The New ERS/ATS Diffusion Of The Lung Technical Standards

It’s As Simple As $E=MC^2$

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Diffusing Capacity - Background

- Evaluates how well oxygen moves into and out of the lungs (alveolar capillary interface)
- Originally described by Krogh in 1915
- Product of two variables; rate of CO uptake and the $V_A$
- Carbon monoxide is used as a surrogate for $O_2$
Diffusing Capacity - Indications

- Evaluation and f/u of parenchymal lung diseases including: idiopathic pulmonary fibrosis (IPF, UIP, BOOP); diseases associated with dusts such as asbestos, silicosis; other lung diseases such as sarcoidosis
- Evaluation and f/u of emphysema and cystic fibrosis and differentiating among COPD patterns
- Evaluation of PV diseases (eg, PPH, PE, or pulmonary edema)
Diffusing Capacity - Indications

- Evaluation of pulmonary involvement in systemic diseases (eg, rheumatoid arthritis, lupus, Wegener’s)
- Evaluation of the effects of chemotherapy agents or other drugs
  - Bleomycin, amiodarone, both require routine DLCO testing as a monitor
- Evaluation of pulmonary hemorrhage
- As an early indication of certain pulmonary infections (eg, pneumocystis pneumonia)
- Quantification of disability
Diffusing Capacity – New Technical Standard

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Diffusion of the Lung

- DLCO vs TLCO
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Equipment Performance Standards

- Volume accuracy (3L syringe check)
- Flow rates 0.5-12L/s
- Within $\pm$ 2.5% (75 mls)
Weekly or whenever problems are suspected
#1. Volume spirometers – leak test
#2. Syringe DLCO
#3. BioQC

DLCO Simulator
(very limited comments)
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**Diffusing Capacity – Quality Assurance**

- **Syringe DLCO**
  - Performed in the patient mode
  - DLCO target <0.5 ml/min/mmHg
  - $V_A$ within 300 mls of 3L (times the STPD to BTPS factor)
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Diffusing Capacity – Quality Assurance

- Biological Model
  - Normal laboratory subjects
  - Two individuals
  - Establish mean and SD
    - <12% or 3ml/min/mmHg of mean
    - Too loose! CV ≤5%
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Diffusing Capacity – Quality Assurance

- Monthly
  - 3L calibration syringe leak test
  - 50 mls (0.17 of full excursion of shaft)
  - Push for 10 sec.
  - Return to within 10 mls
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Diffusing Capacity – Quality Assurance

<table>
<thead>
<tr>
<th>Calibration technique</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow analyser zeroing</td>
<td>Before each test</td>
</tr>
<tr>
<td>Gas analyser zeroing</td>
<td>Before/after each test</td>
</tr>
<tr>
<td>Volume calibration check</td>
<td>Daily</td>
</tr>
<tr>
<td>Biologic control</td>
<td>Weekly</td>
</tr>
<tr>
<td>Calibration syringe $D_{Lco}$ check</td>
<td>Weekly</td>
</tr>
<tr>
<td>Calibration syringe leak test</td>
<td>Monthly</td>
</tr>
<tr>
<td>Linearity check (calibration syringe or simulator)</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

$D_{Lco}$: diffusing capacity of the lung for carbon monoxide.
Evidence of Quality DLCO Testing

Certification of DLCO Measurements for Clinical Trials

- Results of the initial DLco simulation tests from 125 pulmonary laboratories
  - 94 (75.2%) Passed with coaching; no hardware
  - 24 (19.2%) Failed. Passed after servicing
  - 6 (4.8%) Failed. Passed with new equipment
  - 1 (0.8%) Site dropped 1

18 DLCO instruments at 13 Intermountain Health Care sites over 10 months

DLCO instrument accuracy was unacceptable in 22 (33%) of instruments
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Diffusion of the Lung

(Continued for April 5, 2017 - Wednesday)

2:00 pm Desk 18 East
Gonda Building, Eighteenth Floor, Desk 18 East
Pulmonary Function Laboratory
Pulmonary Test

Smoking: Do not smoke for 1 hour before the test.

Eating and drinking: You may eat light foods (for example, yogurt, fruit, a cup of soup) and drink plain water during the hour before your appointment time.

Exercise: Do not exercise (jogging, bicycling, fast walking, aerobics, etc.) for 2 hours before this test.

Medications: Do not take any of the following inhaled medications 6 hours before the test:
- Albuterol (ProAir™, Proventil™, Ventolin™, Accuneb™)
- Albuterol and ipratropium (Combivent™, DuoNeb™)
- Ipratropium (Atrovent™)
- Levalbuterol (Xopenex™)

Do not take any of the following inhaled medications 12 hours before the test:
- Salmeterol (Advair™, Serentil™)
- Formoterol (Foradil™, Perforomist™, Symbicort™, Dulera™)
- Arformoterol (Brintavar™)
- Aclidinium (Tudorza™)

Do not take the following inhaled medications for 24 hours before this test:
- Tiotropium (Spiriva™)
- Indacaterol (AccuPulse™, Ultibo Broezhake™)
- Vilanterol (Broo Brozilpta™, Anoro Ellipta™)
- Olodaterol (Striavent™)
- Glycopyronium (Seebri™, Ultibo Brozhafer™)
- Umclidinium (Incuis™, Anoro Ellipta™)

If your breathing is causing distress:
- You may use your bronchodilator (inhaled) before this test, but using it will affect your results.

Perfumes: Do not wear scented products (for example: perfume, after-shave, powder, lotion) to this appointment. These products can cause breathing problems for some patients.

Dependents: Children are not allowed into the testing room unless they are the patient. Children and dependents may not be left unattended in the waiting rooms.
Pretest Instructions

Patient conditions for measurement

- Factors that affect pulmonary capillary blood volume (e.g. exercise, body position), and hemoglobin affinity for CO (eg alveolar PAO$_2$, COHb) should be standardized.
- If clinically acceptable, the subject should not breathe supplemental oxygen for 10 minutes prior to a standard test.
Recent smoking

- Patient should not have smoked on the day of testing*
- Time of last cigarette should be recorded
- Back pressure of CO in blood will cause measured $D_{LCO}$ to be lower (10% COHb = 10% reduction in $D_{LCO}$)
Inspiratory maneuver

- Exhalation to RV <12 sec*
- Inspiration should be rapid (85% of VC in < 4.0 seconds)
  - DLCO calculation assumes instantaneous introduction of test gas into alveolar regions.
  - Long inspirations result in lower mean lung volume during the measured breath hold time (lower $D_{LCO}$)
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Diffusion of the Lung

Inspired vital capacity

- IVC should be at least 90% of patient’s previous best VC.*
  - Maneuver is also acceptable when;
    - IVC is 85% of largest VC and the VA is within 200 mls or 5% (whichever is greater) of the highest VA among acceptable maneuvers
Breath hold time

- 10 ± 2 seconds
- Avoid valsalva (expiratory efforts against a closed airway) and Müller maneuvers
Classic Systems

Washout volume

- Pre-sample washout volume should be 0.75 to 1.0 liter (clear deadspace)
  - 0.5 liter in patients with IVC < 2.0 liter
  - A gas sample taken before anatomic dead space has cleared will be contaminated by inspired gas (not pure alveolar).
  - In patients with maldistribution of ventilation (COPD) timing of gas collection may be more important.
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Diffusion of the Lung

Classic systems
Sample collection volume

- Sample volume of 0.50 to 1.00 L should be collected for analysis
  - In patients with VC < 1 L, smaller sample volumes below 0.50L may be used if it can be assured that VD has been cleared

- Allow 4 minutes in between tests (especially in patients with obstruction)
• Jones - Meade - 0.70 of inspiratory time and half of sample time
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Diffusion of the Lung

- **Rapid Gas Analyzer**
  - Allows for analysis of lower VC < 1 liter
  - Adjust washout volume once a plateau is achieved
  - Time between tests
    - tracer gas level at end-exhalation must be \( \leq 2\% \)

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Hemoglobin adjustments

- Men (expected Hb 14.6):

\[ D_{LCO}[predicted \text{ for } Hb] = D_{LCO}[predicted] \cdot \left(\frac{1.7Hb}{10.22 + Hb}\right) \]

- Women and adolescents (expected Hb 13.4):

\[ D_{LCO}[predicted \text{ for } Hb] = D_{LCO}[predicted] \cdot \left(\frac{1.7Hb}{9.38 + Hb}\right) \]

Roughly 3.5% per gm Hb below expected
Diffusion of the Lung

- DLCO affected by altitude
  - DLCO varies inversely with changes in alveolar oxygen pressure ($P_{\text{A}O_2}$).
  - $P_{\text{A}O_2}$ changes as a function of altitude, as well as with the partial pressure of oxygen in the test gas.

\[ DLCO[P_{\text{B}} \text{ adjusted}] \approx DLCO(0.505 + 0.00065 P_{\text{B}}) \]
Diurnal variation
- One study showed DLCO fell 1.2-2.2% per hour throughout the day.

Menstrual cycle
- 13% fall during cycle

Alcohol use

Bronchodilators (effect on VA)
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DLCO – Testing technique

- Quiet breathing
- Exhale to RV
- Inhale test gas rapidly
  - 0.3% CO, 10% He, 21% O₂, Bal N₂
- Breath-hold (10 sec) with no leaks (good seal on mouthpiece)
- Exhale (relatively fast)
### TABLE 3 Acceptability, repeatability and quality control in Dlco testing

#### Criteria for acceptability

- A $V_l \geq 90\%$ of the largest $VC$ in the same test session; alternatively a $V_l \geq 85\%$ of the largest $VC$ in the same test session and $V_A$ within 200 mL or 5\% (whichever is greater) of the largest $V_A$ from other acceptable manoeuvres.
- 85\% of test gas $V_l$ inhaled in $<4$ s.
- A stable calculated breath-hold for $10 \pm 2$ s with no evidence of leaks or Valsalva/Müller manoeuvres during this time.
- Sample collection completed within 4 s of the start of exhalation. For RGA systems, virtual sample collection should be initiated after dead-space washout is complete.

#### Criteria for repeatability

At least two acceptable $Dlco$ measurements within $2 \text{mL-min}^{-1}\cdot\text{mmHg}^{-1}$ ($0.67 \text{mmol-min}^{-1}\cdot\text{kPa}^{-1}$) of each other.

#### Quality control grading

<table>
<thead>
<tr>
<th>Score</th>
<th>$V_l/VC$</th>
<th>$t_{BH}$</th>
<th>Sample collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>$\geq 90%$</td>
<td>8–12 s</td>
<td>$\leq 4$ s</td>
</tr>
<tr>
<td>B</td>
<td>$\geq 85%$</td>
<td>8–12 s</td>
<td>$\leq 4$ s</td>
</tr>
<tr>
<td>C</td>
<td>$\geq 80%$</td>
<td>8–12 s</td>
<td>$\leq 5$ s</td>
</tr>
<tr>
<td>D</td>
<td>$\leq 80%$</td>
<td>$&lt;8$ or $&gt;12$ s</td>
<td>$\leq 5$ s</td>
</tr>
<tr>
<td>E</td>
<td>$\leq 80%$</td>
<td>$&lt;8$ or $&gt;12$ s</td>
<td>$&gt;5$ s</td>
</tr>
</tbody>
</table>
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Diffusion of the Lung

- Data is reported in STPD
- Units: ml/min/mmHg or mmol//min/kPa
## 2017 ERS/ATS Technical Standards Reporting Requirements

### TABLE 4 \( DLCO \) reporting requirements

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>( DLCO ) (unadjusted)</td>
<td>Required</td>
</tr>
<tr>
<td>( DLCO ) (adjusted for ( Pa ))</td>
<td>Required</td>
</tr>
<tr>
<td>( DLCO ) (LLN and/or z-score)</td>
<td>Required</td>
</tr>
<tr>
<td>( DLCO ) (predicted)</td>
<td>Required</td>
</tr>
<tr>
<td>( DLCO ) (adjusted, predicted)</td>
<td>Optional (required if any adjustments made - specify adjustments)</td>
</tr>
<tr>
<td>( DLCO ) (% of predicted)</td>
<td>Required</td>
</tr>
<tr>
<td>( V_a ) (BTPS)</td>
<td>Required</td>
</tr>
<tr>
<td>( V_a ) (LLN and/or z-score)</td>
<td>Required</td>
</tr>
<tr>
<td>( V_a ) (% of predicted)</td>
<td>Optional</td>
</tr>
<tr>
<td>( Kco )</td>
<td>Required</td>
</tr>
<tr>
<td>( Kco ) (LLN and/or z-score)</td>
<td>Required</td>
</tr>
<tr>
<td>( Kco ) (predicted)</td>
<td>Required</td>
</tr>
<tr>
<td>( Kco ) (% of predicted)</td>
<td>Required</td>
</tr>
<tr>
<td>( Pa )</td>
<td>Required</td>
</tr>
<tr>
<td>( V_B ) (BTPS)</td>
<td>Required</td>
</tr>
<tr>
<td>Fowler (anatomic) dead-space</td>
<td>Required for RGA systems</td>
</tr>
<tr>
<td>TLCdb</td>
<td>Required for RGA systems</td>
</tr>
<tr>
<td>Reference values source</td>
<td>Required</td>
</tr>
<tr>
<td>Test quality grade</td>
<td>Recommended (include % variability in ( DLCO ) acceptable manoeuvres)</td>
</tr>
<tr>
<td>Operator comments</td>
<td>Required (number of manoeuvres, number of acceptable manoeuvres)</td>
</tr>
<tr>
<td>Graphs</td>
<td>Required (full manoeuvre and exhaled gas concentration versus volume with sample collection indicated for RGA systems)</td>
</tr>
<tr>
<td>Hb</td>
<td>Optional (required if used to adjust ( DLCO ))</td>
</tr>
<tr>
<td>COHb</td>
<td>Optional (required if used to adjust ( DLCO ))</td>
</tr>
<tr>
<td>Alternative calculations (e.g. three-equation ( DLCO ), normalised slope of phase III)</td>
<td>Optional</td>
</tr>
</tbody>
</table>
# Reference Equations

**TABLE 5 Reference values for DLco from studies that complied with the 2005 American Thoracic Society/European Respiratory Society DLco standards**

<table>
<thead>
<tr>
<th>Author#</th>
<th>Year</th>
<th>Country</th>
<th>Age</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson [129]</td>
<td>2008</td>
<td>Australia</td>
<td>45–71 years</td>
<td>498 male/474 female</td>
</tr>
<tr>
<td>Koopman♀ [130]</td>
<td>2011</td>
<td>Netherlands</td>
<td>7–18 years</td>
<td>278 male/265 female</td>
</tr>
<tr>
<td>Garcia-Rio♀ [131]</td>
<td>2012</td>
<td>Spain</td>
<td>65–85 years</td>
<td>169 male/262 female</td>
</tr>
<tr>
<td>Kim [132]</td>
<td>2012</td>
<td>USA and Australia</td>
<td>5–19 years</td>
<td>225 male/254 female</td>
</tr>
<tr>
<td>Thomas [133]</td>
<td>2014</td>
<td>Denmark</td>
<td>5–17 years</td>
<td>male/female (297 total)</td>
</tr>
<tr>
<td>Michailopoulos [134]</td>
<td>2015</td>
<td>Greece</td>
<td>18–91 years</td>
<td>234 male/233 female</td>
</tr>
<tr>
<td>Verbanck [135]</td>
<td>2016</td>
<td>Belgium</td>
<td>20–80 years</td>
<td>128 male/124 female</td>
</tr>
</tbody>
</table>

*DLco*: diffusing capacity of the lung for carbon monoxide. #: only studies with at least 100 males and 100 females are included. All of these reference values were derived using caucasian subjects. ♀: test gas contained 19% oxygen (all other studies used test gas with 21% oxygen).