

GROUND ZERO: NOT ASTHMA AT ALL

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ABSTRACT

Upper airway obstruction is commonly misdiagnosed as asthma. We report on four children with recurrent respiratory symptoms who had been erroneously diagnosed as having asthma and who received antiasthma medication for several years. The evaluation of spirometry tracing was neglected in all cases. Subglottic stenosis, tracheomalacia secondary to tracheo-esophageal fistula,

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double aortic arch, and vocal cord dysfunction were suspected by direct inspection of the flow-volume curves and eventually diagnosed. The value of clinical history and careful evaluation of spirometry tracing in children with persistent respiratory symptoms is critically discussed.

Key words: asthma, spirometry, flow-volume curves, children

If we want things to stay as they are, things have to change
(Giuseppe Tomasi di Lampedusa, "Il Gattopardo")

INTRODUCTION

The sub-heading of this article highlights the inherent paradox that repeated, educative efforts addressed to improve the diagnostic approach to a common clinical disorder as asthma may not change a deep-rooted mindset ("*all that wheezes is asthma*") in the practice of medicine.¹ The literature is fraught with reports of adults and children who received erroneous diagnosis of asthma and were consequently treated with increasing, ineffective and potentially harmful doses of antiasthmatic drugs.

The 2005 ATS/ERS guidelines on spirometry emphasize the importance of inspecting the flow-volume (F/V) curve - that is the graphic expression of airflow at different lung volumes - to reveal intrathoracic and extrathoracic airway obstruction.² After half a century since the first description of characteristic spirometry pattern in patients with upper airway obstruction,³ it is sad to admit that overlooking such international recommendations still results in a diagnostic bankruptcy.

This article describes four cases with airway obstruction due to different causes, who received erroneous diagnosis of asthma and remained symptomatic for several years despite consistent antiasthma medication. It aims to emphasize the value of both clinical history and physical examination, and to remind of the importance of inspecting spirometry tracings in the evaluation of children with otherwise unexplained respiratory problems.

CASE REPORTS

Case 1

A 9-year-old girl presented with a long history of noisy breathing. She had a history of preterm birth, neonatal intubation and early stridor. Over the years, she complained of noisy breathing and recurrent cough especially during exercise. Chest radiograph, allergy testing and cardiologic evaluation were normal. An office spirometry was interpreted normal. She was given a diagnosis of

asthma and received repeated courses of bronchodilators, oral and inhaled corticosteroids (ICS) with poor response.

A biphasic stridor was evident on clinical examination. Spirometry showed Forced Vital Capacity (FVC) 89%, Forced Expiratory Volume in 1 s. (FEV₁) 71%, Peak Expiratory Flow (PEF) 39%, Maximum Mid Expiratory Flow (MMEF) 49% predicted, with no response to salbutamol. The examination of the F/V curve showed flattened inspiratory and expiratory loops consistent with fixed central airway obstruction (Fig. 1). Airway endoscopy revealed severe subglottic stenosis (SGS) (Fig. 2). Endoscopic anterior cricoid split intervention associated with balloon dilation resulted in symptom disappearance and normalization of spirometry.

Case 2

A 13-year-old male was referred for more detailed investigation because of a long history of respiratory symptoms. He had received surgical intervention for esophageal atresia (EA) and tracheo-esophageal fistula (TEF). Since infancy, he complained of frequent respiratory infections, recurrent pneumonia mostly localized at right middle lobe, barking cough and wheeze. Multiple treatments with antibiotics, inhaled bronchodilators and steroids had not helped. Several investigations, such as immunological work up, allergy testing, sweat test, chest radiograph, barium swallow, esophageal pH-monitoring, esophagoscopy, and bronchoscopy with bronchoalveolar lavage were inconclusive. Repeated spirometry showed a mixed restrictive and obstructive pattern. He was given a diagnosis of asthma. A step up treatment with antiasthmatic drugs including regular administration of medium-dose ICS and long-acting beta2 agonists (LABA) was unsuccessful.

Clinical examination was normal. Spirometry yielded a mixed ventilatory pattern (FVC 66%, FEV₁ 66%, PEF 65%, MMEF 66% predicted) with no response to salbutamol. The F/V curve showed flattening of the expiratory loop suggestive of variable intrathoracic airway obstruction (Fig. 3). Bronchoscopy revealed localized tracheomalacia (TM) with transmitted vascular pulse. MR-angiography showed narrowing of distal trachea with biconcave lens aspect due to external compression by innominate artery anteriorly and dilated esophagus posteriorly (Fig. 4). Asthma medication was discontinued. Cardiothoracic surgery intervention with detachment of innominate artery from the aortic arch and anastomosis to ascending aorta resulted in disappearance of vascular pulse at intraoperative bronchoscopy. Substantial symptom improvement was obtained, but the F/V curve remained persistently abnormal at follow up. Repeated MR-angiography revealed partially improved tracheal lumen patency.

Case 3

A 14-year-old male was referred in order to perform an exercise bronchial challenge because of abnormal spirometry (FVC 101%, FEV₁ 89%, PEF 55%, MMEF 76% predicted) at a sport medicine routine assessment. He had a history of respiratory distress at birth and oxygen requirement for 3 days. Early in childhood, recurrent episodes of barking cough and wheeze appeared, which required frequent use of bronchodilators and ICS. Chest radiograph was reported normal. ENT evaluation because of inconstant dysphonia revealed normal vocal cords. Over the years, he complained of increasing respiratory discomfort and chest tightness especially upon exercise. Bronchodilators occasionally helped.

Clinical examination was unremarkable. Spirometry was normal, except for PEF 56% predicted; the F/V curve showed a plateau on both inspiratory and expiratory loops that was consistent with fixed central airway obstruction (Fig. 5). Repeated chest radiograph showed a right sided aortic arch. MR-angiography revealed a complete double aortic arch (DAA) with right arch dominance, surrounding and compressing the trachea and esophagus (Fig. 6). Cardiothoracic surgery intervention with interruption of the left aortic arch distal to the left subclavian artery resulted in substantial improvement of symptom and normalization of spirometry.

Case 4

A 15-year-old girl presented to the emergency department with severe wheeze, dyspnea and chest discomfort. She had a past history of allergy to dust mites and episodic use of bronchodilators. Over the last year, she complained of recurrent episodes of wheezing and chest tightness that required frequent use of emergency resources. Episodes were occasionally precipitated by exercise, had variable duration from minutes to hours and resolved spontaneously; interval periods were silent. Previous investigations including allergy skin testing, spirometry, sweat test, chest radiography, barium swallow, esophageal pH-metry and bronchoscopy were inconclusive. A trial with bronchodilators and ICS had no effect. She received the diagnosis of “poorly controlled asthma” and treatment was rapidly escalated to the combination of high-dose ICS and LABA.

Clinical examination revealed respiratory rate 30/min, stridor and overwhelming anxiety. Pulse oximetry was 97% and arterial blood gas analysis showed reduced partial pressure of carbon dioxide. Spirometry yielded normal expiratory flows and volumes, but blunting of the inspiratory F/V loop which was consistent with variable extrathoracic airway obstruction (Fig. 7). Laryngoscopy revealed abnormal adduction of the vocal cords during inspiration, a characteristic finding of vocal cord dysfunction (VCD). The episode resolved by reassurance and administration of anxiolytics. Speech

and language therapy led to complete resolution of symptoms and discontinuation of asthma medication.

DISCUSSION

Asthma is a common disease in childhood and this is obviously recalled to mind when the physicians face with a wheezy child.⁴ There are several reports on children with airway obstruction due to different causes that were misdiagnosed as asthma, mainly because symptoms and occasionally triggering factors such as exercise overlap those of asthma.⁵ Since wrong diagnosis inevitably leads to improper treatment and to unresolved symptoms, a vicious circle characterized by extensive investigation, unjustified additional therapy and incredibly high consumption of health-care resources is invariably set up in such circumstances.

The series of reported cases illustrates a cultural gap. Due to history of wheezing/noisy breathing, all children received the “pre-packed” diagnosis of asthma and were treated accordingly. Ignoring F/V curves and/or failure to recognize spirometry tracing abnormalities prompted physicians to perpetuate a conceptual error. The unavoidable consequence of such acritical approach was prescription of step up asthma therapy due to ongoing respiratory symptoms. To avoid potential disasters, alternative diagnoses must be considered in this clinical context (Tab. 1).⁶

In childhood, SGS represents a congenital anomaly or is mostly secondary to prolonged endotracheal intubation. Improved techniques of handling neonates who require ventilator support led to a downward trend in the incidence of neonatal SGS which is actually estimated less than 2%.⁷ Stridor following prolonged endotracheal intubation is mainly related to mucosal edema of the larynx and may gradually disappear; however, if fibrotic narrowing of the subglottic lumen occurs, laboured breathing may develop weeks or months after extubation. Stridor is usually inspiratory, but may become biphasic as obstruction worsens.⁸ Rigid bronchoscopy is the best technique to assess the severity of stenosis in the glottis and subglottic region.⁹ The severity of the obstruction can be graded from 1 to 4 according with the narrowing of the lumen: <50%; 51%-70%; >70% with any detectable lumen; no lumen.¹⁰ Treatment of SGS will mainly depend on the severity of clinical presentation and grade of obstruction. Therapeutic interventions include corticosteroids, dilation, surgical or laser resection, tracheal stenting and grafting.¹¹

TM is a consistent finding in most if not all children with a history of neonatal repair of EA/TEF, but is reported to be clinically significant in only 10-20 percent of patients.¹² Complaints in children who have undergone EA/TEF repair are common and include frequent bronchitis and pneumonia, brassy cough, recurrent wheeze, dysphagia and life-threatening apnoea. Recurrent aspiration and

impaired mucociliary clearance are likely causes of respiratory problems. Long-term studies of lung function demonstrated either normal or mildly obstructive/restrictive ventilator pattern.¹²

DAA is the most common cause of vascular compression of the airway in children.¹³ Symptoms include cough, stridor, wheezing, recurrent respiratory infections, dying spells and dysphagia. If there is involvement of the laryngeal nerve, dysphonia may be present because of vocal cord paresis. DAA is usually diagnosed in infancy or early childhood, but occasionally the diagnosis is delayed for years. There are several reports of DAA masquerading as longstanding asthma, both in children^{14,15,16} and in adults.^{17,18,19,20,21} Occasionally, DAA may simulate exercise-induced asthma.^{22,23} DAA may be suspected by chest radiograph, confirmed by echocardiography, bronchoscopy and barium swallow, but is best assessed by CT scan or MR-angiography.¹³ Since chronic airway compression carries a significant morbidity and mortality, both timely diagnosis and surgical intervention are essential. Despite surgical treatment, several children have residual symptoms²⁴ and/or continue to display abnormalities of lung function due to secondary TM.²⁵

VCD is a relatively uncommon disorder characterized by paradoxical adduction of the vocal cords during inspiration - and occasionally during expiration as well - which results in complaints of stridor, wheezing and dyspnoea.^{26,27,28} The exact cause of VCD remain unclear. Social stressors are frequently identified and many children are reported to have excellent academic or athletic performances.^{26,27,28} Diagnosis of VCD is based on clinical symptoms, characteristic flattening of the inspiratory F/V curve at spirometry, as well as the typical laryngoscopic finding of diamond-shaped “posterior chink” of the vocal cords. VCD is frequently misdiagnosed as asthma²⁹ and may also mimic exercise-induced bronchoconstriction.^{30,31,32,33} Notably, asthma may coexist with VCD up to 50% of cases,^{26,29,34} thus increasing intrinsic difficulties in the diagnosis (Tab. 2). VCD can be intermittently symptomatic and the spirometry tracing is very often normal when symptoms are absent.^{26,27,28} Since coordinated timing of performing airway evaluation during an acute episode may be problematic, many clinicians diagnose VCD provisionally without visualizing the larynx. A simple, clinically-centered index has been recently proposed to facilitate the diagnosis of VCD, but validation studies need to be performed.³⁵ Management of VCD is complex. Relaxation techniques including special relaxed-throat breathing patterns may provide temporary control of acute episodes. Long-term treatment includes speech therapy and in some cases psychological counselling.^{26,27,28}

There are three basic learning messages arising from the description of our cases. First, the importance of a detailed clinical history. Three of our patients (cases 1,2,3) had a significant neonatal history and developed respiratory symptoms during the first weeks of life. The cause of central airways obstruction in children is usually congenital and symptoms typically appear early in life, whereas asthma is very unlikely in this age. Second, clinical examination remains a vital part of the

assessment of a patient with respiratory symptoms. Stridor is an important feature and suggests upper airway obstruction. In two of our patients (cases 1,4) stridor had been incorrectly evaluated. This sound is frequently mislabelled by parents as wheeze, thus emphasizing that confirming parental reports of wheeze by an experienced doctor is essential for diagnostic purpose.³⁶ Third, all our patients were refractory to antiasthma therapy. Failure to respond to asthma medication and/or an atypical clinical pattern should promptly suggest an alternative diagnosis. All previous aspects were largely overlooked in our series, thus delaying the correct diagnosis to adolescence.

International guidelines for the management of asthma recommend spirometry for patients older than 5 years of age, in whom the diagnosis of asthma is being considered.³⁷ Despite recurrent respiratory symptoms and regular antiasthma treatment, one patient (case 3) had never been requested spirometry, a finding consistent with underutilization of lung function tests in children with suspected asthma.³⁸ Office spirometry was performed only in one patient (case 1) and reported normal. Perceived barriers to incorporating spirometry in clinical practice, as well as physician's deficiencies in interpreting the results of lung function tests have been described.³⁹ In addition, some office-based spirometry systems only plot expired volume against time and do not offer F/V curve tracings.⁴⁰

Indeed, F/V curves provide additional information over conventional spirometry in determining the site, character and severity of airway obstruction. Obstructive airway lesions can be divided functionally into variable and fixed types, distinguished by the ability or inability of the airway to alter in calibre in response to pressure changes.³ In fixed airway obstruction such as SGS and DAA, a plateau of both inspiratory and expiratory flows may be revealed; in variable intrathoracic obstruction such as TM, a plateau is present only on expiratory tracing; flattening of the inspiratory limb rather suggests variable extrathoracic obstruction, such as VCD.² Abnormalities of the shape of the F/V curve should always prompt clinicians to set further investigation. In alternative to "visual" criteria, "quantitative" criteria have been proposed for detecting structural and functional airway abnormalities, but impractical calculations are required.⁴¹

The patient with TM secondary to EA/TEF (case 2) continued to yield abnormalities of pulmonary function despite being asymptomatic after cardiothoracic surgery intervention. This finding is not unusual, possibly due to persistent TM at the site of tracheal narrowing,²⁵ and should alert physicians to avoid prescribing unnecessary asthma medication in such circumstances. We cannot however exclude that spirometric changes in our patient were related to recurrent pneumonia. Indeed, in a long-term study following repair of EA, abnormal pulmonary function tests were found only in subjects who had a previous history of pneumonia.⁴²

Lesson learned

Patients with misdiagnosed asthma consume consistent health-care resources because of extensive investigations, large prescription of medications, and frequent accesses to emergency departments and physicians’ offices. Early recognition of the underlying condition is therefore crucial. When approaching a patient with recurrent wheezing or noisy breathing, physicians should be more confident with the strategic role of clinical history and physical examination, be aware that spirometry may be critical for addressing the diagnosis, and be able to interpret functional data in the context of the clinical framework. Poor training on lung function testing, unjustifiable attitude to “read” numerical data rather than “interpreting” physiology tracings, rushing in busy clinics, and lack of common sense are the main shortcomings leading to wrong diagnoses.

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Table 1

Conditions that may mimic asthma and tests useful for diagnosis

Alternative diagnosis	Diagnostic test
Structural abnormalities (subglottic stenosis, tracheal stenosis/webs, tracheobronchial malacia)	Bronchoscopy
Extrabronchial compression (vascular rings, cystic lesions/masses, lymphadenopatya, cardiomegaly)	Chest CT scan, MRI
Intrabronchial obstruction (inhaled foreign body, tumors)	Bronchoscopy
Dysfunctional breathing	History, direct observation, laryngoscopy
Gastro-esophageal reflux with/without aspiration	24 hour pH monitoring
Cystic fibrosis	Sweat test
Immune abnormalities	Serum immunoglobulins, vaccine antibody response, lymphocyte subsets
Bronchiectasis (cystic fibrosis, primary ciliary dyskinesia)	High resolution CT scan
Bronchopulmonary dysplasia	History of prematurity and oxygen need
Bronchiolitis obliterans	High resolution CT scan, lung biopsy

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Table 2

Differences between vocal cord dysfunction and asthma

Vocal Cord Dysfunction	Asthma
<i>Symptoms</i>	
Inspiratory stridor with/without wheezing	Expiratory wheezing
Disproportionate dyspnea	Wheezing prevalent
Abrupt onset	Exacerbation over hours or days
May occur at rest, triggers possible	Usually precipitated by triggers
Rare at night	Frequent at night
Few or even absent between episodes	Persistent during an exacerbation
Hoarseness may be present	Normal voice
Frequent anxiety	Anxiety uncommon
<i>Pulse oximetry</i>	
Normal	Decreased
<i>Spirometry</i>	
Abnormal inspiratory pattern	Abnormal expiratory pattern
<i>Response to antiasthmatic drugs</i>	
Absent	Present

Legenda

Figure 1. Flow volume curve: flattened inspiratory and expiratory loops consistent with fixed central airway obstruction

Figure 2. Airway endoscopy: severe subglottic stenosis

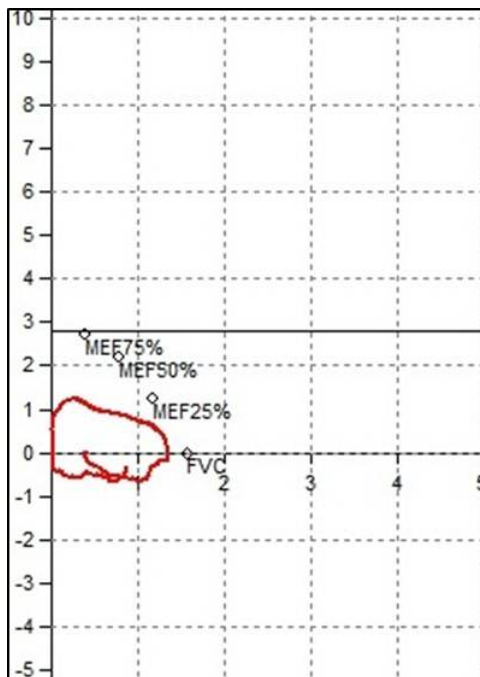
Figure 3. Flow volume curve: flattening of the expiratory loop suggestive of variable intrathoracic airway obstruction

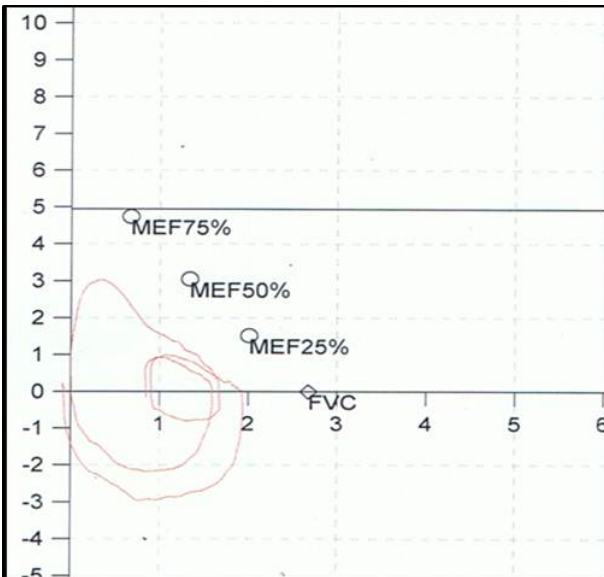
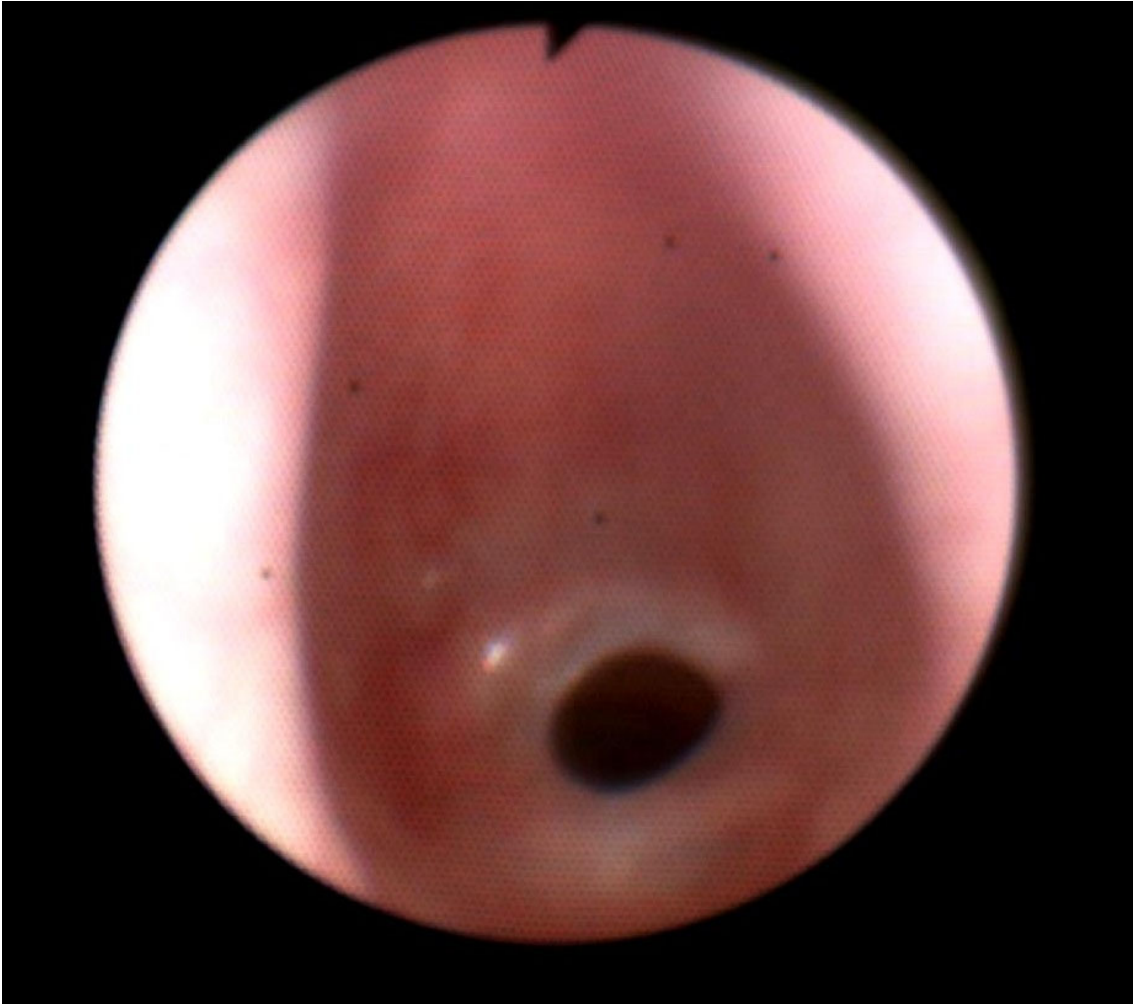
Figure 4. MR-angiography: narrowing of distal trachea with biconcave lens (white arrow)

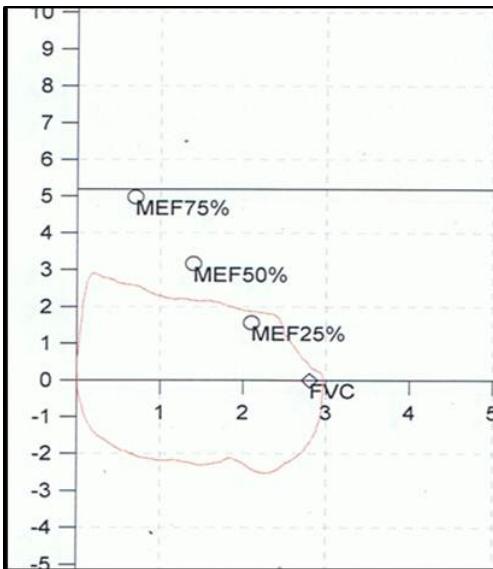
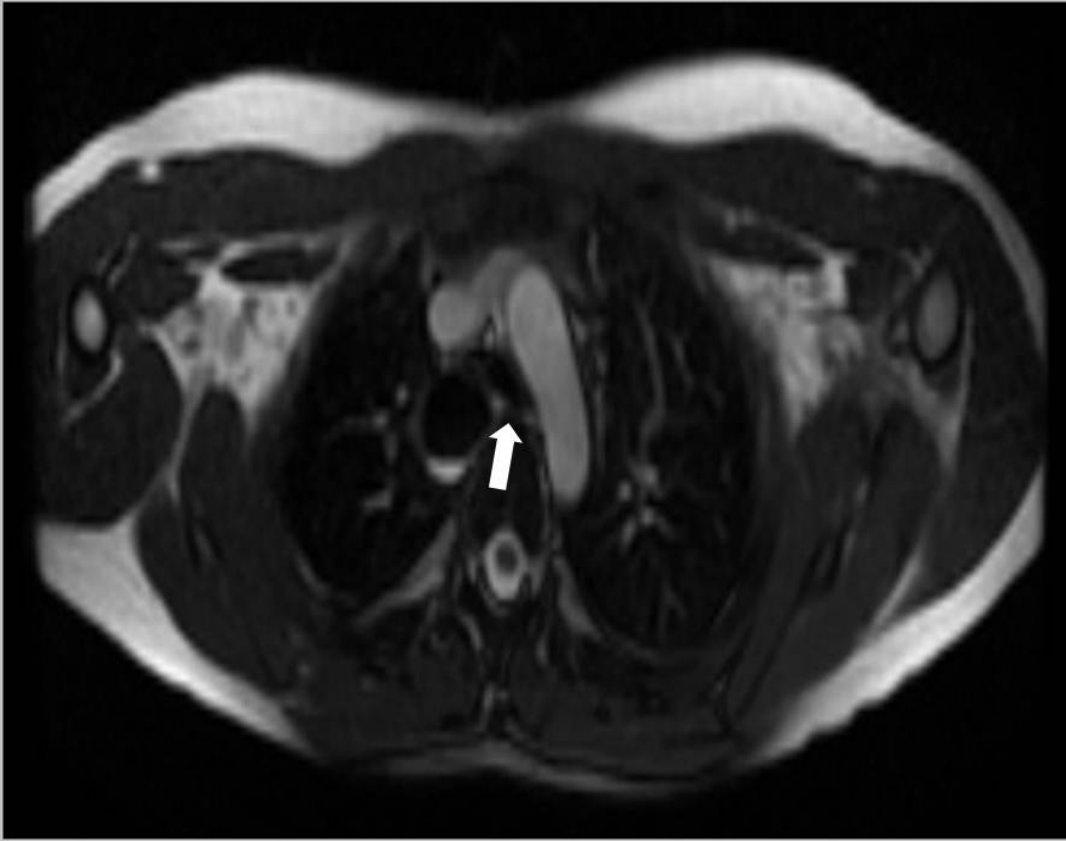
Figure 5. Flow volume curve: plateau on both inspiratory and expiratory loops that was consistent with fixed central airway obstruction

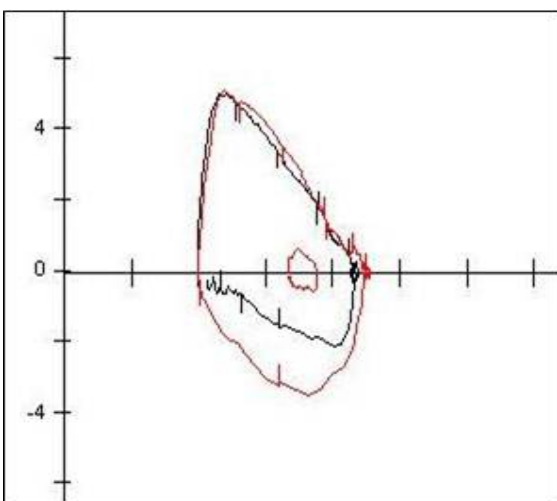
Figure 6. MR-angiography: complete double aortic arch surrounding and compressing the trachea and esophagus

Figure 7. Flow volume curve: blunting of the inspiratory loop which was consistent with variable extrathoracic airway obstruction









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