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Inducible Laryngeal Obstruction (ILO) Coexisting with COPD can Fatally Influence the Course of COPD Exacerbation

Wlodzimierz Mierzwa[1]; Wlodzimierz Wróbel W[1]; Lech Polewiak[2]; Anita Krzywańska-Ferens[2]; Sandra Kucięba[1]; Dariusz Ziora[1]*

[1]Department of Pulmonology, Virgin Mary Provincial Specialist Hospital, PCK 7, 42-202 Częstochowa, Poland.

[2]Department of Radiology, Virgin Mary Provincial Specialist Hospital, PCK 7, 42-202 Częstochowa, Poland.

***Corresponding Author:** Dariusz Ziora*

Tel: +48-607-396-880; Email:zioradar@wp.pl

Abstract

An intermittent extrathoracic airway obstruction due to adduction of vocal cords, formerly referred to as Vocal Cord Dysfunction (VCD) and now as ILO or VCD/ILO, can lead to sudden dyspnoea of varying intensity mimicking asthma attacks. VCD/ILO may often coexist with asthma, but only few reports mention VCD/ILO coexisting with COPD. The course of VCD/ILO is usually mild, especially in young patients, and the attacks resolve spontaneously or after treatment in a few minutes. However, we observed prolonged and repeated VCD/ILO attacks with desaturation in a 65 years old patient with COPD exacerbation. In our opinion, VCD/ILO could increase the risk of death and despite proper intensive treatment; it ultimately influenced the fatal outcome and sudden death.

Keywords: Inducible Laryngeal Obstruction; Vocal Cord Dysfunction; COPD; COPD exacerbation; Upper air-way obstruction; Sudden death.

Abbreviations: ILO: Inducible Laryngeal Obstruction; VCD: Vocal Cord Dysfunction; COPD: Chronic Obstructive Pulmonary Disease; ECG: Electrocardiogram; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume In 1 Sec., MEF50: Maximal Expiratory Flow At 50% Of FVC; MIF50: Maximal Inspiratory Flow At 50% Of FVC; Hb: He-moglobin; WBC: White Blood Cells; CRP: C-Reactive Protein; BNP: Brain Natriuretic Peptide; EF: Ejection Fraction.

Introduction

The paradoxical vocal fold motion disorder, also known as Vocal Cord Dysfunction (VCD), is an intermittent extrathoracic airway obstruction due to adduction of vocal cords mainly during inspiration leading to dyspnea of varying intensity with accompanying cough and stridor [1,2].

In 2013 the European Respiratory Society/European Laryngological Society/American College of Chest Physicians Task Force larynx accepted the definition: “Inducible Laryngeal Obstruction (ILO)” for episodes of breathing problems caused by re-occurring variable airflow obstructions in the larynx [3]. The location of the obstruction can be supraglottic (the arytenoid regions, epiglottis or false vocal folds), glottic (the true vocal folds) or both supraglottic and glottic. The obstruction can be present during inspiratory, expiratory, or both inspiratory and expiratory phases of the respiratory cycle [3]. During International Round table Conference in Melbourne (Australia) the term ‘VCD/ILO’ was used and several phenotypes, such as: classic VCD/ILO, lung-disease associated VCD/ILO, exercise -VCD/ILO, incident- associated VCD/ILO, and cough-associated VCD/ILO, were recognized [4].

VCD/ILO is most likely caused by laryngeal hyperresponsiveness, with increased sensitivity of the laryngeal sensory receptors and heightened response of the glottic closure and cough reflexes [2,4,5]. There are several known inducers causing VCD/

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ILO: mainly exercise, nonspecific airway irritants, such as odors, perfumes or cold air. In some cases, the psychological origin for of VCD/ILO has been suggested [1-5]. Emotional stress, anxiety and panic attacks, depression or mental illness are well known VCD/ILO triggers [1,6-8]. Among 42 patients with pure VCD, 73% had a major psychiatric disorder and 37% had a personality disorder [1]. In others patients the Gastroesophageal Reflux Disease (GERD) was associated with intermittent laryngeal obstruction. In some cases, the inducer/s could not be identified [3-5]. Hence VCD/ILO still remains a poorly understood and characterised entity and should be carefully differentiated from vocal cord paresis, laryngomalacia, vocal fold polyps, malignant tumors of larynx or thyroid carcinomas [8]. Upper airway obstruction may be also due to other etiologies, including papilloma formation in the larynx, subglottic stenosis, or benign thyroid tumors causing extrinsic compression. Rheumatoid arthritis, lupus, or Wegener's granulomatosis can also have laryngeal manifestation [2,5].

The true incidence of VCD/ILO is unknown. Brugman et al. [9] observed this pathology both in very young and very old patients and noticed a broad overall age range from 0.02 to 82 years and the median age 36.5 years in adults and 14 years in children. The clinical presentation of VCD/ILO is widely variable and most often it can mimic asthma attacks [1,2,10,11]. Patient reported symptoms may be both chronic or acute and besides shortness of breath also include a choking sensation, chest tightness, a globus sensation, intermittent aphonia or dysphonia, fatigue and throat clearing. Very often the symptoms are refractory to the anti-asthmatic therapy. Many authors believe that VCD/ILO is a widely underappreciated clinical problem, diagnosed relatively late and consequently improperly treated [1,4-8,10,11].

We would like to present a patient with COPD exacerbation diagnosed with coexisting VCD/ILO, which in our opinion significantly contributed to the fatal course of the disease and the patient's sudden death.

Case presentation

A 65 years old male, former heavy smoker, was admitted the Dept. of Pulmonology in the Virgin Mary Provincial Specialist Hospital in Czestochowa on 02.03.2023 with the initial diagnosis: Of exaggerated dyspnea due to COPD exacerbation. The patient-reported symptoms included dyspnea at rest with abrupt intensification and a sensation of globus and choking from time to time. During chest auscultation diminished vesicular breath sounds were present. Additionally, stridor was periodically audible during dyspnea intensification and/or sudden dyspnea attacks, which were evidently elicited by fear, panic, and anxiety, periodically observed in the patient, further leading to the worsening of the shortness of breath.

Comorbidities recognized previously in the patient were: Atherosclerosis with the history of NSTEMI myocardial infarction in 2016, and a minor ischemic stroke without significant neurological deficits, also in 2016. At the admission to hospital on 03.03.2023 his vital lab parameters, i.e.: Hb, WBC, ALT, AST, creatinine, BUN, Na, K , Troponin TsTnI, pro-calcitonin, and BNP levels were within normal range. Only CRP was very slightly elevated (11.,1 mg/ml) and the D-dimer level was increased to 4568 FEU/ml on 05.03.2023 (normal values<500 FEU/ml), but in 4 days the D-dimer concentration dropped to 2400 FEU/ml. In ECG a normal sinus rhythm 80/min without evident signs of any pathology was observed. A blood gases analysis revealed pH=7.41, PaO_2 = 57 mmHg, $PaCO_2$ = 36 mmHg, blood pressure was 140/80 mmHg. The calculated BAP-65 score predicting in-hospital mortality was 1.0% and the calculated need for mechanical ventilation within 48 hours was 0.2% [12]. However, the DECAF score = 2 indicated an intermediate risk and the in-hospitality mortality rate=5.4% [13].

The echocardiography performed on 03.03.2023 revealed normal EF (55%) and normal left ventricular contractility, but the right ventricle was enlarged and the calculated TAPSE (tricuspid annular plane systolic excursion) = 12 mm was below the normal range, which altogether was suggestive of pulmonary hypertension.

A CT scan was performed on 05.03.2023 by means of a 32-slice multidetector CT scanner GE Healthcare Revolution EVO, Waukesha, USA. The laryngeal CT protocol included a standard neck CT and a dedicated larynx scan [14]. The neck CT images were obtained from the base of the skull to the arch of the aorta while the patient performed quiet breathing. Coronal and sagittal reformatted images of the entire neck were also obtained. The images were reviewed with soft-tissue window and bone window settings. The larynx scans were obtained through the area from the hyoid bone to the bottom of the cricoid cartilage, with 1.25 mm axial images during inspiration and normal breathing.

CT was repeated on 06.03.2023 and revealed significant narrowing of the glottis and supra-glottis patency to 2 mm in diameter (Figure 1). Additionally, centrilobular emphysema with emphysematous bullae was detected in both lungs. Due to of the suspected extrathoracic upper airway obstruction coexisting with severe COPD a laryngological consultation was suggested. During the stabilization period on 08.03.2023 the flexible, transnasal fiberoptic laryngoscopy revealed no significant organic larynx pathology covering epiglottis, false vocal folds, and true vocal cords motion during phonation. The spirometry obtained on 10.03.2023 revealed a very severe obstruction with FVC=1.6 l (41%), FEV_1=0.62.(21%), and FEV_1/FVC= 38%. The flow volume loops demonstrated flattening in both expiration and inspiration, suggesting an upper airway obstruction.

Unfortunately, over the next few days, the patient relapsed with panic attacks and anxiety, with intensification of the shortness of breath, desaturation of up to 88% SaO_2, choking, productive cough, and hemoptysis. During one of these shortness of breath attacks on 13.03.2023, we performed a larynx ultrasound examination at the patient's bedside. We used the Arietta S 70 Hitachi Aloka ultrasound system with a 10-12 MHz linear transducer and a 1-5 Hz convex transducer. We applied a conventional middle transverse procedure for the assessment of the vocal cord movement, as previously described [15,16]. The linear and convex transducers were placed transversely over the middle portion of the thyroid cartilage [17]. The adduction of the true vocal cords during inspiration was visualized. On the same day, i.e. on 13.03.2023 the fiberoptic bronchoscopy was performed (Olympus- Japan) for the visualization of the upper and lower airways. We found normal epiglottis; arytenoid and postarytenoid mucosa showed no oedema and no collapse. The true and false vocal cords (folds) were relatively easily visualized. The patient was asked to perform a forced expiratory and inspiratory vital capacity maneuver after panting, which may be helpful in discovering any abnormal vocal cord movement. The true and false vocal folds adducted paradoxically during inspiration, reducing of the cords luminal area by more than 80%. During exhalation both the false and true vocal cords adducted

almost completely. No subglottic stenosis was present. The trachea and bronchi available for the BF examination were patent, with normal mobility during coughing and breathing. Only the bronchial mucosa was reddened and swollen in some places and bleed easily when touched by the tip of the endoscope. Therefore, we finally diagnosed VCD/ILO coexisting with very severe COPD. The consulting psychiatrist stated no psychosis and ordered psychotherapy and eventual benzodiazepines, if necessary, during anxiety and panic attacks.

Despite intensive treatment using beta-2 mimetics and anticholinergics nebulizations, systemic steroids, antibiotics, LMW heparin, oxygen therapy via nasal prongs (1-2 l/min) and sedative drugs, rehabilitation and psychotherapy, we observed no significant clinical improvement. The sudden cardiac arrest took place on 21.03.2023 during the next dyspnea attack and the patient died. Post mortem autopsy was not performed.

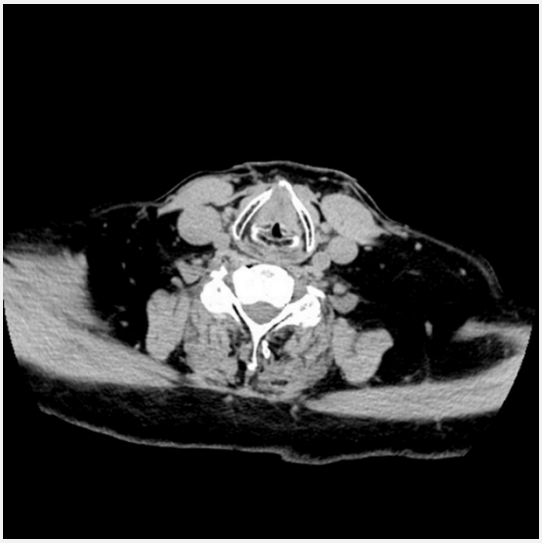

Figure 1a: Patient R.A. aged 65. CT scan revealed airway narrowing at glottis level during dyspnea exaggeration (normal breathing).

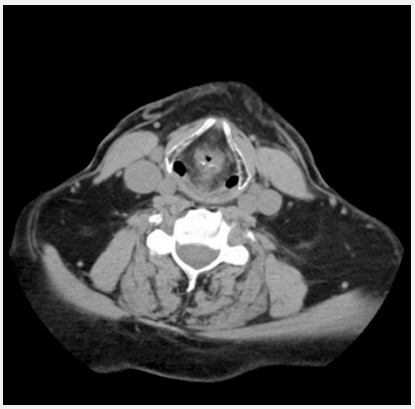

Figure 1b: Patient R.A. aged 65. CT scan revealed airway narrowing at glottis level during dyspnea exaggeration (normal breathing).

Discussion

We present a case of an elderly patient with exacerbation of COPD and undiagnosed VCD/ILO before admission to the hospital. In our opinion, this coexisting VCD/ILO adversely affected the course of the disease and may have directly contributed to the patient's death via several pathomechanisms. Ten years ago, Cho et al. [18] reported a fatal course of VCD in a 76- years old female exhibiting asthma-like symptoms with hypoxemia and acute respiratory failure. This female with resting dyspnea was first diagnosed with acute exacerbation of bronchial asthma. However, her symptoms were not controlled with the antiasthmatic treatment. The laryngoscopic examination confirmed a severe upper airway obstruction due to adduction of the vocal folds during inspiration. Unfortunately, on the day of the laryngoscopy a sudden cardiopulmonary arrest occurred. The vocal cord dysfunction and stridor may also account for unexpected sudden death in patients suffering from progressive neurologic disorders, namely: amyotrophic lateral sclerosis [19] and multiple system sclerosis [20].

Typically, VCD is described as a solitary pathology suggesting attacks and/or exacerbations of bronchial asthma [8,10,11]. However, it should be underlined that VCD/ILO can often coexist with asthma [1,2]. In some case series of 95 patients with VCD, 53 also had asthma [1]. Some authors pointed to a 27% (42/155) prevalence of VCD in asthmatic patients. They underline the association of VCD with asthma especially in persons with airflow limitation (FEV_1<80% of predicted) and dysfunctional breathing [21]. Among patients previously thought to have asthma with frequent emergency room visits, even 22% had VCD [22]. The recently published meta-analysis involving 21 studies and 1637 patients showed that the pooled prevalence of VCD/ILO in adults with asthma was 25% [23]. The airway obstruction in asthma with associated dysfunctional breathing may cause laryngeal activation leading to VCD/ILO in many patients. This pathophysiology may also be applicable in COPD. However, to the best of our knowledge only few studies indicate the coexistence of VCD/ILO with COPD [24-26]. Using the dynamic 320-slice computerized tomography of the larynx, Leong et al. [24] reported the inspiratory closure of the vocal folds in 21/76 (27.6%) patients with stable COPD and in 19/61 (31.1%) subjects with exacerbation of the disease. Additionally, the closure of the vocal cords during expiration was observed in 28.9% and 27.9% of patients with stable and exacerbated COPD, respectively. Among 34 hospitalized patients with asthma exacerbations and 37 patients with COPD exacerbations Ruane et al. [25] revealed VCD more often in COPD patients (14/37, 38%) than in asthmatics (6/34, 17.6%). Interestingly, VCD was more than twice as common in severe/very severe COPD than in mild/moderate COPD (71% vs 31%). Nevertheless, it was postulated that in COPD the expiratory laryngeal closure during exercise, may be regarded as a compensatory strategy, like as pursed-lip breathing, in order to generate the positive intrinsic end-expiratory pressure and to optimize lung mechanics during breathing [26]. In our patient VCD/ILO was diagnosed by ultrasonography at bed side during an attack and confirmed by flexible bronchoscopy after a suspicion of a laryngeal obstruction at the glottis and supraglottic levels during CT examinations. The endoscopic examination with direct visualization of the vocal cords via the flexible, transnasal fiberoptic laryngoscopy, or bronchoscopy possibly after a bronchial challenge or during an acute attack, is the gold standard for the diagnosis [2-4,8,15,16]. Surprisingly, a laryngoscope examination in our patient revealed no VCD/ILO but it was done during a clinical stabilization period and no panting and forced inspiration and expiration maneuvers were applied during examination. During VCD/ILO episodes non-invasive ultrasonography may identify paradoxical abnormal vocal cord adduction during inspiration [27]. However, according to Fukuhara et al. [15] and Kandil et al. [16], the reported successful visualization rate the vocal cord movement is approximately 50 to 70% and is significantly lower than usually achieved by laryngoscopy [15,16]. Nevertheless, recent studies show greater effectiveness of ultrasonography in

the VCD or vocal cord palsy diagnosis than previously reported [28]. In comparison to laryngoscopy, the sensitivity, specificity, positive predictive value, and negative predictive value of ultrasonography for assessment of the vocal fold mobility was even 80%, 96%, 89%, 93%, respectively [28]. Male gender, older age, and increased height and weight are potential obstacles in obtaining proper visibility of the vocal folds [29]. In our patient we were able to visualize the true and false vocal folds and their movement.

A new imaging technique that enables dynamic viewing of larynx structures is the four dimensional high resolution 320-slice computed tomography. This scanning technology uses a unique 320-slice detector ray to scan a 16 cm Z-axis 'volume' of structures over time and therefore is potent to provide accurate images of the vocal folds function during respiration and enable a non-invasive diagnosis of VCD/ILO [30,31]. We were able to apply only the conventional 3D tomography during inspiration and normal breathing but twice on separate days, receiving identical results, i.e.: upper airway obstruction due to a larynx lumen obstruction at the glottic and supraglottic levels.

The inspiratory flow loop obtained between attacks was flattened, but the FEF50/FIF50 ratio was below 1.0 due to severe obturation. For patients with VCD/ILO and a concomitant expiratory obstruction due to comorbid asthma or COPD, the FEF50/FIF50 ratio, which is usually less than one in healthy individuals and greater than 1 in patients with inspiratory VCD/ILO, may be difficult to interpret [5]. In our patient desaturation during attacks was observed at 88% despite the oxygen therapy via nasal prongs with the 2 l/min flow. There is no doubt that hypoxemia may occur in association with the severe VCD/ILO syndrome, but it is an exception rather than a rule [10,11]. However, in our patient VCD/ILO attacks were longer in duration than usually described in younger patients with asthma or patients with VCD/ILO mimicking asthma (where VCD/ILO related dyspnea is characterized by a sudden onset, duration below 2 minutes, and is typically self-limited [2,5]. Additionally, the closing of both the false and true vocal folds took place during inspiration, like in laryngospasm. The term 'laryngospasm' refers to a sustained intense, virtually complete closure of the vocal folds following direct laryngeal stimulation by irritants. Laryngospasms are a well- known complication in anesthesiology after intubation, extubation, certain anesthetics, and visceral sensory stimulation, such as mucus, blood or touching the mucosa of the larynx with a laryngoscope [32]. The Laryngospasms can also be observed in patients respirated spontaneously with a face or laryngeal masks during induction or maintenance of anesthesia [33]. Other triggers for laryngospasms are similar to those evoking VCD/ILO, hence laryngospasms may represents the most severe pathophysiological consequences of the glottic closure reflex. In a rat model of a seizure-induced laryngospasm, Nakasa et al. [34] confirmed that the cessation of airflow due to a complete glottic closure with an increase in recurrent laryngeal nerve activity was followed within tens of seconds by the ECG ST-segment elevation, bradycardia, an increase of respiratory effort, and respiratory arrest. Respiratory arrest was associated with an elevation of the systemic blood pressure, left ventricular dilatation, and eventual asystole, i.e.: sudden death. Nakasa et al. [34] suggested that this mechanism could contribute to unexpected sudden death in epilepsy.

A prolonged upper airway obstruction, i.e. laryngospasm or VCD/ILO can result not only in stridor, dyspnea, and cough but also in apnea and clinically evident desaturation and hypoxemia. The heart rate and blood pressure fluctuations initially mediated by the vagus nerve are thereafter overridden by a sympathetic stimulation resulting in tachycardia and hypertension. A continued upper airway obstruction can finally result in bradycardia and cardiac arrest because of severe hypoxemia [35,36]. It should be kept in mind that during obstruction of the upper airways large inspiratory forces are generated which can lead to a high negative intra-pleural pressure (even -50 to -100 cm H_2O) and in consequence to the extravasation of the fluid from the pulmonary capillaries into the interstitial and alveolar spaces [35,36]. Additionally, a large increase in venous return resulting in increased preload can be observed. Hence, upon relief of obstruction the so called Negative Pressure Pulmonary Edema (NPPE) can occur [35,36]. NPPE is a relatively rare condition secondary to laryngospasm (4%) occurring after extubation during the emergence and recovery stages associated with oto-laryngological and oral surgery [35,36].

It is worth remembering that a well-known reason for the upper airway obstruction is Obstructive Sleep Apnea (OSA) with a reduction or complete blockage of airflow during sleep and accompanying intermittent hypoxia. Patients with OSA demonstrate the risk of sudden death and cardiovascular mortality twice as high as the general population [37]. One of several mechanisms responsible for sudden death can be desaturation during apneas with a transient increase in both systolic and diastolic blood pressure and acute sympathetic activation [37]. Furthermore, in patients with OSA even a temporary airway obstruction can also generate NPPE very rapid in onset due to great intrathoracic negative pressure after efforts at inspiration [38].

Summarizing, in our opinion VCD/ILO coexisting with severe COPD in the presented patient additionally suffering from atherosclerosis, ischemic heart disease, and pulmonary hypertension could have increased the risk of death via several mechanisms and affected the fatal course of COPD exacerbation. We postulate considering VCD/ILO in patients with COPD who do not respond successfully to a properly administrated treatment.

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