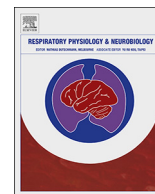




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Editorial

Cough and airway defence – Special issue of respiratory physiology and neurobiology

Airway defensive reflexes serve an important role for the respiratory system to fulfil physiological gas exchange at a rate which matches metabolic demands of tissues. These reflexes are specific, spatio-temporally orchestrated motor acts, main purpose of which is to prevent aspiration of liquids or corpuscular material into the airways, or eventually expel mucus and other potentially harmful substances out of the respiratory tract.

These motor acts are precisely regulated to provide sufficient airway protection and defence. Decreased performance of these complex neuromuscular behaviours can lead to the aspiration with further consequences, e.g. aspiration pneumonia, which considerably increase respiratory morbidity and mortality in specific populations of patients. Strategies serving to increase effectiveness of these motor acts or to substitute them are of high clinical importance.

On the other hand, exaggerated airway defensive reflexes – mainly cough – to otherwise innocuous stimuli lead to intractable coughing, which manifests as hypersensitive cough syndrome. It considerably decreases patient's quality of life, and may lead to secondary damage of the airway wall. Therapeutic strategies developed in this field so far are of debatable efficacy. Further research is necessary to understand pathogenesis of this syndrome to find reliable treatment.

Both up-regulation and down-regulation of airway defensive reflexes should be studied to develop optimal clinical approaches. In this special issue, Spinou introduces the clinical entity of cough as the continuum with two extremes at its sides. From extremely exaggerated cough, which reduces quality of life to attenuated cough, which represents a risk of aspiration pneumonia. Together with the extensive research of pharmacological strategies, non-pharmacological approaches were developed and validated to help patients with either cough control or cough augmentation. The main direction of these techniques is the support of cough motor output and exercising the cognitive control on coughing. Their article discusses the techniques which can empower patients to increase their supramedullary control of cough or augment the cough motor drive e.g. manual or mechanical hyperinflation, manually assisted cough or respiratory muscles training (Spinou, 2018).

Chronic hypersensitivity cough syndrome, which was recently defined as a new clinical entity to embrace all coughers with “unknown” cause of cough but hypersensitivity of airway sensory afferents (Morice, 2013) affects mainly postmenopausal women. Why hypersensitivity develops in this demographic group is not entirely understood, but Kavalcikova-Bogdanova and co-workers threw some light to this field. They showed that sensitivity of airway afferents to the tussive agent

capsaicin varies during menstrual cycle and this functional change is not present in women taking contraceptive pills. According their findings the cough sensitivity to capsaicin correlates with ratio of progesterone/oestrogen and relative lack of oestrogen in luteal phase is associated with higher sensitivity to inhaled capsaicin. The ratio of progesterone/oestrogen seems to be the target for further studies to elucidate relationships between hormonal withdrawals in menopause and cough hypersensitivity (Kavalcikova-Bogdanova et al., 2018).

Next contribution points to the not entirely understood pathogenesis of cough in sarcoidosis. Cough is a common and significant symptom in sarcoidosis, which is a multisystem disease of unknown aetiology characterized by presence of non-caseating granulomatous inflammation. Objective cough monitoring proved that sarcoidosis patients have significantly higher cough frequency compared to control subjects. Their cough exhibits diurnal variation, it is gender specific and shows racial differences. While it correlates with the presence of the airway inflammation, it shows relationship neither with the X-ray staging, nor the degree of airway obstruction. The most relevant cough triggers interacting with the airway sensory nerves are not only the airway inflammation with its consequences, but also the presence of considerable biomechanical forces in pathologically changed airways (Kovacova et al., 2018). Better understanding of the pathogenesis of cough in sarcoidosis patients may lead to the improvement of their quality of life by application of targeted treatment.

Chronic cough is frequently associated with the gastroesophageal reflux (GER). Subjects with reflux have heightened cough sensitivity, and this phenomenon is attributed to the neuroplastic changes of vagal C-fibres innervating the airways and oesophagus, as well. Sensations perceived in reflux patients such as heartburn is however perceived via fibres derived from dorsal root ganglia. Relationship between cough sensitivity measured by inhalation of capsaicin and oesophageal sensitivity measured by intensity of heartburn induced by oesophageal acid infusion was studied by Duricek and his team in patients with symptomatic GER. The measurement was repeated after 3 months on treatment by proton pump inhibitors. This medication substantially reduced oesophageal sensitivity to acid but it did not influence sensitivity of airway afferents to inhaled capsaicin. The results of this group indicate that spinal and vagal afferents are influenced separately in patients with GER (Duricek et al., 2018).

Cough and airflow limitation are predominant symptoms and signs in chronic obstructive pulmonary disease (COPD). The natural history of the disease includes progressive development of mentioned problems punctuated by acute exacerbations COPD during which they rapidly

deteriorate. The increased risk of resulting disability places significant burden on health and social care system. Cough is the second most common symptom reported by COPD patients and it is a source of significant distress associated with adverse outcomes. It is linked with exacerbation frequency and predicts clinical deterioration. A paper by Crooks and co-workers discusses that whilst the precise mechanism of cough in COPD is not understood, but airway inflammation and neurogenic factors are clearly important. Even though the suppression of cough is not the goal of COPD treatment, normalising the cough reflex intensity and frequency will alleviate patient's suffering. On the other hand, detection of an increased cough frequency may prove to be a useful predictor of exacerbation allowing timely intervention (Crooks et al., 2018).

Clinical evaluation of cough is difficult, because physicians do not have objective information about the cough frequency during the day or night-time, so they can barely recognize its true significance for the patient's quality of life or observe the success or a failure of applied treatment regimes. The objective assessment of cough frequency is essential for evaluation, nonetheless, available algorithms for automatic detection of cough sound have limited sensitivity and the analysis of cough sound often requires a human observer. Klco and co-workers developed a novel algorithm of automated cough sound recognition based on eight dimensional numbers called "octonions" and compared it with the algorithm based on classic neuronal network. The authors showed that use of octonions for classification of cough sounds improves sensitivity and specificity of cough sound detection. Hopefully, their further research can provide accurate devices useful for objective measurements of cough frequency in everyday clinical setting (Klco et al., 2018).

Along with the cough frequency, another parameter of cough is clinically relevant – it is cough intensity, which defines how strong the expiratory expulsion removing the mucus and other potential hazards out of the airways is. One can easily assume that robust cough sound indicates also high speed of expiratory expulsions. McGuinness with his team studied the effects of cough effort and the volume inspired prior to coughing on surrogate measures of cough intensity measured by respiratory muscle electromyogram, intrathoracic and intraabdominal pressure and finally the cough sound. They found that effort and operating volume have important influences on cough mechanics in healthy volunteers, but they modulate muscle activation, pressure and sound differently. Importantly, this study showed that cough sound poorly represents the cough mechanics and has limited potential as a surrogate intensity measure (McGuinness et al., 2018).

Cough challenges in specialized cough clinics are usually performed by inhalation of a tussive agent in doubling concentrations, until the cough threshold is reached. The current guidelines recommend inhalation of either capsaicin or citric acid. Citric acid has been used for over six decades to induce cough; however, the mechanism of its pro-tussive effect is still not fully understood. Rai and co-workers evaluated the response to inhalation of citric acid at varying levels of acidity to determine if the pH of the solution plays a role in the induction of cough. Study was conducted in both healthy volunteers and patients with chronic cough. The subjects were inhaling aerosol of 300 mM citric acid solution, while the concentration of the citrate anion remained constant, the pH of the solution was altered by the addition of sodium bicarbonate to 3, 5 and 6, representing the pKa values of the individual acid moieties. The total number of coughs elicited was recorded for each inhalation. The study showed that chronic cough patients coughed more than healthy volunteers and did not exhibit a clear pH response. There was also a greater variability in their response to individual challenges (Rai et al., 2018).

An interesting study was performed by Wasilewsky and co-workers. The study assessed the effect of deep inspirations (DIs) on airway behaviour in individuals with classic asthma, cough-variant asthma, and methacholine (MCh)-induced cough but normal airway sensitivity during bronchoprovocation to understand whether this manoeuvre can

help to distinguish these three clinical entities to establish the proper treatment for either classic asthma, cough variant asthma and cough respectively. Twenty-five adults assigned to groups according to the inclusion criteria completed two single-dose MCh challenges, with and without DIs. Bronchoprotection was assessed by comparing changes in bronchoconstriction (according FEV₁, FVC, FEV₁/FVC, FEF₅₀, FEF₂₅₋₇₅), gas trapping (RV, RV/TLC) and impulse oscillometry (IOS) measurements. This study found that deep inspirations triggered bronchoconstriction in the group with classic asthma, provided bronchoprotection in subjects with cough-variant asthma and prevented gas trapping in group with methacholine induced cough (Wasilewski et al., 2017). The results of this study indicate that DI manoeuvres can be a helpful tool in differential diagnostic protocols.

Clinical approach to a patient suffering from cough requires special attention when it comes to the children and the elderly. Obviously, there are specific features of children that must be taken into consideration in clinical settings, e.g. aetiology, diagnostic tools, age restrictions for cough sensitivity tests, treatment options etc. However, there are specific features of cough in elderly patients, as well. Chronic cough is more prevalent in elderly than in young subjects, and more challenging to manage due to frequent comorbidities and possible side effects from medication. Cough reflex does not decrease with natural ageing but it is often impaired by ongoing pathological circumstances, such as stroke. The impairment of cough reflex may lead to fatal complication such as aspiration pneumonia. Therefore, it is important to note that there are well developed methods and approaches which can augment the cough reflex to prevent aspiration pneumonia. These are e.g. treatment by ACE inhibitors, which improve both cough and swallowing very likely due to the accumulation of substance P and bradykinin. Also, intensive oral care together with oral administration of capsaicin troches or use of black pepper oil prior to food have clinical significance (Won et al., 2018).

There are two contributions discussing cough in paediatric population. Since the cough associated with exercise is common symptom in children with bronchial asthma, cough reflex sensitivity to capsaicin was studied in children with asthma after the exercise. The authors examined 42 children with asthma by standardized capsaicin inhalation test and they found out that exercise in asthmatic children does not influence their cough reflex sensitivity (Ferenc et al., 2018) like in healthy children and adults, where exercise significantly reduces this parameter (Demoulin-Alexikova et al., 2017). Since the cough reflex is not down-regulated in asthmatic subjects, authors hypothesize that this dysregulation may contribute to the increased frequency of coughing during and after exercise in this demographics (Ferenc et al., 2018). Cough sensitivity was also tested in children with adenoid hypertrophy, which is together with cough a frequent manifestation of the atopy in childhood. Children in which the adenoid hypertrophy was verified by fibre-optic endoscopy underwent the capsaicin cough sensitivity tests prior to the adenoidectomy and after the recovery. The study does not show significant changes of cough reflex sensitivity after the recovery period in children after adenoidectomy (Ferenc et al., 2018) This phenomenon is worth of detailed follow-up studies to elucidate the effect of adenoidectomy on neurophysiology of the cough reflex in children.

Cough is modulated by many processes, either physiological (e.g. sleep, exercise) or pathological (e.g. inflammation, oxidative stress). This modulation may manifest by attenuation or exaggeration of cough response to the defined stimulus in experimental conditions. Brozmanova and Hanacek (2018) summarize the results of their previous studies in the guinea pig model exposed to hyperoxia. The authors documented that hyperoxia-induced damage of the airway epithelium together with the oxidative stress attenuate cough response in this animal model. These studies also demonstrated that supplementation of suitable antioxidants has had beneficial effect in restoring the cough responsiveness to physiological range. Series of these studies have direct clinical application as majority of airway diseases are associated with oxidative stress, which could be successfully managed by

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