Diffusion

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Diffusion

- Primary function of lung – gas exchange
- Movement of gas across the blood-gas interface is by simple passive diffusion
- “Net transfer of molecules from a zone with high partial pressure to a zone with lower partial pressure”
- Partial pressure v/s concentration gradient
Components of diffusion pathway

- Gas space within the alveolus
- Alveolar lining fluid – surfactant rich
- Tissue barrier – alveolar capillary membrane
- Plasma layer
- Diffusion into and within the RBC
- Uptake of CO by hemoglobin
Transfer factor

• CO uptake reflects number of processes – not just diffusion
• CO uptake is a submaximal value and not truly a ‘capacity’
• So, TLco – probably better term
Indications

• Specific indications not defined -
  - variety of testing procedures in use
  - complexity of physiologic determinants of CO uptake

• Most commonly used in evaluation of -
  - diffuse interstitial lesions
  - suspected emphysema
  - pulmonary vascular obstruction

• Useful in diagnosis as well as follow up
Why carbon monoxide??

• Gas that is more soluble in blood than in lung tissues (O₂ and CO)
• High affinity for hemoglobin (250 times of O₂)
• Transfer is diffusion limited rather than perfusion limited
• Not present in lung normally
• CO diffusion is less affected by other factors

DLO₂ = DLco x 1.23
Measuring diffusion capacity

- DLco = CO transferred from alveoli to blood (ml/min)
  mean alveolar CO pressure – mean capillary CO pressure (mm Hg)

- Five methods:
  1. Single-breath method
  2. Steady-state method
  3. Rebreathing method
  4. Three-Gas Iteration method
  5. Intra-breath method
Single breath method

• Most widely used and best standardized of the various methods

• System design:
  - source of test gas
  - method of measuring inspired and expired vol over time
  - gas analysers

• System types:
  - with alveolar sample bags
  - with rapid gas analyzer
Systems with Alveolar Sample Bag

- Test gas
  - 10% helium (He)
  - 0.3% carbon monoxide (CO)
  - 21% oxygen (O₂)
  - Balance nitrogen (N₂)

- Breath-hold for approximately 10 sec

- After breath-hold, wash out dead space

- Collect alveolar sample
Systems with Continuous Rapid Analysis

- Test gas contains methane (CH$_4$) as trace gas
- Uses rapid gas analyzer to continuously analyze - expired gas sample
Performing the Test

- Patient connects to instrument
- Unforced exhalation to RV
- Valve is opened to test gas
- Patient rapidly inhales a full breath of test gas
- Holds breath for about 10 sec
- Patient exhales without max force
- After dead space is cleared, sample is collected/analyzed
Test Gases

- Tracer gas to measure $V_A + CO$
- CO approximately 0.3%
- Tracer gas:
  - relatively insoluble
  - chemically and biologically inert
  - gaseous diffusivity similar to CO
  - not interfere with measurement of CO
  - not present normally in alveolar gas
- Gas mixture should be similar to reference set
Procedure

- Inspiratory maneuver
- Sample collection volume
- Dead space washout
- Breathhold
Diffusion Data

Helium Inspired 13.94
Co Inspired .259
Helium Expired 11.23
Co Expired .092
Diffusion Time 10.66
Inspired Volume 4.02
DLCO Result: 28.90
O2 Expired 15.70
1/Theta 0.934
Hgb : 15.00
V Insp BTPS : 4.41

Hit any key when ready
Technical Sources of Variability

- Patient conditions
- Inspiratory maneuver
- Breath-hold and expiratory maneuver
- Washout and sample collection volume
- Inspired gas composition
- Interval between tests
- Miscellaneous factors
Patient Conditions

- Explain and demonstrate the test maneuver
- If possible, no supplemental O₂ for >10 min
- Patient seated before and throughout test
- Increased COHb decreases DLCO
  - No smoking on day of test
  - Note time of last cigarette
  - Correction for CO back pressure

Eur Respir J 2005; 26: 720–735
**Inspiratory Maneuver**

- Exhalation to RV limited to 6 sec
- Suboptimal $V_i$
  - Suboptimal exhalation to RV
  - Suboptimal inhalation from RV
- $V_i \geq 85\%$ of largest VC
- $85\%$ of $V_i < 4$ sec
- Smooth inspiration with no stepwise changes
Breath Hold & Expiratory Maneuver

- No excessive “+” or “−” intrathoracic pressure
- Breath hold of 10 ± 2 sec
- Exhalation time < 4 sec
- Sample collection time < 3 sec
Start of inspiration

Start of alveolar sample collection

Jones-Meade
Washout and Sample Collection Volume

- Anatomic & mechanical dead space gas must be discarded (washed out)
- Underestimate DLco if not enough washout
- Too much delays alveolar sampling and increases BHT
- Washout volume = 0.75 to 1.0 L (BTPS)
- Sample volume = 0.5 to 1.0 L

Eur Respir J 2005; 26: 720–735
Interval between tests

• At least 4 min between tests
• Longer period (~10 min) in obstructive diseases
• Subject should remain seated

Eur Respir J 2005; 26: 720–735
Miscellaneous factors

• Diurnal variation in DLco
• Menstrual cycle
• Ingestion of ethanol or smoking
• Bronchodilator use
Acceptable DLco test criteria

- Use of proper quality-controlled equipment
- Inspired volume of >85% of largest VC
- Inspired volume obtained within 4 sec
- A stable breath hold for 10 ± 2 sec
- No evidence of leaks, or Valsalva or Mueller maneuvers
-Expiration < 4 sec with appropriate clearance of dead space and proper sampling of alveolar gas

Eur Respir J 2005; 26: 720–735
Repeatability and Number of Tests

- Obtain at least 2 acceptable tests
- Repeatability requirement – 2 acceptable tests
  - within 3 units, OR
  - 10% of the highest value
- Report the average of 2 acceptable tests
  - that meet repeatability requirement
- More than 5 tests are not recommended

Eur Respir J 2005; 26: 720–735
Reference Values

- Reference equations provide widely discrepant values

- For a 45 yr old man, 175 cm tall - DLco values range from 29.3 to 38.4 units

- Choose based on biologic and technical comparability

- Don’t be tempted to just adopt the manufacturer’s default

Eur Respir J 2005; 26: 720–735
Reporting

• Average of at least 2 acceptable and repeatable tests
• Report includes:
  Measured DLco
  Predicted and percent predicted
  DLco/VA or Kco
  Predicted and percent predicted DLCO / VA
  Any adjustments for Hb, COHb or VA

• If using continuous analyzers, manual adjustments must be noted on report so interpreter can review and verify the adjustments

Eur Respir J 2005; 26: 720–735
Steady-State Method

• Pt. breathes a mixture of 0.1% CO in air for several min through one way valve system
• During last 2 min exhaled gas is collected and analyzed
• ABG also drawn and analyzed for Pco₂
• Can be measured during tidal breathing, anesthesia, sleep, and exercise
• Results are markedly affected by uneven distribution of ventilation or V/Q abnormalities
Rebreathing Method

- Pt rebreathes the test gas from reservoir, the volume of which equals pt’s FEV₁
- Rebreathing continues for 30-45 s, at controlled rate of 30 per min
- More variable
- Requires considerable patient cooperation to attain rapid respiratory rate required
Three-Gas Iteration Method

• Uses separate equations for inhalation, breath-hold, and exhalation phases
• More reproducible, and
• Unaffected by a variety of factors esp. abnormalities in distribution of ventilation
Intra-Breath Method

• DLco is measured at increments of the exhaled volume
• Requires a special, very rapid infrared analyzer
• Does not require a breath hold
• Probably easier for sick patients
• Needs validation
Unit of DLco

• Traditional:
  \( \text{mL (STPD).min}^{-1}.\text{mmHg}^{-1} \)

• SI units:
  \( \text{mmol.min}^{-1}.\text{kPa}^{-1} \)

Traditional = SI x 3

Eur Respir J 2005; 26: 720–735
Factors affecting diffusion capacity

- Changes in the membrane surface area
  - body size
  - lung volume
  - V/Q mismatch
  - posture
  - pathology

- Changes in physical properties of membrane
  - chronic heart failure and pulmonary edema

- Changes related to uptake of gases by RBC’s
  - Hb conc and COHb
Hemoglobin concentration

- DLco directly correlates with Hb
  - 1g/dl decrease Hb – 4% decrease DLco
  - 1g/dl increase Hb – 2% increase DLco
- Cotes and associates* –
  \[ \text{Hb adjusted DLco} = \text{measured DLco} \times (14.6 \times \frac{DM}{VC}) + \text{Hb} \]
  \[ \text{Hb} \times (1 + \frac{DM}{VC}) \]

* Clin Sci 1972;42:325-335
  Eur Respir J 2005; 26: 720–735
Carboxyhemoglobin

- COHb affects DLco in two ways -
  - occupying Hb binding sites i.e. “anemia effect”
  - reduced driving pressure for CO transport
- 1% increase in COHb decreases DLco by ~1%
- Heavy smokers may have 10-12% COHb in their blood
- Equation –
  \[ DLco\, pred\, for\, COHb = DLco\, pred\times (102\% - COHb\%) \]

Am J Respir Crit Care Med 2002;165:1504-1510
Lung volume

• DLco decreases as lung deflates as a function of both membrane and capillary configuration changes
• Complex relationship, probably non-linear
• Expansion of lung - thinning of ACM, increase in diameter of corner vessels
• $K_{co} = \frac{DL_{co}}{V_A}$

J Appl Physiol 1994;76:2356-63
Factors affecting....

• Body size: DLco varies with BSA better predicted by height & weight
• Age: DLco declines in linear fashion with age
• Gender: Reduced DLco in females
  Highest just before menses, least 5-10 days after it
• Ethnicity: lower in African-Americans, Asians
• Posture: increased in supine position (15-20%)

Am J Respir Crit Care Med 1996;153:656-64
Factors affecting....

• Exercise:
  - by ↑sing CO → decrease capillary transit time
  - capillary recruitment in non-dependent zones
  - exercise may double value obtained at rest
  - recovery after high-intensity exercise - 24 hrs

• Smoking:
  - reduced in proportion to no. of cigarettes per day currently smoked, and
  - total lifetime no. of cigarettes ever smoked

J Appl Physiol 1990;68:94-104
Am J Respir Crit Care Med 1996;153:656-64
Alveolar oxygen pressure

- Inversely related
- DLco increases by 0.31% per mm Hg decrease in PiO₂
- USA: FiO₂ 0.21
  Europe: FiO₂ 0.17
  PGI: FiO₂ 0.18
- Discontinue suppl. O₂ >10 min before procedure

Am Rev Respir Dis 1986; 133:676–678
Subdivisions of total diffusing capacity

- Roughton and Forster equation*
  \[ \frac{1}{DL} = \frac{1}{DM} + \frac{1}{\theta \cdot Vc} \]
- Increasing alveolar PO2 reduces DLco as CO has to compete with O2 for hemoglobin
- If \( \frac{1}{DL} \) is plotted against \( \frac{1}{\theta} \): the slope of line is \( \frac{1}{Vc} \) and the intercept on vertical axis is \( \frac{1}{DM} \)

* J Appl Physiol 1957;11:290-302
Increased DLco

- Diseases that ↑se θVc and thus ↑se DLco
  - Polycythemia
  - Left-to-right shunt
  - Pulmonary hemorrhage (not strictly an increase in θVc, but effectively an increase in lung Hb)
  - Asthma

Eur Respir J 2005; 26: 720–735
Decreased DLco

- Reduced $\theta V_c$
  - anemia
  - pulmonary emboli
- Reduced $D_M$
  - Emphysema
  - Interstitial lung diseases (e.g. IPF, sarcoidosis)
  - pulmonary edema
  - pulmonary vasculitis
  - pulmonary hypertension
  - lung resection

Eur Respir J 2005; 26: 720–735
Abnormal DLco

• ILD
  - early though nonspecific manifestation
  - monitoring progress & Rx
  - monitoring people at risk

• COPD
  - diagnosis of emphysema
  - correlates with severity
  - predicts exercise limitation
  - predicts mortality


Respir Med. 2007 Sep;101(9):1961-70
Abnormal DLco

• Pulmonary Embolism
  - unexplained dyspnea + reduced DLco
  - correlates with degree of obstruction
  - reductions persist for 3 yrs


• CHF
  - Increased in early CCF
  - Decreased in advanced & chronic cases
  - correlates with NYHA class

Heart 2005;91:1473–1474
Eur Heart J 2006;27:2538–2543
Interpretation

• Lower 5th %tile of the reference population should be used as LLN for DLco and Kco
• Relationship between DLCO and lung volume is not linear, so DLco/VA or DLco/TLC do not provide an appropriate way to normalize DLco for lung volume
• Conceptually, low DLco but high DLco/VA: extraparenchymal abnormality (e.g. pneumonectomy or chest wall restriction)
• Low DLco and low DLco/VA: parenchymal abnorm

Eur Respir J 2005; 26: 948–968
## Degree of severity

<table>
<thead>
<tr>
<th></th>
<th>DLco % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;60% but &lt;LLN</td>
</tr>
<tr>
<td>Moderate</td>
<td>40-60%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;40%</td>
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</tbody>
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Eur Respir J 2005; 26: 948–968