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Review

Dyspnea related to reversibly-binding $P2Y_{12}$ inhibitors: A review of the pathophysiology, clinical presentation and diagnostics

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ABSTRACT

Dyspnea is a common symptom physiologically associated with strenuous exercise and pathologically reflecting well-known diseases and conditions that are predominantly pulmonary, cardiovascular, and weight-related in origin. Dyspnea improves with appropriate measures that enhance physical performance and treatment of the underlying diseases. Dyspnea is less commonly triggered by other causes such as the environment (e.g., ozone), drugs, and others, some of which do not seem to affect bronchopulmonary function as evidenced by normal results of comprehensive pulmonary function testing. In cardiovascular medicine, dyspnea has recently attracted attention because it has been reported that this symptom occurs more frequently with the administration of the new oral reversibly-binding platelet $P2Y_{12}$ receptor inhibitors ticagrelor [1–6], cangrelor [7–10], and elinogrel [11].

This paper succinctly addresses the current understanding of the pathophysiology, clinical presentation, and diagnostics of dyspnea, associated either with bronchopulmonary function impairment, as triggered mainly by pulmonary and cardiovascular diseases, or without bronchopulmonary function impairment, as induced by endogenous or external compounds such as drugs in order to provide a context for understanding, recognizing and managing $P2Y_{12}$ inhibitor-induced dyspnea.

1. Introduction

The American Thoracic Society defines dyspnea as "… a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity, …" [12], which has not been changed since 1999 [13]. This definition emphasizes the subjectivity of the sensation where the affective domain with the emotional (angst, anxiety, hopelessness) and physical components (effort, rapid, shallow, work) play important roles [14–17]. Although physicians may settle with the obvious when interpreting dyspnea as physiologic breathlessness occurring at the end of exhaustive exercise in healthy individuals, they may miss either enhanced bronchial hyper-responsiveness in 5% to 70% of the cases [18–22] or vocal cord dysfunction [23], possibly resulting in a missed treatment opportunity. Dyspnea is the third most common symptom reported in internal medicine [24] and was observed among community-residing adults in 9% to 13% overall [25–27], in 15% to 18% aged 40 years or older [27–29], and in 25% to 37% of adults aged 70 years and older [30]. Dyspnea affects quality of life [31] and is also an indicator of long-term mortality [27], reflecting diseases and conditions such as pulmonary diseases (chronic obstructive pulmonary disease [COPD], asthma, pneumonia, pulmonary embolism, pulmonary arterial hypertension), cardiovascular disease (acute myocardial infarction, chronic heart failure [32]), cancer of any type, in particular end-stage cancer [32], anemia, and lack of general physical fitness ("being out of shape").

From a therapeutic perspective, there are ample opportunities for improvement: In the United States, an estimated 1.4 million patients die with inadequately managed dyspnea [33].

The multifactorial organ-related causes of dyspnea, the occurrence as a drug-induced side effect [1,7–11], along with the breadth of the clinical symptoms, the prognostic implications, the huge armamentarium of diagnostic tools, and the plethora of therapeutic options, warrant this review. In particular, it is important to recognize differences in pathophysiology and presentation of pathological causes of dyspnea compared with benign, drug-related dyspnea.

2. Pathophysiology and clinical presentation

This section will discuss the current understanding of neurophysiology, i.e., the receptors, afferents, efferents, and cerebral centers involved in the context of dyspnea, followed by the clinical presentation.

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2.1. Neurophysiology

The main functions of the bronchopulmonary system are to clear carbon dioxide from the blood, enrich the blood with oxygen, and balance the blood pH according to the needs of the body to support the renal and other organ systems [34]. Involuntary breathing centers in the brain stem are predominantly regulating these functions (medulla, pons, nucleus tractus solitarius) by controlling the respiratory muscles. This is complicated by the fact that cortical voluntary centers themselves also drive these respiratory muscles and may overrule the involuntary ones to an extent that is trainable, as demonstrated by free divers who can hold their breath for several minutes while reaching depths of more than 100 m (300 ft). In critical and life-threatening situations, however, the involuntary centers take over [35,36], indicating that sensory input is a critical and, in some instances, insuppressible determinant of balancing efferent breathing commands.

Anatomically, breathing encompasses the macro level organ systems such as the conductive airways from the mouth/nose to the alveoli, the lung parenchyma, the thoracic cage with its bones, cartilages and muscles, the cardiovascular system, and the inner layers ("lining") of these organs. These organs are regulated and modulated by a complex system of varied receptors, such as the slow-acting (SAR) and rapid-acting receptors (RAR), the chemoreceptors in the aorta and the carotid artery, the mechanoreceptors of the chest wall, and the metaboreceptors within the muscles, and by afferent and efferent nerves including bronchopulmonary and jugular vagal C-fibers [37]. These receptors register the position, force and tension of a muscle [38], the pressures within the participating systems, the pH and other parameters before sending a plethora of signals to sensory respiratory control centers in the brainstem [37]. Then the somatosensory cortex and other higher centers, such as the posterior cingulated gyrus, appear to elicit and modulate the sensation of dyspnea [37,39].

In addition to the peripheral afferent input, these cerebral sensory centers obtain "copies" of both involuntary and voluntary motor command centers that stimulate the peripheral muscles, a principle commonly referred to as "corollary discharge" [40,41]. This critical mechanism sets the reference of what is supposed to happen in the periphery following a particular stimulus. If the feedback from the periphery does not meet these expectations then sensations of discomfort may occur, i.e., dyspnea [42,43]. A straightforward example is the well-known interaction between the intrafusal muscles and the main (respiratory) muscles.

Some receptors, as described later for those on C-fibers, demonstrate "plasticity", i.e., their sensitivity may be modulated by inflammatory mediators like bradykinin and acid aerosols [44–46], enhancing protection of the airways when needed but producing annoying cough when overreacting.

It is tempting to assume that the sensory feedback from distinct types of peripheral receptors is qualitatively distinct [47] and that this feedback is further processed by centers in the brain (medulla, pons, cerebellum) to create different sensations that should ultimately be perceived as dyspnea of distinct qualities [35]. However, it appears that the sensation of dyspnea is almost always based on the input from multiple types of receptors and not just a single sensor [44]. It has been proposed, and scientifically substantiated, that the dyspnea triggered by each disease may be represented by a cluster of symptoms as each disease is associated with the activation of a variety of very different pathophysiologic mechanisms [47,48]. Although cluster analysis of several symptoms may enhance the predictive power for mortality in patients with COPD [49], the discriminatory power of the obtained clusters does not seem high enough to establish them as a tool to unequivocally differentiate between diagnoses based solely on the quality of dyspnea [50].

Higher levels of the brain have the ability to "interpret" these incoming sensations (emotional processing) [39,51], gauging them as positive, i.e., in sports, or negative, as in disease. This perception is modulated by past experience: the brain seems to memorize the level and the characteristics/quality of dyspnea induced by a previous activity, effort, or situation, to set the expectations accordingly, and ultimately compare the current input with that in the past [52,53]. It has been shown that, following conditioning, even harmless cues per se may trigger dyspnea with varying susceptibilities in different groups of individuals [54]. This reference is subject to changes at the conscious level using cognitive processes such as experience, learning, and interpretation [16,39,51]. A forward mechanism in the perception of dyspnea has also been hypothesized: current breathing may meet the current demands but may be considered insufficient for the anticipated effort of the task to come [51]. This concept gives rise to a therapeutic intervention by explaining to the patient what is expected to come.

The airways and the lungs need protection from foreign bodies, irritants, and chemically harmful substances including cigarette smoke [55], capsaicin [56], acids [56] such as citric acids, air pollutants such as ozone [57,58], sulfur dioxide [59] and acrolein [60], and a plethora of others [61–63]. These substances stimulate a host of specialized receptors that generate afferent signals [64]. Subtypes of non-myelinated C-fibers transmit these signals from the mucosa and the deeper lung structures [65] to the brain and are part of a system that, in the animal model, may trigger reactions such as irritation, burning and choking sensations in the throat, neck and upper chest, mucus secretion, and tachypnea [61,62,64]. Moreover, not just external chemicals including drugs [66,67] but also physiologic metabolic degradation products from the blood, such as adenosine, have been identified as direct stimuli of bronchopulmonary sensory C-fibers [6,68–71]. Specifically, A_1 and A_{2A} receptor subtypes have been implicated in triggering dyspnea without bronchopulmonary function impairment, as demonstrated in rats [69,71] and guinea pigs [68]. Stimulation of bronchopulmonary C-fibers by other substances [72–74] via an increasing number of channels (e.g., the transient receptor potential cation channel, member A1 [75]) elicits different symptoms such as cough and a burning sensation. Interestingly, jugular C-fibers or pulmonary stretch receptors [68] are not an adenosine target as they appear to be of a different phenotype [76] with distinct activation profiles from bronchopulmonary C-fibers [37].

In addition to internal compounds, external substances such as drugs have been reported to increase adenosine concentrations through interference with the physiologic cellular adenosine uptake. Inhibition of the sodium-independent equilibrative nucleoside transporter (ENT)-1 has been identified as the key mechanism that raises adenosine concentrations, ultimately triggering dyspnea [6,70].

2.2. Clinical presentation and related physiology

Clinically, the differentiation of four qualities of dyspnea has been suggested. Several attempts have been undertaken to associate them with physiologic mechanisms even down to the receptor level [12]. These have been identified as the following:

- Work/effort
- Tightness
- Air hunger/unsatisfied inspiration
- Other qualities.

Work/effort is commonly associated with progressing asthma attacks [48,77,78] and chronic obstructive and interstitial pulmonary disease, as well as conditions in which ventilation is affected, such as with weakened respiratory muscles [42,47,79–81]. The receptors implicated seem to be located within the lungs and the respiratory muscles (dynamic hyperinflation [38]) and also appear to be involved in triggering air hunger [44]. The physiologic correlates include (enhanced) cortical motor commands to the respiratory muscles [82] and corollary discharge [38,82,83], although some hypercapnic and limited muscular metaboreceptor contribution is being accounted for [82]. It is also