The Clinical Physiologist

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The Corseted Alveolus

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The Clinical Challenge

A 43-year-old African American man was referred to pulmonary clinic for evaluation of several years of progressively worsening dyspnea on exertion. Approximately 8 years before presentation, he was diagnosed with pulmonary sarcoidosis after a thorough work-up that included transbronchial biopsies showing nonnecrotizing granulomas. He was initially placed on prednisone with mild relief of his symptoms; however, in the past few years, the symptoms returned, and were slowly worsening. He was previously in good physical shape, but was now unable to exercise without significant difficulty. Recently, his symptoms prevented him from playing outside with his young son. He noted mild nasal congestion and an occasional cough, but denied other respiratory symptoms. Notably, there was no temporal or positional worsening of dyspnea. He also denied chest pain and leg swelling. His other medical problems included hypertension and long-standing, poorly controlled type I diabetes mellitus.

During his initial visit, he was afebrile, his heart rate was 81 beats/min, his blood pressure was 119/78 mm Hg, his respiratory rate was 20 breaths/min, and his oxygen saturation was 93% on ambient air. His exam was notable for significantly hardened, discolored, and thickened skin circumferentially around his chest (Figure 1), and his chest wall excursion was visibly impaired. His breath sounds were

Figure 1. A photograph of the patient showing thickened skin on the superior surface of his back (large oval).

symmetrically diminished bilaterally without crackles, wheezes, or rhonchi; diaphragmatic excursion, as assessed via percussion of his posterior chest wall, was approximately 4 cm and symmetric. On cardiovascular exam, he had normal heart

sounds without murmurs or gallops, no jugular venous distension, and no peripheral edema. On neurologic exam, strength and reflexes were symmetrically intact, without muscular atrophy, hypertrophy, or fasciculations. Pertinent laboratory findings

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Table 1. Patient's pulmonary function tests

	Predicted	LLN	Measured	% Predicted
Spirometry				
FVC, L	4.45	3.5	2.98	67
FEV ₁ , L	3.61	2.8	2.48	69
FEV ₁ /FVC, %	81	70.9	83	
Lung volumes				
TLC, L	7.12	5.5	3.41	48
VC, L	4.45	3.5	2.98	67
ERV, L	1.72	1.4	0.84	49
RV, L	1.95	1.2	0.44	22
Diffusing capacity				
DL _{CO} , ml/mm Hg/min	32.7	24.7	19.6	60
DL _{CO} cor, Hb = 14.1 g/dl, ml/mm Hg/min	32.7	24.7	19.9	61
DL/VA, ml/mm Hg/min/L	4.7	3.5	5.81	124
DL/Vacor, ml/mm Hg/min/L	4.7	3.5	5.89	125
VA, L	6.95	5.6	3.38	49

Definition of abbreviations: DL_{CO} = diffusing capacity of the lung for carbon monoxide; DL_{CO}cor = DL_{CO} corrected for hemoglobin; DL/VA = rate of alveolar CO uptake at the measured VA; DL/Vacor = rate of alveolar CO uptake at the measured VA corrected for hemoglobin; ERV = expiratory reserve volume; FEV₁ = forced expiratory volume in 1 second; FEV₁/FVC = ratio between FEV₁ and FVC; FVC = forced vital capacity; Hb = hemoglobin; LLN = lower limit of normal values from the reference population; RV = residual volume; TLC = total lung capacity; VA = alveolar volume; VC = vital capacity.

included a hemoglobin of 14.1 g/dl, a hematocrit of 41%, a serum creatinine of 2.6 mg/dl, a serum bicarbonate of 25 mEq/L,

and a hemoglobin A1c of 9.6%. Before his visit, he was sent for a computed tomography (CT) scan of the chest, which

showed no chest wall or parenchymal lung abnormality, and was otherwise normal aside from minimal dependent hypoventilatory changes within both lungs. The results of his pulmonary function testing (PFT) can be seen in Table 1, and are notable for normal airflows, severe restriction, reduced residual volume (RV), and a mild decrease in diffusing capacity of the lung (DL) for carbon monoxide (DL_{CO}) corrected for hemoglobin with an increased DL/alveolar volume (VA).

Questions

1. What are the major pathophysiologic categories of restrictive ventilatory defects?
2. What is the significance of this patient's abnormally low DL_{CO} in the setting of an elevated DL/VA?

[Continue onto next page for answers]

Figure 2. Normal respiratory system compliance. (A) Total respiratory system compliance is determined by the relationship between lung and chest wall elastic recoil pressure, and functional residual capacity (FRC) is the point at which those two pressures are equal and opposite. Total lung capacity (TLC) is determined by the balance between the pressure generated by the respiratory muscles (not pictured) and the inward elastic recoil pressures generated by the lungs and chest wall. (B) A schematic depicting the balance of forces that determine lung volumes at FRC. CW = chest wall; RV = residual volume.

Clinical Reasoning

The differential diagnosis for a patient with a restrictive ventilatory defect presenting with progressively worsening dyspnea is broad, and includes both intrinsic pulmonary and extrinsic etiologies. In this case, the clear lung parenchyma noted on his CT scan was not suggestive of pulmonary sarcoidosis or other intrinsic lung disease. In addition, the low DL_{CO} , in conjunction with a low VA and elevated DL/VA , suggested an extrinsic cause of restriction. On further questioning, he reported a previous diagnosis of scleredema, a rare complication of diabetes that typically leads to skin hardening and thickening around the shoulder and arms. In his case, substantial skin thickening was present on the shoulders, back, and sides of his chest wall, leading to a persistent, vise-like sensation with associated visible reduction in anterior chest wall excursion during inspiration. Other potential extrinsic etiologies of his restrictive physiology were thought to be less likely; in particular, the possibility of respiratory muscle weakness due to neuromuscular disease was lower on the differential diagnosis given his reduced RV on PFTs, lack of other neuromuscular symptoms, including weakness, and absent upper or lower motor neuron signs. Based on the data obtained before his pulmonary clinic visit and his history and examination findings, scleredema was believed to be the most likely explanation for his respiratory symptoms.

The Clinical Solution

Owing to the rarity of the disease and the fact that its self-limiting nature usually

obviates the need for specific therapies, there is little controlled data to be found in the literature on the treatment of scleredema. Further discussions with dermatology revealed that it does not generally respond well to therapy, but has been shown in case reports to potentially respond to phototherapy, intravenous immunoglobulin, corticosteroids, methotrexate, plasmapheresis, and cyclosporine. Dermatology recommended a course of psoralen and long-wave ultraviolet radiation given the patient's severe chest wall restriction. Monoclonal gammopathy (another cause of scleredema) was ruled out by serum and urine protein electrophoresis, and his primary care provider was notified of the complication and asked to generate a more intensive plan for the treatment of his diabetes (another key component in the management of scleredema). He reported symptomatic improvement on re-evaluation after a few weeks of phototherapy. Unfortunately, he unexpectedly moved to another state thereafter, and was lost to follow-up before obtaining repeat PFTs to assess for objective improvement in his restrictive physiology.

The Science behind the Solution

Intrinsic and Extrinsic Restrictive Ventilatory Defects

A restrictive ventilatory defect, defined by joint American Thoracic Society/European Respiratory Society guidelines as a reduction in total lung capacity (TLC) below the fifth percentile of the values from the reference

population, with a normal forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC), can result from causes both intrinsic and extrinsic to the lung. Recognizing the balance between lung and chest wall elastic recoil is the key to differentiating the underlying pathophysiology (Figure 2). In both intrinsic and extrinsic restriction, inspiratory capacity is usually reduced, as are functional residual capacity (FRC) and expiratory reserve volume. The DL_{CO} (discussed further below) will also generally be reduced in both categories of restrictive ventilatory defects.

Potential etiologies of intrinsic restriction include parenchymal sarcoidosis, idiopathic pulmonary fibrosis (IPF), and hypersensitivity pneumonitis, among many others, all of which should be visible on high-resolution imaging, particularly if the abnormality is severe. In this patient's case, long-standing, poorly controlled type I diabetes mellitus, leading to nonenzymatic glycosylation and irreversible cross-linking and accumulation of pulmonary collagen, could also be a potential etiology of intrinsic restrictive physiology, though this would not be appreciated on conventional CT imaging. With these parenchymal diseases, the reduction in lung compliance shifts the balance between the lungs and the chest wall toward a smaller FRC, and consequently reduces other lung volumes (Figure 3).

Extrinsic causes of restriction prevent the patient from achieving full inflation of the lungs, but are generally associated with normal parenchymal findings on imaging. Respiratory muscle weakness due to amyotrophic lateral sclerosis, myasthenia

Figure 3. Pathophysiology of reduced lung compliance. (A) A reduction in lung compliance alters respiratory system compliance by shifting the lung compliance curve down. Functional residual capacity (FRC) and total lung capacity (TLC) are reduced as a result. (B) A schematic depicting the change in the balance of forces that results from a reduction in lung compliance. At a normal FRC, inward lung elastic recoil pressure is increased such that lung elastic recoil pressure exceeds chest wall elastic recoil pressure. This results in a decrease in FRC to the point that these pressures are equal and opposite. CW = chest wall; RV = residual volume.

gravis, multiple sclerosis, Guillain-Barré syndrome, or Parkinson's disease can lead to extrinsic restrictive physiology. Additional potential etiologies of extrinsic restriction include morbid obesity, severe kyphoscoliosis, or the chest wall abnormality seen in the present case. Finally, prior lung resection (pneumonectomy or lobectomy) may alter chest wall mechanics as well as reduce lung volumes and capillary bed, independent of any intrinsic disease. In this case, it was believed that the corset-like tightening of the skin around the patient's chest led to reduction of chest wall compliance and impaired the ability of the

chest wall to expand, thereby altering the balance of forces between the lungs and the chest wall and reducing lung volumes (Figure 4). Of note, use of esophageal manometry to directly measure lung and chest wall compliance would have been very useful to confirm our suspicion for reduced chest wall compliance. An objective assessment of chest wall excursion using maximum and minimum chest circumference would have also been a useful way to assess his response to treatment longitudinally.

Although there was little concern for neuromuscular disease in this patient, there

are several pulmonary tests that can aid in diagnosis of extrinsic restrictive physiology due to respiratory muscle weakness; supine compared with upright vital capacity may be significantly reduced, RV may be increased due to expiratory muscle weakness, and static mouth maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) are characteristically reduced. It should be noted that MIP is performed from RV and MEP from TLC to limit variability, and maximum mouth pressures can be low in the absence of muscle weakness if subjects do not achieve normal RV and TLC values.

Figure 4. Pathophysiology of reduced chest wall compliance. (A) A reduction in chest wall compliance alters respiratory system compliance by shifting the chest wall curve down. As in the case of reduced lung compliance, functional residual capacity (FRC) and total lung capacity (TLC) are reduced. (B) A schematic demonstrating the change in the balance of forces that results from a reduction in chest wall compliance. At a normal FRC, outward chest wall elastic recoil pressure is decreased such that lung elastic recoil pressure exceeds chest wall elastic recoil pressure. This results in a decrease in FRC to the point that these pressures are equal and opposite. CW = chest wall; RV = residual volume.

Figure 5. An idealized plot of alveolar gas concentration versus time during the single-breath maneuver to calculate diffusing capacity of the lung for carbon monoxide (DL_{CO}). To measure the DL_{CO} , a patient first exhales to residual volume before rapidly inhaling a mixture of 0.3% CO, air, and a nonabsorbable gas (usually 1–5% helium). After a 10-second breath-hold, calculated by the Jones and Meade method, the patient rapidly exhales and the expired gas is collected for analysis.

DL_{CO}

The single-breath method used for clinical measurements is based on Ogilvie's modifications of concepts first described by Marie and August Krogh in the early 1900s. The DL_{CO} makes use of two separate measurements to provide clinical information: the rate of uptake of CO from alveolar gas (DL/VA) and the VA . The DL/VA is more appropriately thought of as representing the rate of alveolar CO uptake at a given VA , rather than a DL_{CO} "corrected" for VA , and is alternatively called and mathematically equivalent to the "transfer coefficient," or K_{CO} . In fact, the 2017 European Respiratory Society/American Thoracic Society guidelines recommend reporting the term K_{CO} rather

than DL/VA to avoid any confusion that this ratio generates. For historical context and to highlight key concepts, we will continue to use the term DL/VA for the remainder of this review.

To measure the DL_{CO} , a patient first exhales to RV before rapidly inhaling a mixture of 0.3% CO, air, and a nonabsorbable gas (usually 1–5% helium). After a 10-second breath-hold, the patient rapidly exhales and the expired gas is collected for analysis (Figure 5). The DL_{CO} is calculated as the product of the DL/VA and VA , and offers useful data on the etiology of a patient's lung disease. A low DL_{CO} implies a decreased surface area available in the lung for diffusion, which can occur in a wide variety of pathophysiologic states; examples

include microvascular damage due to pulmonary arterial hypertension (PAH) or diabetes mellitus, loss of lung units after pneumonectomy, alveolar capillary damage secondary to diffuse parenchymal lung disease, or lack of alveolar expansion due to chest wall abnormalities or neuromuscular disease. An increased DL_{CO} has been associated with diseases or pathologic states that increase cardiac output and/or pulmonary blood flow to increase perfused alveolar capillary surface area, such as exercise, hyperthyroidism, Paget's disease, left-to-right shunting or large systemic arteriovenous shunts or fistulas, or conditions that increase hemoglobin in the lung available to bind CO, such as alveolar hemorrhage or polycythemia.

The DL/VA (K_{CO})

Significant controversy exists regarding the utility of the DL/VA . When Marie Krogh first described the DL_{CO} , she believed it to be linearly proportional to the VA and believed that the DL/VA was a constant. She was proven incorrect by later studies, which showed that the relationship between DL_{CO} and VA is not linear, and therefore that DL/VA is not a constant. Despite these latter findings, the phrase "diffusing capacity per unit alveolar volume" is sometimes inappropriately interpreted to mean that the DL_{CO} is being "corrected" for VA , when, as previously mentioned, it reflects the DL_{CO} at the specific value of VA measured during the test. As such, evaluating the DL/VA independently of VA may lead to faulty assumptions. In addition, diseases in which

Figure 6. A diagram depicting the physiology of diffusing capacity of the lung for carbon monoxide (DL_{CO}) depending on the value of alveolar volume (VA) and the DL/VA . DL/VA = rate of alveolar CO uptake at the measured VA ; IPF = idiopathic pulmonary fibrosis; PAH = pulmonary arterial hypertension

ventilation is uneven (such as emphysema) may limit tracer gas dilution, with resultant underestimation of V_A and overestimation of D_L/V_A . In light of these limitations, some argue that the D_L/V_A has no utility in routine evaluation. Nevertheless, the index can potentially provide useful information, and an understanding of the basic concepts underlying it may help put the data that it provides in the proper context.

D_L/V_A is directly proportional to the alveolar–capillary membrane diffusing capacity relative to V_A and pulmonary capillary volume relative to V_A . A low D_L/V_A in the setting of a normal V_A usually implies a reduced rate of CO uptake due to microvascular destruction or remodeling, resulting in reduced membrane diffusing capacity and/or capillary volume (Figure 6B). A high D_L/V_A in the setting of a normal V_A implies an increased rate of CO uptake due to an increase in pulmonary blood flow and pulmonary capillary volume (Figure 6C). A low D_L/V_A in the setting of a low V_A implies a reduced rate of CO uptake, frequently due to either alveolar and/or microvascular destruction, which results in decreased membrane diffusing capacity and/or capillary volume; this may be seen in disease states associated with restriction intrinsic to the lung, such as IPF (Figure 6D). Of note, performing the measurement of D_{LCO} at two different fractions of inspired oxygen may aid in

differentiating between abnormal membrane diffusing capacity and capillary volume. A normal or high D_L/V_A in the setting of a low V_A is usually seen in disease states associated with incomplete alveolar expansion, increased pulmonary blood flow, or microvascular congestion; this may be seen in disease states associated with restriction extrinsic to the lung, such as alveolar hypoventilation due to neuromuscular weakness or chest wall abnormalities (Figure 6E). Pertinent information is potentially overlooked when the D_L/V_A is ignored, because multiple pathophysiologic states, ranging from IPF to PAH, can all lead to a decrease in D_{LCO} alone. The additional information provided by the V_A and D_L/V_A may help narrow the differential diagnosis in the appropriate context when uncertainty exists.

Answers

1. What are the major pathophysiologic categories of restrictive ventilatory defects?

Restrictive ventilatory defects can either be intrinsic or extrinsic to the lung.

2. What is the significance of this patient's abnormally low D_{LCO} in the setting of an elevated D_L/V_A ?

An abnormally low D_{LCO} corrected for hemoglobin, in this case 61%, in concert with a high D_L/V_A (124%) and low V_A

(49%), pointed toward a restrictive abnormality extrinsic to the lung and away from the diagnosis of worsening parenchymal sarcoidosis or some other new parenchymal pathology. This pattern can be seen in a relatively limited number of disease processes, including chest wall deformities, such as kyphoscoliosis, or respiratory muscle weakness from neuromuscular diseases, such as amyotrophic lateral sclerosis or myasthenia gravis. This patient's history, physical exam findings, and reduced RV on PFTs indicated that his symptoms were most likely attributable to reduced chest wall excursion from scleroderma; however, diabetic lung disease and neuromuscular disease were not entirely ruled out, and could potentially have been evaluated with esophageal manometry (to calculate chest wall and lung compliance) and additional measurements of respiratory muscle strength, such as supine FVC, MIPs, and MEPs. This case demonstrates how knowledge of core physiology can point to even exceedingly rare diagnoses. The presumptive diagnosis of scleroderma was, in turn, used to generate a management plan for this disease in the hope that the skin around the patient's chest could be loosened enough to allow for normal chest wall excursion and full alveolar expansion. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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