Chest Heart Journal
Vol. 44, No. 1, January 2020

REVIEW ARTICLE

Diffusing Capacity of Lung for Carbon Monoxide (DLCO) in evaluation of lung function.

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Abstract:

Diffusing capacity of lung for carbon monoxide (DLCO), also known as transfer factor of the lung for carbon monoxide (TLCO)[1], is a measurement to assess the ability of the lungs to transfer gas from inspired air to the bloodstream [2]. In the United States, the test is known as the DLCO and the units of measure are mL/min/mm Hg. DLCO is indicated in the evaluation of parenchymal and non-parenchymal lung diseases in conjunction with spirometry. A D_{LCO} of less than 60% predicted portends a poor prognosis for lung cancer resection. Inability to follow instructions is a contraindication to a DLCO test (CPT code 94729). In the single breath method, the patients are asked to take normal resting breaths initially; this is followed by full exhalation up to residual volume (RV), after which the patient is asked to rapidly inhale the test gas up to vital capacity (VC). Anemia can reduce DLCO. Hence DLCO is adjusted for hemoglobin values. ***KCO*** *is CO transfer coefficient, usually written as DLCO/Va, which indicates the efficiency of CO transfer by alveoli. High KCO occur in extra-parenchymal restriction and in "Extra-Hb". Low DLCO and Low KCO is seen in COPD with emphysema due to alveolar destruction. Decreased DLCO seen in obstructive lung diseases, cardiovascular diseases also in systemic disease involving lungs. Causes of increased DLCO includes polycythemia , obesity, asthma, which are characterized by large lung volumes.[11] High DLCO also seen in pulmonary hemorrhage. A normal DLCO with a restrictive pattern on PFT suggests neuromuscular or chest wall disorder.*

Key words: *DLCO, hemoglobin, KCO, PFT.*

[Chest Heart J. 2020; 44(1) : 43-47]
DOI: http://dx.doi.org/10.33316/chab.j.v44i1.2019616

Diffusing capacity of lung for carbon monoxide (DLCO), also known as transfer factor of the lung for carbon monoxide (TLCO)[1], is a measurement to assess the ability of the lungs to transfer gas from inspired air to the bloodstream [2]. Carbon monoxide (CO) has high affinity for hemoglobin (200-250 times that of oxygen) and follows the same pathway as that of oxygen to finally bind with hemoglobin. It should be noted that different units of measure exist worldwide. In the United States, the test is known as the DLCO and the units of measure are mL/min/mm Hg (traditional unit of measure). In contrast, the test is also known as the TLCO and the units of measure are mmol/min/kPa (International System of Units or SI units). The conversion from SI units (mmol/min/kPa) to traditional (mL/min/mm Hg) can be done by multiplying the SI value by 2.987. The test was introduced in 1909[3]. The respiratory membrane forms the diffusing barrier. It separates air within the alveoli from blood flowing in the pulmonary capillaries. It consists of the following layers:

alveolar epithelium , interstitium ,capillary endothelium.

According to the Fick's equation for the diffusion of gas[4]:

Vg=[k*(A)("P)] / T

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Submission on: 21 December, 2019 **Accepted for Publication:** 24 January, 2020
Available at http.//www.chabjournal.org

V = volume of gas transferred per unit time ,K = diffusion coefficient of the gas ,A = surface area for gas exchange ,"P = partial pressure difference of gas ,T = membrane thickness from this law, factors that influence the movement of gas molecules across the capillary membrane are the surface area of the membrane (A), the thickness of the membrane (T), driving pressure/pressure gradient across the capillary membrane ("P)[5].

As a consequence, the diffusion of gas across the alveolar membrane increases with:

Increased surface area of the membrane (A) , increased alveolar pressure gradient("P) ,increased solubility of the gas ,decreased membrane thickness (T)

Indications

DLCO is indicated in the evaluation of parenchymal and non-parenchymal lung diseases in conjunction with spirometry. The severity of obstructive and restrictive lung diseases, pulmonary vascular disease, and preoperative risk can be assessed using DLCO[8]. A D_{LCO} of less than 60% predicted portends a poor prognosis for lung cancer resection. FEV_1 is of lesser prognostic value for lung resection survival[14].

Contraindications

Inability to follow instructions is a contraindication to a DLCO test (CPT code 94729). Patients should be alert, oriented, able to exhale completely and inhale to total lung capacity, able to maintain an airtight seal on a mouthpiece, and able to hold a large breath for 10 seconds. DLCO also contraindicated in case of the chest and abdominal pain, oral or facial pain, dementia, or stress incontinence[10]. It is usually recommended to postpone pulmonary function testing by a month in case of acute coronary syndrome or myocardial infarction. PFT is also contraindicated in case of pneumothorax, ascending aortic aneurysm, pulmonary embolism, severe hypertension, hemoptysis, and major surgeries like thoracic/ abdominal /brain/eye/ear/otolaryngological surgery[9].

DLCO is measured using the following techniques[1]:

Single breath method ,intra-breath method ,re-breathing technique.

Procedures

In the single breath method, the patients are asked to take normal resting breaths initially; this is followed by full exhalation up to residual volume (RV), after which the patient is asked to rapidly inhale the test gas up to vital capacity (VC). The test gas contains: 0.3% CO ,0.3% tracer gas (helium, methane or neon), 21% oxygen ,balance nitrogen. Recommendations for a standard technique for the test were first published by the American Thoracic Society (ATS) in 1995. A joint task force from the ATS and the European Respiratory Society (ERS) published updated standards in 2017[8].The updated standards include some important changes in the criteria used to determine the technical acceptability and expected repeatability of

Technical Mistake	Consequences	Recommendation
Failure to reach residual volume before inhalation of the gas mixture Failure to inhale completely from residual volume to total lung capacity	↓D_{LCO} ↓↓V_A ↑Kco	• The inspired volume should be within 85 % of the largest vital capacity • VA within 200 mL or 5 % (whichever is greater) of the highest VA among acceptable maneuvers
Slow inspiration	"!D_{LCO} Slower lung filling decreases the amount of time the lung is at full inspiration	Inspiration of test gas should be sufficiently rapid such that 85 % of the air must be inspired in < 4.0 s
Valsalva maneuver during breath hold	"! D_{LCO} Lower pulmonary blood volume	Avoid the maneuver
Muller maneuver during breath hold	'! D_{LCO} Higher pulmonary blood volume	Avoid the maneuver

measurements, as well as recommendations on the increased utility of the procedure when rapid-responding gas analyzer (RGA) technology is used. RGA technology has been available for over a decade and most commercial equipment currently sold uses the RGA technology. It is likely that most of the slower-responding analyzer technology will phased out by equipment replacement over the coming decade.

The patient is asked to hold his breath for 10 seconds at total lung capacity (TLC). Subsequently, the patient exhales out completely, and exhaled gas is collected for analysis after excluding the initial amount of gas from dead space. The collected gas is analyzed for CO and tracer concentrations. Total lung volume, initial and final CO concentration, and breath-holding time are used to calculate DLCO. The recommended timing method used is the Jones and Meade method, which measures breath holding time at thirty percent of inspiratory time up to half of the sampling time. Usually, an average of two or more attempts is considered for DLCO calculation in the single breath-holding technique.

Another method to calculate DLCO is the intrabreath method, which is calculated during exhalation. The gas that exits during the initial phase of exhalation has less time to diffuse from alveoli to capillaries and will have a higher concentration of CO as compared to the gas during later stages of exhalation. The difference between various exhaled gas samples can be used to calculate DLCO.

Key problems in respiratory maneuvers

- Role of Registered Respiratory Therapist

  An optimal test performance requires optimal patient performance. It is important to coach patients to adapt instructions in different ways, including exaggerated body language. Registered respiratory therapists and other laboratory personnel play an important role in achieving acceptable and repeatable trails. [9]

  The 2017 ATS/ERS criteria for acceptability of DLCO efforts are as follows[2]:

- VI (inspired volume of test gas) greater than 90% of the largest VC measured by same-day slow or forced spirometry (2005 standard was >85%) or
- VI greater than 85% of largest VC and alveolar volume (VA) within 0.2 L or 5% (whichever is greater) of the largest VA from other acceptable maneuvers
- 85% of test gas VI inhaled in less than 4 seconds (unchanged from 2005 standards)
- Breathe hold time of 10 + 2 seconds without evidence of significant leaks, Valsalva maneuver, or Mueller maneuver (unchanged from 2005 standards)
- Sample collection completed within 4 seconds of the start of exhalation (was 3 seconds in 2005 standards); for RGA systems, virtual sample collection should be initiated after dead-space washout is complete

  The 2017 criterion for DLCO repeatability is as follows:

- At least two acceptable DLCO measurements within 2 mL/min/mm Hg (0.67 mmol/min/kPa) of each other (2005 standard was 3 mL/min/mm Hg or 1 mmol/min/kPa)

Quality grading for DLCO measurements is as follows:

- Score of A: (1) VI/VC 90% or VI/VC greater than 85% and VA within 0.2 L or 5% of largest VA from another acceptable maneuver; (2) breath hold time of 8-12 seconds; and (3) sample collection less than 4 seconds
- Score of B: (1) VI/VC greater than 85%; (2) breath hold time of 8-12 seconds; and (3) sample collection less than 4 seconds
- Score of C: (1) VI/VC greater than 80%; (2) breath hold time of 8-12 seconds; and (3) sample collection less than 5 seconds
- Score of D: (1) VI/VC greater than 80%; (2) breath hold time of less than 8 seconds or greater than 12 seconds; and (3) sample collection less than 5 seconds
- Score of F: (1) VI/VC less than 80%; (2) breath hold time of less than 8 seconds or greater than 12 seconds; and (3) sample collection greater than 5 seconds

Only grade A maneuvers meet all acceptability criteria. The average DLCO values from two or more grade A maneuvers that meet repeatability criterion should be reported. If only one grade A maneuver is obtained, the DLCO value from that maneuver should be reported. If no grade A maneuver is obtained, maneuvers of grades B to D might still have clinical utility, and the average of such maneuvers should be reported. However, these deviations from the acceptability criteria must be noted to caution the interpreter of the test. Maneuvers of grade F are not useable.

Severity and classification of DLCO reduction[9]:

- Normal DLCO: >75% of predicted, up to 140%
- Mild: 60% to LLN (lower limit of normal)
- Moderate: 40% to 60%
- Severe: <40%

Interfering Factors

DLCO adjustment:

- Effect of hemoglobin on DLCO: Anemia can reduce DLCO. Hence DLCO is adjusted for hemoglobin values. Various calculators are available to calculate DLCO adjusted for hemoglobin but following is applied usually.
- For men normal value is 14.6 g/dl and
- For women and children under 15 years - 13.4 g/dl

So, Hb adjusted for men:

$$\text{Observed DLCO} \times \frac{(10.22 + \text{Hb})}{1.7 \times \text{Hb}}$$

and for Women :

$$\text{observed DL CO} \times \frac{(9.38 + \text{Hb})}{1.7 \times \text{Hb}}$$

4 % DLCO decrease for each g/dl below normal Hb
2 % increase for each g/dl above normal Hb

- DLCO may need to be adjusted for several other factors like carboxyhemoglobin

Interpretation of DLCO

- DLCO= Va X KCO

Va: number of contributing alveolar units measured by tracer gas (helium)

- KCO: CO transfer coefficient, usually written as DLCO/Va, which indicates the efficiency of CO transfer by alveoli.
- KCO occurs in
- *Parenchymal* lung diseases like IPF ,Sarcoidosis ,Asbestosis,Other ILDs
- *Pulmonary vascular abnormality:*Pulmonary Hypertension,Pulmonary Embolism, Vasculitis , Chronic Heart Failure.
- *Intrapulmonary right to left shunt:* PAM, Hepato pulmonary syndrome
- *Obstructions:* Emphysema, Cystic Fibrosis, Bronchiectasis, Bronchiolitis

*'!*KCO occur in

Extra-parenchymal restriction

Incomplete expansion like: Pleural diseaseses , NMD ,Chest wall diseases.

Discrete loss of units: Pneumonectomy ,Local destruction/,Infiltrates, atelctasis.

"Extra-Hb"

Extra vascular: PulmonaryHemorrhage,Wegener's Capillaritis

Intra-vascular: Asthma, Obesity, Polycythemia ,L-to-R shunting

A decrease in DLCO will be due to a decrease in Va, Kco, or both.

Low DLCO and Low KCO: seen in COPD with emphysema due to alveolar destruction (usually normal in chronic bronchitis) with an obstructive pattern on PFT.

Smoking can also cause a decrease in DLCO[10]

Causes of decreased DLCO

- Obstructive Lung Diseases
  - Emphysema
  - Cystic Fibrosis
    Parenchymal Lung Disease
  - Interstitial Lung Disease
    Idiopathic
    Asbestosis,
    Allergic alveolitis
    Drug induced
- Pulmonary involvement in systemic disease
  - SLE
  - Progressive systemic sclerosis
  - Mixed connective tissue disease
  - Rheumatoid arthritis
  - Dermatomyositis
  - Polymyositis
  - Wegeners granulomyositis
  - Inflammatory bowel disease
- Cardiovascular disease
  - Pulmonary edema
  - Chronic heart failure[12]
  - Pulmonary thrombo-embolism
  - Primary pulmonary hypertension
  - Acute myocardial infarction
  - Fat embolization
- Others
  - Anemia
  - Chronic renal failure
  - Marijuana smoking
  - Acute and chronic ethanol ingestion
  - Cigarette smoking
  - Bronchiolitis obliterans with organizing pneumonia

Causes of increased DLCO

- Polycythemia
- obesity, asthma, which are characterized by large lung volumes.[11]
- Pulmonary hemorrhage
- Increased pulmonary blood flow
- *Left to right intracardiac shunts*
- Exercise
- Mueller maneuver

Abnormal pattern of DLCO,KCO and VA in various disease states:

Conditions	VA	KCO	DLCO
Incomplete lung expansion (Diaphragm palsy, collapse)	↓↓↓	↑↑	↓
Loss of lung units (lobectomy, fibrosis)	↓↓↓	↑	↓↓
Diffuse alveolar damage(ILD)	↓↓	↓	↓↓↓
Emphysema	↓	↓↓	↓↓↓
Pulmonay vascular disease	Normal	↓↓	↓↓
High pulmonary blood volume (Shunt, cardiac failure)	Normal	↑	↑
Alveolar hemorrhage	↓	↑↑↑	↑↑

Both DLCO and KCO are also reduced in interstitial lung diseases, pulmonary fibrosis due to the thickening of the alveolar-capillary membrane with a restrictive pattern on PFT.[8]

A normal DLCO with a restrictive pattern on PFT suggests neuromuscular or chest wall disorder.

In cases of dyspnea of unknown etiology, the pattern of normal spirometry with low DLCO increases the likelihood of pulmonary vascular disease. However, this pattern may also be seen in other disorders, e.g., mild ILD.[1]

High DLCO and high KCO may also be observed in conditions involving profuse pulmonary hemorrhage (e.g. Goodpasture's syndrome, systemic lupus erythematosus, granulomatosis with polyangiitis). This is due to increased uptake of CO.

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