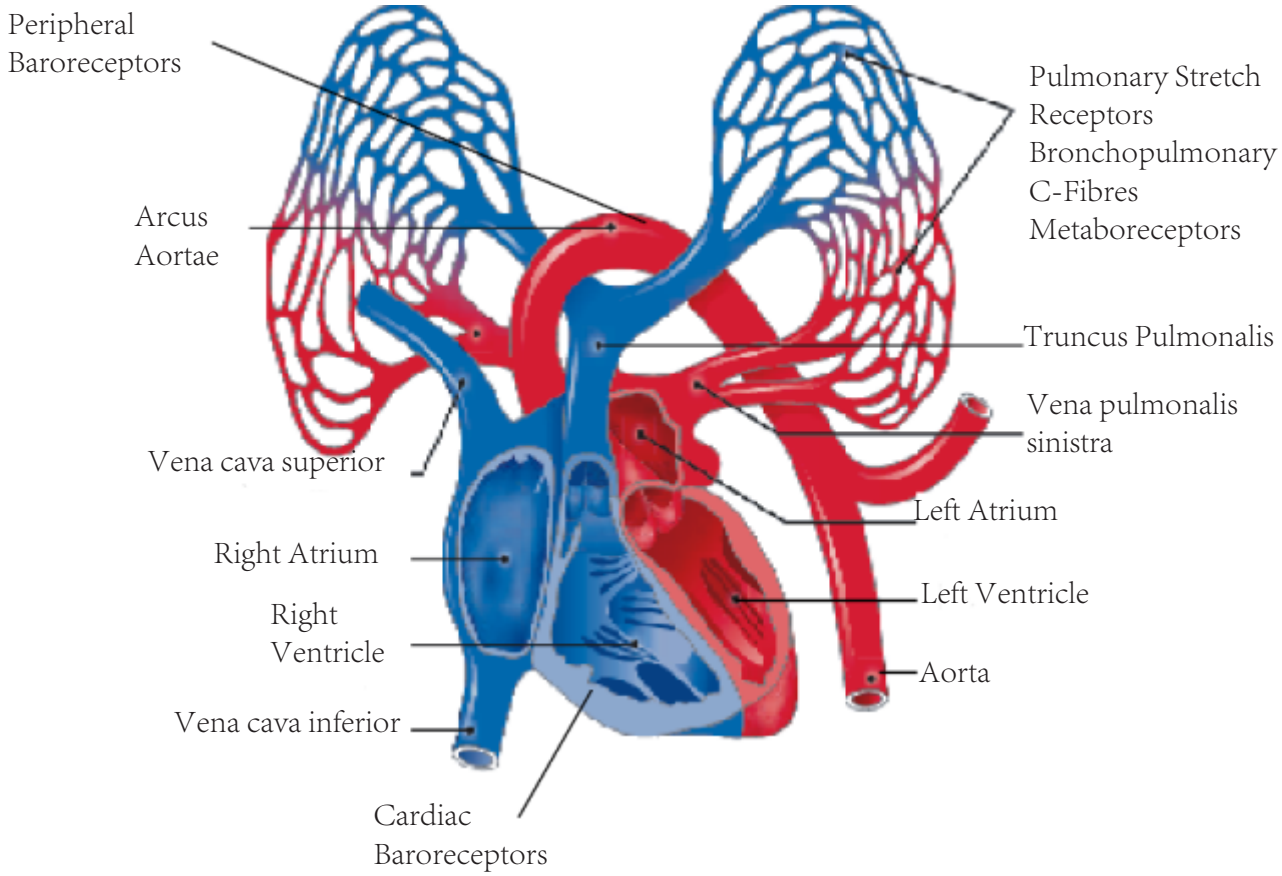

Fig 2. Internal thoracic cave with diaphragm and thoracic blood vessels. Overview of important sensory receptors which might affect the autonomic nervous system in patients with COPD.

VT) and respiratory rate (FR) (35, 36). One would expect different patterns of activity of cardiac autonomic modulation influenced by the extent to which lung hyperinflation (tidal volume VT) and respiratory rate (FR) change in patients with COPD. Slow breathing reduces sympathetic activity quickly, tends to increase baroreflex sensitivity and reduces chemoreflex sensitivity (37, 18) in COPD patients (90). Higher respiratory rate (FR) above a characteristic frequency causes sympathetic activation and vagal withdrawal (21, 38). However, it should be stressed, that breathing at lower respiratory rates does not lead to a normalization of baroreflexes and sympathetic activity in patients with COPD (21). Furthermore, no causal link has been found between breathing pattern, altered baroreflexes and heightened sympathetic activity in COPD (21). Instead, it is reasonable to suggest that a number of other synergistic mechanisms, including lung inflation reflexes, contribute to sympathetic activation in COPD. It may be postulated, that the development of a rapid shallow breathing pattern during an exacerbation or exercise probably is a contributor to autonomic dysfunction in patients with COPD.

Metaboreceptors

The increased work of breathing due to severe obstructive and restrictive breathing in patients with chronic lung disease could lead to sympathetic activation through stimulation of local metaboreceptors. Oxygen radicals and products of ischemic metabolism generated during muscular contraction (e.g., isometric exercise) have been shown to stimulate local receptors and cause increases in heart rate, arterial pressure, and sympathetic activity (39, 40). In healthy humans, repeated contractions of respiratory muscles inducing fatigue have also been shown to increase metaboreflex-mediated sympathetic excitation (41, 12).

The role of local metaboreceptors on cardiac autonomic dysfunction in patients with COPD has not yet been investigated. As diaphragm remodeling (42) and even injury of the diaphragm (43) has been observed, it is reasonable to believe

that stimulation of local metaboreceptors occurs in patients with COPD.

Pulmonary stretch receptors

Lung inflation reflexes mediated by pulmonary vagal afferents may also contribute to sympathetic activity in patients with COPD (41). It was hypothesized that pulmonary stretch receptors may play a role in the regulation of systemic vascular tone and cardiac autonomic modulation in healthy humans (69). Pulmonary stretch receptors can be divided in two types: slowly adapting (tonic) and rapidly adapting (phasic) receptors. Slowly adapting receptors (SAR) convey information about the level of inflation of the lung while rapidly adapting receptors (RAR) fire in response to transient changes in lung volume. When the lungs are adequately inflated, pulmonary stretch receptor excitation terminates inspiration, initiates expiration and decreases parasympathetic output (Hering-Breuer reflex, HBR) (44, 45). However, the exact explanation of how mechanical energy of pulmonary tissue distention is transduced to neural activation in pulmonary stretch receptors is unknown. A potential contribution may be that breathing at a state of hyperinflation increases the activity of the SAR fibers (44, 46). If the respiratory rate increases, a corresponding increase in activity of RAR fibers may follow (44). Due to chronic hyperinflation of the lungs, SAR fibers may be permanently active and therefore diminish their responses to other stimuli. As a result the activity of mechanosensitive afferent nerves is grossly altered (44) and HBR is diminished (45), which could eventually lead to the alteration in vagal nerve activity in these patients.

Bronchopulmonary C-fibers

The lungs, both bronchi and parenchyma, are innervated by thin nonmyelinated fibers, afferents capable of signaling local mechanical and chemical properties. Pulmonary C-fibers (J-receptors), and nociceptive C-fibers in general, are designed to respond to tissue inflammation (44), local edema and a variety of chemicals that may accumulate in COPD. Pulmonary C-fibers are capable of triggering ventilatory, bronchomotor, and cardiovascular effects. Numerous inflammatory mediators, a decrease in pH in the interstitial fluid, hypoxemia and nicotine can effectively activate bronchopulmonary C-fibers in patients with COPD. Furthermore, in several animal studies it has been shown that transient hypercapnia (47) and decreased lung compliance (48) markedly increase the responses of bronchopulmonary C-fiber afferents to various chemical stimulants.Use of betasympathomimetics increases the sympathetic nervous activity of COPD patients (57). Inhalation of therapeutic doses of betasympathomimetics in healthy subjects results in significant haemodynamic changes and a shift of sympathovagal balance towards increased sympathetic tone (58). Silke et al have demonstrated that inhaled betasympathomimetics increase sympathetic activity, as measured by heart rate variability analysis, in healthy persons, however, these agents do not change the parasympathetic (HF) cardiac modulation (59, 60). In patients with COPD the use of betasympathomimetics is associated with significant increases in heart rate, and it has also been associated to be related to increase in cardiovascular morbidity and mortality (61). may directly trigger sympathetic activation. There is growing evidence that persistent low-grade systemic inflammation is present in COPD (53) and it may be postulated that this may contribute to the pathogenesis of cardiac autonomic dysfunction among COPD. The exact interaction between systemic inflammation and the autonomic nervous system is complex. The effects of systemic inflammation range from cytokine--induced priming of peripheral leukocytes, to muscle wasting induced by cytokines such as tumour necrosis factor-alpha (49). Accordingly, recent clinical studies have found a significant association between autonomic dysfunction and increased markers of inflammation in several populations, including apparently healthy subjects (50, 51), and patients with congestive heart failure (52). In patients with COPD, enhanced systemic inflammation is linked to profound neurohumoral activation (53). Furthermore it may be postulated, that an imbalance of the autonomous nervous system activity, characterized by a predominance of sympathetic activity, may favour the inflammatory state (54, 55).

Pulmonary hypertension

Pulmonary hypertension due to pulmonary arterial vasoconstriction causes right ventricular wall stress and has been shown to play a role in the attenuation of baroreflex responses in COPD patients (56). It has been demonstrated, that attenuation of baroreflex responses leads to an increase in sympathetic activity through inhibitory afferents (21, 18).

Sympathoexcitatory medication

Use of betasympathomimetics increases the sympathetic nervous activity of COPD patients (57). Inhalation of therapeutic doses of betasympathomimetics in healthy subjects results in significant haemodynamic changes and a shift of sympathovagal balance towards increased sympathetic tone (58). Silke et al have demonstrated that inhaled betasympathomimetics increase sympathetic activity, as measured by heart rate variability analysis, in healthy persons, however, these agents do not change the parasympathetic (HF) cardiac modulation (59, 60). In patients with COPD the use of betasympathomimetics is associated with significant increases in heart rate, and it has also been associated to be related to increase in cardiovascular

morbidity and mortality (61).

Dyspnoea

Although dyspnea is a frequently encountered clinical symptom in patients with COPD, the impact of breathlessness on autonomic dysfunction remains uncertain. Acute dyspnea is often associated with anxiety and emotions. Specifically the perception of respiratory discomfort is represented in the sensorimotor integration area of the limbic system that governs autonomic control, (62) and central respiratory motor drive is linked with central sympathetic output in the brainstem (63). Increased endogenous release of catecholamines influences objectively ventilation and subjectively breathlessness in healthy persons (64).

Summary

Expiratory flow limitation in patients with chronic obstructive pulmonary disease (COPD) results from progressive airway inflammation causing parenchymal destruction, mucosal oedema, airway remodelling, mucoid impaction and increased cholinergic airway smooth muscle tone (65). Increasing evidence indicates that COPD is a complex disease resulting from more than airflow obstruction. It has been recognized that COPD is a systemic disease which has been shown to negatively affect the cardiovascular and autonomic nervous system (4, 5). In COPD patients the activity of sympathetic nerves may be affected by recurrent hypoxemia, hypercapnia, increased intrathoracic pressure swings due to airway obstruction, increased respiratory effort, systemic inflammation and the use of betasympathomimetics. Autonomic dysfunction is another important factor of the pathophysiological mechanism of COPD because of the multiple parameters that are under control of the autonomic nervous system. Furthermore, experimental findings suggest that autonomic dysfunction characterized by a predominance of sympathetic activity can significantly modulate inflammatory reactions. Cardiac autonomic dysfunction encompasses various and multiple disorders and might be associated with increased incidence of cardiovascular diseases in patients with COPD (66). Although several studies have demonstrated that the ventilatory response to exercise performance is limited in patients with COPD (67, 68), the role of autonomic dysfunction on exercise intolerance is mostly unknown. In patients with chronic heart failure, increased sympathetic activity is related to muscular wasting and impaired exercise tolerance (69).

The exact relationship between autonomic dysfunction and health status in COPD remains to be elucidated. Treatment aimed to restore the sympathovagal balance towards a reduction of resting sympathetic activity may modulate the inflammatory state, and possibly contributes to improved health status in COPD.

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