Research Article

Differential Diagnosis of Bronchial Obstructive Syndrome

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ABSTRACT

Bronchial obstruction, a frequently encountered medical condition, is caused by a mechanical or immunological response or pathological blockage of any part of the airways. It causes acute or chronic respiratory failure. Irrespective of the cause, symptoms are usually similar: cough, difficulty in breathing, wheezing, etc. Its differential diagnosis is sometimes challenging; however, a careful history-taking and function testing usually leads to diagnosis, and thus appropriate treatment strategies. Radiologic imaging, inflammatory marker testing, and additional tests may also help differentiate the condition. We have reviewed and summarized bronchial obstruction, with special reference to its differential diagnosis. This review may help physicians better tailor their therapy.

Keywords: Differential diagnosis, Bronchi obstruction, Wheezing, Pulmonary function test, Breathlessness, Asthma, COPD, Cytokines.

Introduction

Bronchial obstruction can be localized or generalized. This may lead to the absorption of the air from the lung tissue distal to the obstruction resulting in pathological shrinkage and collapse of the alveoli.

This causes a traction force to be exerted upon the more proximal airways, distorting and dilating them. The elastic and muscle tissue is destroyed, and the mucous lining is replaced by granulation tissue with a loss of cilia. Therefore, the mucociliary transport mechanism is disrupted, and the passage of mucus passage out of the lungs is hindered.

Pathologically, there are various types including tubular, fusiform, or saccular. The hemoptysis results are due to increased anastomosis within the pulmonary vasculature.

The diagnosis of chronic bronchial obstruction can be made by clinical history and pulmonary function tests. It is not radiological (unable to visualize obstruction) or laboratory diagnosis. However, they can help rule out other pulmonary pathologies such as infiltrations, over-inflation, cysts, and inflammatory lung diseases.

The cause of the obstruction may lie within the lumen of a bronchus, as in bronchial foreign body or it may originate within the bronchial wall, as in bronchogenic carcinoma, or it may lie entirely out of the bronchial wall in the peri bronchial tissue, as in an aneurysm, causing squeeze and obstruction of a bronchus [1].

The common causes of wheezes, cough, and difficulty in breathing are Chronic Obstructive Pulmonary Disease (COPD) and asthma. However, the presence of these symptoms is not always in asthma and COPD [2]. COPD presents a high prevalence, and about 200 million people worldwide give the disease, posing as the leading cause of morbidity and mortality among chronic diseases. COPD is the 4th major cause of death globally, and it has been predicted that this disease will become the 3rd

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one by 2030 [3]. The Global burden of disease project carried out in 2001 identified COPD as the 6th leading cause of death in the developing or underdeveloped world, resulting in 4.9% of total deaths [4]. A recent study identified COPD as the 4th leading cause of chronic morbidity and mortality and reported that the disease's incidence and prevalence are continuously on the rise [5].

Bronchial obstruction is a frequent medical condition in practicing physicians with different etiologies and some similarities in cough symptoms; difficulty in breathing and wheezing that needs proper diagnosis and treatment [1, 6]. It is more difficult to determine the type of disease that is obstructing the airway. Differentiation of airway obstruction regarding their clinical studies, prognoses, and treatments make their distinction clinically significant. [6] The current review describes and outlines the major disorders with airway obstruction and reveals vital critical points in each case.

■ Major clinical categories of obstructive bronchial syndrome

Wheezing: Wheezing is a high-pitched, continuous, adventitious lung sound. The chest's net positive pressure during expiration compresses the intra-thoracic airways; therefore, wheezing is initially an expiratory phenomenon [7]. Wheezes are classified into a polyphonic or monophonic wheezes. Monophonic wheezing consists of a single musical note starting and ending at different times. A local pathology-like bronchial obstruction by the tumor, Broncho stenosis by inflammation, mucus accumulation, and the oral foreign body can produce it [7, 8]. Polyphonic wheezing consists of multiple musical notes starting and ending simultaneously and is typically produced by the dynamic compression of the large, more central airways [9]. When obstruction occurs in the extrathoracic airways during inspiration, the noise is referred to as stridor [10]. Stridor is a special kind of wheeze described as a loud musical sound of constant pitch, which is heard in patients with tracheal or laryngeal obstruction. The full differential diagnosis of airway obstruction should be carefully considered in any patient with wheezing or stridor [11].

Cough: Coughing is an important defensive reflex action to clear airways from mucus and dust, irritants, and foreign bodies [12]. Cough enhances clearance of secretions and particulates from the airways and protects from aspiration of foreign materials occurring due to aspiration or inhalation of particulate matter, pathogens, accumulated secretions, postnasal drip, inflammation, and mediators associated with inflammation [13, 14]. Clinical importance plays the character of cough as dry or sputum production, occurrence time as daytime or nocturnal, intensity, and association of triggers.

Breathlessness and chest tightness: Breathlessness is an uncomfortable abnormal awareness of breathing. It is a common symptom impacting millions of people and may be the primary manifestation of respiratory, cardiac, neuromuscular, psychogenic, systemic illness, or a combination of these [15].

■ Classifications of diseases with similar symptoms such as difficulty in breathing and wheezes

Intrathoracic central and lower airways

1. COPD
2. Asthma
3. Congestive heart failure
4. Bronchiolitis
5. Bronchiectasis
6. Bronchogenic carcinoma
7. Churg-Strauss syndrome
8. Ortner's Syndrome

Extra-thoracic upper airways

1. Anaphylaxis
2. Vocal cord paralysis
3. Laryngeal and tracheal stenosis

Mechanical obstruction of the airways

1. Goiter
2. Aspiration of foreign bodies

COPD

Regarding the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report, COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by long-term and significant exposure to noxious particles or gases [16]. The common symptoms of COPD are wheezing chronic

cough and sputum production, and dyspnea. Diagnostic criteria in COPD age of patients under 40 years old and older, history of long-term smoking, exposure to indoor air pollution, pulmonary function test: FEV1/VC<0.7, reduced FEV1, and not fully reversible bronchodilation test [17]. COPD is triggered when bronchial epithelial cells become damaged because of exposure to air pollution, dust, chemicals, respiratory infections during childhood, and pro-inflammatory mediators' release to stimulate leukocyte recruitment [15]. When the exposure is chronic, structural, and inflammatory cells in the respiratory tract become activated [18, 19]. For example, smoking activates the pulmonary innate immune defense mechanism altering the epithelial barrier, stimulating clearance in mucosal tissue, and releasing antimicrobial peptides, complement components, and surfactants. The immune response reduces the motility of cilia, which affects mucus removal and causes tissue damage.

In patients with COPD, the innate immune mechanism is activated when respiratory infections are sensed via pathogen-associated molecular pattern–pattern recognition receptors and damage-associated molecular pattern pathways [20, 21]. The receptor stimulation results in the activation of alveolar macrophages, monocytes, mast cells, natural killer cells, dendritic cells, neutrophils, and CD8+ T cells. These are the prime cells involved in the immunological changes of COPD [18, 19, 22]. On the other side, inhaled irritants can activate pro-inflammatory mediators, such as interleukin (IL)-8 (IL8)/CXCL8, IL-1β, and tumor necrosis factor-α (TNF-α) [23, 24]. Typically, phagocytes control infections, but they also control the associated inflammation in healthy subjects; alveolar macrophages phagocytose infiltrated neutrophils and regulate the extent of inflammation by anti-inflammatory processes [25,26]. However, patients with COPD present a reduced self-limitation of inflammation by macrophages, which, in addition to the induction of neutrophil survival, cause the airways to become loaded with neutrophils explaining the increase in induced sputum [27, 28]. An increase in oxidative stress markers, including nitric oxide (NO), hydrogen peroxide, and lipid peroxidation products, has been reported in COPD [29-31]. In severe cases, the disturbance in oxidative stress causes enhancement of activity and expression of enzymes like inducible NO synthase (NOS_2) and neuronal NOS (NOS_1), increasing NO and H_2O_2 production in the lung [32, 33]. Unlike patients with mild asthma, who exhale high NO levels, COPD patients exhale near-normal NO levels. Still, during exacerbations, NO levels increase [33-35]. It has been suggested that this NO increase might be related to the formation of nitrotyrosine adducts, which also increased in COPD [36]. On the other hand, H2O2 production leads to endothelial dysfunction, atherosclerosis, and hypertension **Figure-1** [37, 38].

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; CXCL8 = chemokine (C-X-C motif) ligand 8; DAMP = damage-associated molecular pattern molecule; DC = dendritic cell; GARP = glycoprotein A repetitions predominant; G-CSF = granulocyte colony-stimulating factor; MDSC = myeloid-derived suppressor cell; TGF-b1 = transforming growth factor b1; Th = helper T cell; TLR = Toll-like receptor; Treg = regulatory T cell.

Asthma

According to the Global Initiative for Asthma (GINA) 2018, report, asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary over time and intensity, together with variable expiratory airflow limitation. The variations are often triggered by exercise, allergen, or irritant exposure, change in weather, and respiratory tract infections.

Inflammatory cells in asthmatic airways

Mast cells -activated mucosal mast cells release bronchoconstrictor mediators–histamine, cysteinyl leukotrienes, prostaglandin D2. Allergens activate them through IgE receptors or by osmotic stimuli [39]. Eosinophils are an increased number in airways, release basic proteins that may damage epithelial cells, and have a role in releasing growth factors and airway remodeling [40], T lymphocytes are in increased number and release specific cytokines, including IL-4, IL-5, and IL-9, IL-13 that orchestrate eosinophilic inflammation and IgE production by B lymphocytes [41]. There may also be an increase in KT cells, which release large amounts of T helper: T1 and T2 cytokines [42, 43]. Dendritic cells and Macrophages are in increased number and release inflammatory mediators and cytokines that amplify the inflammatoryresponse [44, 45]. Neutrophils are in increased number in the airways and sputum of patients with severe

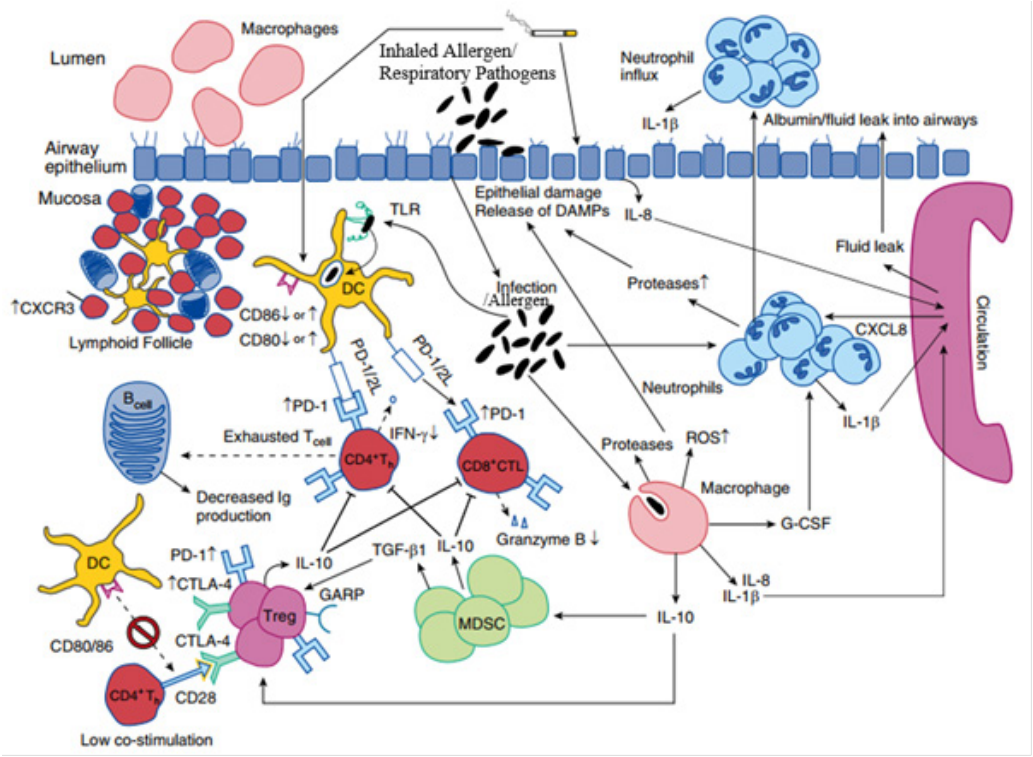

Figure 1: Dysfunction of the Immune system due to Respiratory pathogens in COPD patients

asthma and smoking asthmatics, but the role of these cells is uncertain, and their increase may even be due to steroid therapy [44-46].

■ Inflammatory mediators involved in asthma

Chemokines are important in the recruitment of inflammatory cells into the airways and are expressed in airway epithelial cells [47]. Eotaxin is selective for eosinophils, whereas thymus and activation-regulated chemokines (TARC) and macrophage-derived chemokines (MDC) recruit T2 cells [47]. Cysteinyl leukotrienes are potent broncho-constrictors and pro-inflammatory mediators mainly derived from mast cells and eosinophils [48]. Cytokines orchestrate the inflammatory response in asthma. Key cytokines include IL-1β and TNFα and GM-CSF. T2-derived cytokines include IL-5, which is required for eosinophil differentiation and survival; IL-4, which is for T2 cell differentiation; and IL-13, which is needed for IgE formation [49]. Histamine is released from mast cells and contributes to bronchoconstriction and inflammation [47]. Nitric oxide (NO), a potent vasodilator, is produced from syntheses in airway epithelial cells [50]. Exhaled NO is increasingly being used to monitor the effectiveness of asthma treatment [51]. Prostaglandin D2 is a bronchoconstrictor derived predominantly from mast cells and is involved in T2 cell recruitment to the airways [39]. Airway structural cells involved in the pathogenesis of asthma are airway epithelial cells, airway smooth muscle cells, endothelial cells, fibroblasts and myofibroblasts, and airway nerves [45, 46, 52]. A typical patient with asthma symptoms onset early in life, other atopic conditions, spirometry with positive bronchodilatation test variability FEV1 after inhalation SABA- at least 200ml. As well as the bronchoprovocation test **Figures 1 and 2** [53].

■ Congestive heart failure

Chronic left-sided chronic heart failure is characterized by decreased cardiac output and increased venous pressure [54]. The left ventricle of the heart no longer pumps enough blood around the body. As a result, blood building up in the pulmonary veins (the blood vessels that carry blood away from the lungs) leads to congestion of pulmonary circulation. In this case, initial symptoms, wheezes, shortness of breath, and cough, often may be difficult to differentiate from COPD [55]. Diagnosis of congestive heart failure is often a process of exclusion. A history of coronary artery disease, chronic rheumatic disease, clinical symptoms of orthopnea and paroxysmal nocturnal dyspnea,

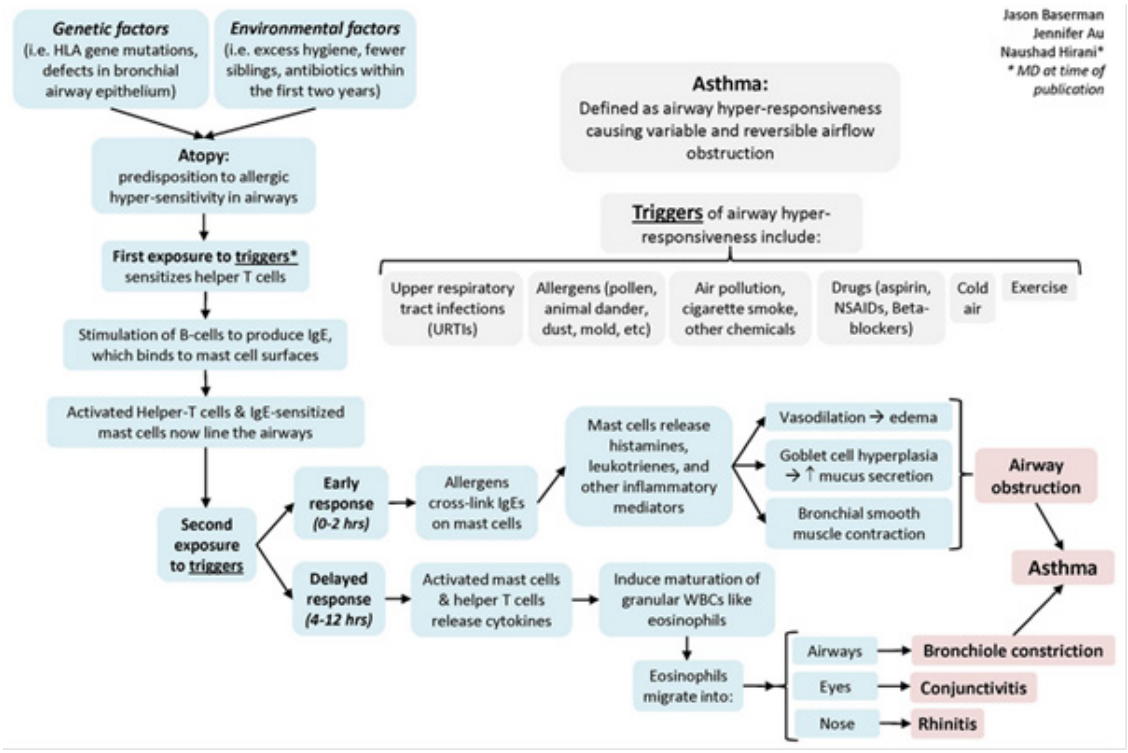

Figure 2: Involvement of different triggers, Inflammatory mediators, cells, and organs in Asthma.

fine basal crackles on chest auscultation the presence of rhythm distribution, and changes on electrocardiography suggest low ejection fraction, hypertrophies, hypokinesia, valve regurgitation or stenosis can lead to diagnosis congestive or chronic heart failure.

■ Bronchiolitis in adults

Bronchiolitis is an inflammatory process resulting from damage to the bronchial epithelium of the bronchioles. Bronchioles are small airways (2 mm or less in diameter without cartilage) that connect breathing tubes (bronchi) to tiny air sacs of the lung the lung's tiny air sacs. It leads to a progressive decrease in lung function and has variable outcomes [56, 57]. The common symptoms are persistent, progressive cough, and dyspnea accompanied by wheezes. The spirometry can show reduced FEV1, subnormal, or reduced FEV1/FVC and decreased FEF [58]. The differential diagnosis may help history of any risk factors of bronchiolitis and chest CT scan. Typical radiological signs of bronchiolitis tree-in-bud pattern, air trapping phenomena, or mosaic attenuation on inspiratory CT scan [59].

■ Bronchiectasis

Bronchiectasis is permanent, irreversible dilatation of the airways and occurs in a variety of pathologic processes. Long-term recurrent infection and inflammation and the resulting chemical and cellular cascade lead to irreversible architectural changes in the airways leading to bronchial obstruction [60]. The primary clinical manifestation of bronchiectasis is a daily cough and large sputum production in 90% of cases [61, 62]. Decreased forced expiratory volume in 1sec, forced vital capacity, lung volumes, and diffusion capacity. The frequency of dyspnea in 60% of cases wheezes in 22% of cases [63]. Differential diagnosis bronchiectasis determines underlying causes and clinical history of clubbing, coarse crackles on auscultation, and using chest computed tomography [63]. HRCT is the most sensitive and specific non-invasive method for diagnosing bronchiectasis. Certain descriptive terms have been used in the reporting of bronchiectasis. Typical CT signs of bronchiectasis tram track sign, signet-ring sign, and a cluster of thin-walled cystic space [64].

■ Carcinoma of the bronchus

Bronchogenic carcinoma is a malignant cancerous tumor of the bronchi and the lung tissue. The frequent symptoms of bronchogenic carcinoma cough and hemoptysis may produce wheezing. Diagnosis is made based on systemic symptoms of cachexia, fatigue, and loss of appetite; signs of

anemia and bronchoscopy allow confirmation of the primary tumor with a sensitivity of 0.88 for central tumors and 0.78 for peripheral tumors [65].

■ Churg-Strauss syndrome (CSS)

Churg-Strauss syndrome is a systemic autoimmune vasculitis characterized by inflammation of blood vessels. In CSS, vasculitis is associated with asthma and eosinophilia [66]. Patients have a history of asthma that is most often adult-onset, usually in the fourth decade. Allergic rhinitis, nasal polyps, and sinusitis are standard accompanying features [67]. Classic diagnostic findings: Eosinophilic pneumonia, necrotizing vasculitis eosinophilia, and granulomatous inflammation [68].

■ Ortner's Syndrome

This syndrome was described by Norbert Ortner in 1897 [69]. In this syndrome, the problem is hoarseness of voice due to recurrent laryngeal nerve involvement secondary to cardiovascular disease that requires differentiate hoarseness between wheezes.

■ Extra thoracic upper airways obstructions

Obstructive lesions of the upper airway, such as post-traumatic strictures, bilateral vocal cord paralysis, chronic inflammatory foci, and foreign body aspiration, are relatively uncommon compared to the obstruction of lower airways [69]. The common symptoms of upper airway obstruction are exertional dyspnea and stridor. Pulmonary Function Tests (PFTs) including the flow-volume loop is the most specific method that shows airway obstruction and deference upper airways from lower airways obstruction [70]. Diagnostic fiberoptic bronchoscopy may also help in diagnosis as well as deferential diagnosis of airway obstructions.

■ Goiter causing airway obstruction.

Enlargement of the thyroid gland compresses the trachea esophagus, recurrent laryngeal nerve, and superior vena cava. Compressive manifestations of goiter may produce wheezes or stridor and difficulty in breathing, sometimes asthma-like symptoms [71]. Other symptoms are dysphagia and hoarseness. Nandwani noted a case in which upper airway obstruction and dyspnea were confused with asthma. They used a flow-volume loop, as this test serves to aid in the diagnosis and control of expected airway obstruction., The particular figure of the flow volume loop can help with differential diagnosis [72, 73]. Russian authors Chukaeva I at all reported tumors of the mediastinum. The clinical feature of this case is severe dyspnea with symptoms of compression of the superior vena cava and trachea. This case's specific symptoms are a plethoric swelling of the face and arms, neck, and upper part of the torso. Diagnosis is confirmed by using chest radiography [74, 75].

■ How to diagnose broncho-obstruction

Pulmonary function tests: In clinical practice, spirometry plays a crucial role in the diagnosis. Spirometry is an essential tool in the diagnosis of bronchial obstruction. It is a simple, cheap, and quick procedure to perform airway abnormality [76]. Global Initiative for Chronic Obstructive Lung Disease criteria (FEV1/FVC ratio less than 70%) to diagnose obstructive lung defect [77]. Moreover, spirometry uses for bronchodilation tests for the differential diagnosis of asthma and COPD. Variability of FEV1 or FVC at least 200ml or 15% after short-acting bronchodilators indicates a positive test or reversible bronchi obstruction. More information diagnosis of the small airway pathology is the mid-portion of expiratory flow. For the diagnosis of small airways, important pathology role-plays measurement of The Forced Expiratory Flow between 25 and 75% of the FVC (FEF) [78]. Upper airflow obstruction was revealed by calculating the ratio of forced expiratory volume to the peak expiratory flow rate (FEV1/PEFR). A ratio FEV1/PEFR>10 indicates significant UAO. Flow volume loops the flow-volume loop is a plot of inspiratory and expiratory flow (on the Y-axis) against volume (on the X-axis) during the performance of maximally forced inspiratory and expiratory maneuvers **Figure 3** [79].

■ The role of chest radiography

Chest X-ray (CXR) is a rapid imaging tool that allows early identification of lung pathologies. It is a high-yield test, providing crucial clinical information rapidly, at low cost, and with low radiation exposure, but with many unnecessary examinations [80]. Chest radiography is neither a sensitive nor specific diagnostic tool for bronchi obstruction. The bronchi obstruction is not visible, and thereby, it is not a radiologic diagnosis. In bronchi obstruction, chest radiography is aimed to diagnose the underlying causes or exclusion of disease such as any consolidation, infiltration, inflation or nodules, and masses of the lung through foreign body aspiration [81, 82].

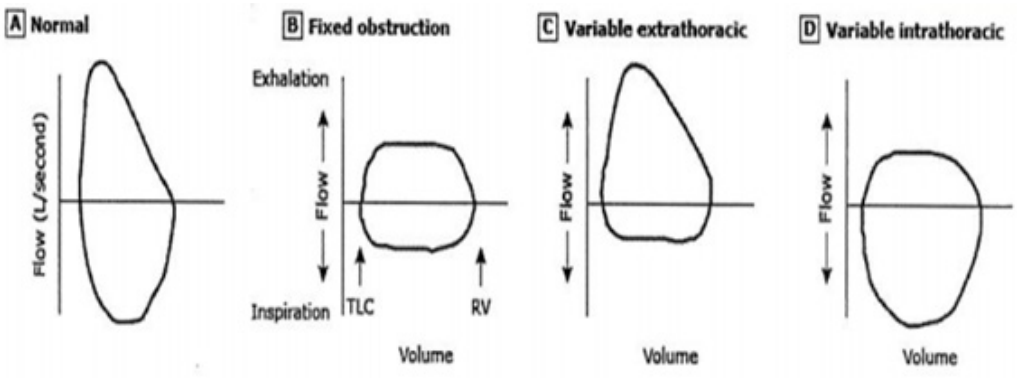

Figure 3: Flow-volume loops in upper airway obstruction

■ The role of ECG and Echocardiography

Increased bronchi obstruction and increased pulmonary vascular résistance lead to right-sided heart problems [83].

Electrocardiographic (ECG) findings may help in clinical decision-making regarding this disease entity. Although, ECG may help in the differential diagnosis of cardiogenic wheezes in congestive heart failure, and arrhythmias. The common ECG of right-sided heart problems are P-pulmonale, right axis deviation, prominent R wave in V1 and deep S wave in V6, and right bundle branch blocks. The ECG of left heart problem including P-mitral, Sokolov-Lyon criteria (S wave depth in V1 + tallest R wave height in V5-V6 > 35 mm) in LVH [84, 85]. LBBB, depression, or elevation ST segment.

In differential diagnosis between cardiogenic and bronchogenic wheezes, echocardiography is an important tool. Matthias Schneider. reported that echocardiography is usually used as the initial diagnostic tool to assess the right heart and left heart's size and function [86]. The right ventricle is directly involved in a variety of diseases. Right, ventricular size and function play a crucial role in patients with pulmonary hypertension, pulmonary embolism, right ventricular infarction, pulmonary and tricuspid valvular heart disease, and intracardiac shunts [87].

■ The role of bronchoscopy

Bronchoscopy allows direct visualization of the trachea and bronchi by rigid open tube bronchoscope or flexible fiberoptic scope [88]. Flexible and rigid bronchoscopy is widely available for use. The main diagnostic indications for bronchoscopy in bronchi obstructive syndrome include suspected airway foreign bodies, airway stenosis, and bronchogenic carcinoma.

Conclusion

Many diseases produce similar symptoms wheezes, cough, and dyspnea in family practice. The common causes of these symptoms are asthma and COPD. However, not all wheezes and coughs are asthma or COPD. As we noted, there are quite different causes of obstruction. That requires detailed history is taken, an intentional investigation plan, and clinical thinking.

Conflict of interest

Statement, we declare that we have no conflict of interest.

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Author Contributions

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