



## Early View

Research letter

### **Inspiratory vocal cord closure in chronic obstructive pulmonary disease**

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**Title:** Inspiratory vocal cord closure in chronic obstructive pulmonary disease

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*Dear Editor,*

During normal inspiration, vocal cord movements are limited although mild abduction (widening) can occur[1]. Inspiratory closure is characteristic of vocal cord dysfunction (VCD), a condition that can cause refractory breathlessness[1, 2]. VCD may occur in otherwise healthy individuals and 20-40% of stable asthmatics[3], however, abnormal inspiratory vocal cord activities and putative VCD have not been investigated in other obstructive lung diseases. It is therefore of interest to determine whether inspiratory closure occurs in chronic obstructive pulmonary disease (COPD).

We hypothesized that inspiratory closure may occur frequently in COPD as well as during acute exacerbations of COPD (AECOPD) and dynamic computed tomography (CT) of the larynx was used to evaluate three groups. Healthy individuals and patients with COPD who had participated in studies examining excessive dynamic airway collapse (EDAC)[4] were assessed. A control group consisted of healthy older volunteers without respiratory symptoms (n=40). The stable COPD group was comprised of patients in the original cohort[4] as well as additional outpatients with breathlessness on exertion (n=76). No patients had acute exacerbations of COPD (AECOPD) in the preceding three months. The third group consisted of consecutive patients with hospitalised AECOPD (n=61) and in this group pulmonary function testing was performed after recovery from AECOPD. Individuals with AECOPD underwent dynamic CT of the larynx as soon as possible after admission ( $12\pm 7$  hours; mean $\pm$ SD). COPD was diagnosed by specialist pulmonologists and verified by spirometry, with airflow limitation classified according to the Global Initiative for Chronic Obstructive Lung Disease[5]. No patients had a history or other evidence of asthma. Studies were done at Monash Medical Centre, Melbourne, Australia and all studies were approved by Monash Health Human Research Ethics Committee. Patients gave informed consent.

Although the diagnostic gold standard for inspiratory closure is nasal laryngoscopy, this technique has limitations[6, 7] and we have developed an alternative approach: dynamic CT of the larynx. The method can be used to diagnose inspiratory closure and presumptive VCD in chronic asthma[6] and we have recently reported studies in acute asthma exacerbations[8]. In brief, measurements of vocal cord diameter are made at 0.35s intervals, normalised to tracheal measurements and integrated into a diagnostic algorithm. Patient curves covering the breathing cycle are generated and compared to standard curves and inspiratory closure can be

detected if the patient curve is below the lower limit of normal curve during inspiration (or during both inspiration and expiration but not expiration only). The method has been shown to have good specificity and to be equivalent to laryngoscopy in stable disease[3, 6]. In the current studies patients without and with inspiratory closure were compared using Fisher's exact test (categorical data) and appropriate non-parametric tests (continuous data).

Patient characteristics are shown in the Table. No healthy volunteers had abnormal vocal cord movement. However, inspiratory closure was detected in the stable outpatient COPD group in 21/76 patients (27.6%) and the AECOPD group in 19/61 patients (31.1%). Within the stable COPD group, demographic variables (age, sex, body mass index, spirometry including bronchodilator response and diffusing capacity) did not differ between patients with inspiratory closure detected and not detected. Age, sex, smoking history, body mass index, FEV<sub>1</sub>, bronchodilator response and diffusing capacity were similar as were exacerbation characteristics including BAP65[9] class and length of stay. In both COPD groups, inhaled medications did not significantly differ between patients with or without inspiratory closure.

The current studies therefore did not detect inspiratory closure in healthy individuals but the abnormality was noted in approximately one quarter of patients with COPD. In a separate group with AECOPD the prevalence was similar. These preliminary findings indicate that the quintessential inspiratory abnormality of VCD may be common in COPD and that VCD may be happening 'under our noses'[5]. Whether patients had 'true' VCD requires further study considering the need to have abnormal inspiratory vocal cord movement occurring with commensurate symptoms in an applicable clinical context. Our findings also infer that VCD may compound symptoms, at least in some individuals with COPD; this aspect also requires future study.

The findings are not entirely surprising. Our previous studies in asthma suggested that airway obstruction with associated dysfunctional breathing may cause laryngeal activation leading to VCD in many patients[3]. This pathophysiology may also be applicable in COPD given the high prevalence of dysfunctional breathing in COPD[10]. Other explanations are possible. For example, functional expiratory laryngeal changes have been reported in COPD[11] with expiratory laryngeal closure during exercise which may be a plausible physiological mechanism to generate positive end-expiratory pressure. Although inspiratory closure is generally considered abnormal[12], inspiratory closure may be part of a compensatory strategy in COPD that remains to be elucidated.

Why has inspiratory closure of the vocal cords and putative VCD not been suspected in COPD? There are several possibilities but a likely reason is that patients with COPD have impaired respiratory function (as part of the diagnosis) and therefore an attributable cause for their breathlessness. Additionally, COPD symptoms are often not resolved by treatment. Asthma, in contrast, is characterised by (mostly) normal lung function leading to early suspicion of VCD if breathlessness is unresponsive to treatments. Overall, our findings emphasise the importance of the 'middle airway', a key part of the airway long ignored[7] that may play a cardinal role in the generation of more severe symptoms in asthma and COPD.

There are important aspects to consider in the interpretation of this preliminary data. Care was taken to exclude asthmatic patients but it is possible that a small number may have been included. Careful repeat review of patients with COPD found no evidence of asthma. All were smokers (>40 pack-years in both COPD groups), had impaired pulmonary function and had been diagnosed and treated for COPD by a respiratory specialist. The COPD groups were also older than the healthy controls. Since age has not been linked to VCD this factor appears unlikely to explain our findings, particularly since there was a large overlap in age and many healthy individuals were older than persons with COPD and VCD. Finally, initial validation of the algorithm used to detect inspiratory closure was conducted in asthma. Similar validation in COPD has not been done but it appears unlikely that application of the technique in COPD is not valid.

In summary, we report inspiratory vocal cord closure coexisting with COPD, which may amplify breathlessness and blunt pharmacological and other treatments. VCD should be considered as a comorbidity not only in asthma, but also in COPD and further investigation is merited.

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**Table: Demographic characteristics of subjects included in studies**

	Healthy individuals (n=40)	Stable COPD (n=76)	Acute exacerbations of COPD (n=61)	P-value for group comparison
Age (years)	61.6±12.0	69.3±10.2	71.5±11.1	0.70
Sex (F/M)	25/15	33/43	23/38	0.35
Body mass index (kg/m <sup>2</sup> )	29.5±5.7	28.3±7.4	24.9±4.9	0.19
Smoking (pack-years)	8.6±13.6	41.1±25.6	59.1±51.9	0.027
Lung function				
FEV <sub>1</sub> post bronchodilator (% predicted)	100.9±16.7	55.6±23.3	48.2±19.8	0.062
FEV <sub>1</sub> /FVC	76.1±7.6	46.2±13.3	48.8±15.0	0.31
Bronchodilator response (%)	3.5±3.7	9.0±9.4	6.2±7.9	0.21
TLCO (% predicted)	89.6±13.6	58.9±21.7	49.9±21.3	0.032
Inhaled treatment(s)				
Inhaled corticosteroids	nil	14 (18.4%)	43 (70%)	<0.0001
Long acting beta agonist	nil	59 (77.6%)	43 (70%)	0.43
Long acting muscarinic antagonist	nil	58 (76.3%)	38 (62%)	0.09
Inspiratory vocal cord closure	nil	21 (27.6%)	19 (31.1%)	0.71
Expiratory vocal cord closure	nil	22 (28.9%)	17 (27.9%)	1.0

Values are mean±SD or n (%). P values from ANOVA, or Fisher's exact test as appropriate.



Abbreviations: COPD – Chronic Obstructive Pulmonary Disease; FEV<sub>1</sub> – forced expiratory volume in one second; FEV<sub>1</sub>/FVC – forced expiratory volume in one second/forced vital capacity; TLCO – diffusing/transfer capacity for carbon monoxide