Diffusing Capacity: 2017 ATS/ERS Standards for single-breath carbon uptake in the lung

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Joint ATS/ERS Taskforce

- Recent literature reviewed
- Surveyed current technical capabilities of instrumentation manufactured
- Recommendations reflect consensus of task force related to
  - Evidence
  - Expert opinion where peer-reviewed evidence was not available or incomplete
Update of 2005

- Update in regards to RGA systems
- Provide new calculation standards incorporating continuous gas analysis
- Standard restricted to single-breath technique
- Five committee members from 2005 and four new members
**RGA versus Current Systems**

- **Focused on Rapid-response Gas Analyzers (RGA)**
  - new suggestions and requirements for labs and manufacturers required for systems with a RGA
  - gas analyzers with a 0 to 90% response time of less than or equal to 150 ms
  - Real-time, continuous gas analyzers but tend to use discreet measurements
  - Allow marked improvements using data with continuous measurements
RGA versus Current Systems

- Authors do state that the new standards do not make older systems that use discrete alveolar sampling and slower gas analyzers obsolete (classical systems)
Equipment Requirements

- A reminder that any error in flow and the calculation of volume results in a corresponding error in DLCO
- Requirements are included for both RGA systems and classical discrete sampling systems
**Equipment Requirements**

- Flow accuracy required to be $\pm 2\%$ over a range of $\pm 10$ L/sec

- Volume accuracy required to be $\pm 2.5\%$ ($\pm 75$ ml) instead of $\pm 3.5\%$ with a 3-L syringe
  - Volume accuracy must be maintained across range of gas compositions and concentrations
Equipment Requirements

- RGA response time (analyzer rise time) required to be $\leq 150$ milliseconds (new)
  - Not required for classical discrete samples

- Analyzer linearity for both RGA and discrete sample systems $\pm 1.0\%$ from $\pm 0.5\%$ in the 2005
Equipment Requirements

- RGA systems have both a lag time for the sample to reach the analyzer and the analyzer response time to consider

- Gas concentration signal must be shifted and precisely aligned with the flow signal
  - 100 ms increase in 0-90% response time, error in DLCO increases 0.7%
Graphic Display
Phase Alignment

![Graph showing concentration over time with labels for lag time, flow, and carbon monoxide.](image)
Equipment Requirements

- CO analyzer accuracy for both RGA and discrete sample systems is ≤10 ppm
  \((±0.3\% \text{ of } 0.3\% \text{ CO}) \text{ (2005 was } ± 0.5\% \text{ of } 0.3\% \text{ CO)}\)

- Interference from CO2 and water vapor for both RGA and discrete sample systems is
  ≤10 ppm error in CO (when CO2 and water vapor are ≤5)
Equipment Requirements

- Digital sampling rate now specified as a minimum of $\geq 100$ hz with a resolution of 14 bits. A 1000 hz sampling rate recommended.

- Analyzer drift should $\leq 10$ ppm for CO and 0.5% of full scale for the tracer gas over 30 seconds.
  - manufacturers should provide a test mode to test

- Barometric pressure sensor accuracy is required to be within $\pm 2.5\%$. 
Manufacturer Requirements for RGA

- Monitor and report end-expiratory tracer gas and CO concentrations
  - alert the operator if washout from previous testing is incomplete.

- Compensation for end-expiratory gas concentrations prior to test gas inhalation in the calculation of VA and DLCO.

- Ensure proper alignment of gas concentration signals and the flow signal
Manufacturer Requirements for RGA

- Measure anatomic dead-space using the Fowler method.
- Display a graph of exhaled gas concentration versus volume (not time) to confirm point of dead-space washout and to report the amount of manual adjustment if this was done.
- Measure VA using all of the tracer gas data from the entire maneuver in the mass balance equation.
Manufacturer Requirements for RGA

- Report the DLCO adjusted for the change in PAO2 due to barometric pressure.
  - recommended (but not required)
  - Ability to input simulated digital test data and compute DLCO, VA, TLC and Vb with ± 2% accuracy expected.
  - Report the DLCO adjusted for change in PAO2 due to PACO2 with ± 2% accuracy.
**Additional requirements**

- Maximum inspiratory pressure for demand valves has been reduced to <9 cmH2O

- Machine deadspace for adult testing has decreased to 200 ml from 350 ml
  - machine deadspace should be smaller for children and patients with a VC <2.0 L
Calibration and QC Requirements

- Daily volume calibration must now be performed three times with a 3-liter syringe with varying flow rates between 0.5 and 12.0 L/sec (injection times 0.5 – 6.0 seconds). Accuracy was not previously specified and now must be <2.5% error.
  - Disposable flow sensor from the batch used must be tested each day
  - Recheck if temperature changes 3 degrees C or relative humidity changes by more than 15%
Calibration and QC Requirements

- Calibration recheck also recommended when differences between VI and VC or VA and TLC are apparent.

- Timer accuracy was specified in the 2005 standards. There are no timer specifications in the 2017 standards.
Calibration and QC Requirements

- Flow sensor zeroing prior to testing is now required.

- Gas analyzer linearity must now be checked monthly. The 2005 standards specified every three months. Manufacturers are urged to automate this process.

- A monthly calibration syringe leak test is now required.
Analyzer Linearity Check

- Serial syringe dilutions
- DLCO simulation with high precision gases
- In absence of above, manufacturer must provide test option like patient, but reported VA at ATP with 3-L syringe
Calibration and QC Requirements

- Both biological and calibration syringe QC testing are now required weekly. Previously either biological or calibration syringe QC were to be performed weekly.
Calibration and QC Requirements

- BioQC requiring action are relaxed to a >12% change or >3 ml/min/mmHg (whichever is larger) from a simple >10% change ***
  - 2017 standards also state that a mean of 6 prior tests should be used
  - Manufacturers urged to developed automated QC

- QC and calibration records can be kept in a digital file
Calibration and QC Requirements

- Syringe QC required measured VA to be within ±300 ml of 3-L
  {STPD to BTPS conversion factor} 24% factor
  - Absolute DLCO less than 0.5 ml CO/min/mmHg (.166 SI)

- ERROR NOTED: Correction factor should be ATPD to BTPS
  "The calculation of VA must be within 300 mL of 3 L times the
  ATPD to BTPS (body temperature, ambient pressure, saturated with
  water vapour conditions) correction factor, which is 310/Tamb x
  PB/(PB - 47), where PB is the barometric pressure in mmHg and
  Tamb is the ambient temperature in degrees kelvin."

  - With 72 degrees Fahrenheit = 295.4 degrees kelvin, this would be
    approximately a 12% correction factor.
**Calibration and QC Schedule**

**TABLE 2 Equipment calibration schedule**

<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.
Additional Maintenance

- Replace permeable tubing according to manufacturer recommendations
- Chemical gas analyzers should have a replacement schedule
Patient Condition

- Subject should not breathe supplemental oxygen for $> \text{ prior to the test}$

- Refrain from smoking on day of test

- Record time of last cigarette
  - Correct for COHb
Test Performance

- Deep breaths during TV pre-test avoided in the 2005, not included in 2017 standards
- Maximum time for exhalation to RV is 12 seconds
- Inhale rapidly to TLC in less than 4 seconds
- VI target based on patient’s largest VC ≥90
  - VI of ≥85% of the patient’s largest VC is acceptable if VA is within 200 ml or 5% (whichever is larger) of the patient’s highest VA from acceptable DLCO maneuvers.
Test Performance

- With RGA exhalation following BHT continue to RV to calculate VA using a mass-balance equation
  - Total expiratory time for discrete sample systems (washout and sample collection time) is still ≤4 seconds but is specified as ≤12 seconds in RGA systems

- DLCO test mixture required to contain 21% O2, .3% CO, tracer, balance N2
Test Performance

- Wait between tests (4 minutes minimum, 10 minutes for patients with severe obstruction)
  - tracer gas concentration at end-exhalation (prior to the inhalation of the test gas mixture) should be $\leq 2\%$ of the inspired concentration

- Recommend end-exhalation concentrations of CO (prior to inhalation of the test gas mixture) be used to adjust DLCO tests for CO back-pressure, to calculate COHb and to compensate for the effects of water vapor and CO2 on gas analyzers
Potential Problems in Breathing Maneuver

- Transient overshoot
- Stepwise inhalation or exhalation
- Inhalation too slow
- Exhaled volume larger than inhaled volume
- Possible exhaled gas leak
- Breath-hold leak
- Inspiratory leak
- Methane
- Carbon monoxide
Washout and Sample Collection

- **RGA systems**
  - Collection prior to point of deadspace washout underestimates DLCO
  - Collection beyond will overestimate DLCO

- **Classical systems**
  - Washout volume .75 to 1.0 L
  - Decrease to .5 L when VC less than 2 L
Analysis Window
Breath Hold Time
Test Performance

- Effect of prior testing (spirometry, bronchodilators and N2 washouts) on DLCO
  - bronchodilators are unlikely to affect DLCO and may therefore be used prior to DLCO testing
  - prior spirometry efforts may affect DLCO but this has not been proven and therefore makes no recommendations against performing spirometry prior to DLCO testing
  - After N2 washout, time for alveolar O2 levels to return to normal is needed (2 times O2 wash-in time)
VA Calculation

- Classical systems
  - Reported at BTPS, converted to STPD to calculate DLCO
  - Need VI and change in tracer gas
  - Need to know equipment and anatomical DS

- RGA systems
  - DS is measured by Fowler method
  - Anatomic is Fowler minus equipment DS
  - Higher VA and DLCO (8 to 15% in COPD and uncontrolled asthma)

- May want to report 2005 DLCO and RGA
Fowler Dead-Space
# Test Quality Grading

<table>
<thead>
<tr>
<th>Score</th>
<th>$V_t/VC$</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>F</td>
<td>$\leq 80%$</td>
<td>$&lt;8$ or $&gt;12$ s</td>
<td>$&gt;5$ s</td>
</tr>
</tbody>
</table>

$V_t$: inspired volume; $VC$: vital capacity; $V_a$: alveolar volume; $t_{BH}$: breath-hold time; $Dlco$: diffusing capacity of the lung for carbon monoxide. *: only grade A manoeuvres meet all acceptability criteria. The average $Dlco$ values from two or more grade A manoeuvres that meet the repeatability criterion should be reported. If only one grade A manoeuvre is attained, the $Dlco$ value from that manoeuvre should be reported. If no grade A manoeuvre is obtained, manoeuvres of grades B to D might still have clinical utility. The average of such manoeuvres should be reported but these deviations from the acceptability criteria must be noted to caution the interpreter of the test results. Manoeuvres of grade F are not useable. †: or $Wt/VC \geq 85\%$ and $V_a$ within 200 mL or 5% (whichever is greater) of the largest $V_a$ from another acceptable manoeuvre.
Grading System

- This is considered an interim grading system until studies can be completed to validate it based on the 2017 standards

- Further research is needed
Which DLCO to report?

- Average 2 or more grade A maneuvers that are repeatable
- Average DLCOs from all grade A if not repeatable
- Only 1 grade A, report result
- If no acceptable, average maneuvers with B, C, and D scores
- If only F grade, no DLCO reported
Other Recommendations

- RGA systems calculate VA using mass-balance equations
- Equation for calculating anatomical deadspace using height is different from 2005
- Measurement of anatomical dead space using the Fowler technique discussed in detail
- Discuss flow and gas analyzer signal alignment in detail.
- Discuss KCO
Other Suggestions

- Phase III slope for ventilation inhomogeneity
- Repeatability 2.0 ml/min/mmhg
- Scoring/grading system for test quality based on inspired volume, breath-holding time and sample collection time
- New equation to correct DLCO for end-exhalation CO, altitude and barometric pressure correction
Other Suggestions

- Equations to estimate barometric pressure at altitude that were not in the previous standards.
- 2005 standards included equations to correct DLCO for alveolar volume that are not discussed and not included in the 2017 standards.
- Adjustments are made in predicted value, not measured.
Available Results to Report

- DLCO adjusted for barometric pressure
- DLCO LLN and/or Z-score
- VA LLN and/or Z-score
- KCO (instead of DLCO/VA)
- KCO LLN and/or Z-score
- Barometric pressure
- Breath-hold time
- Fowler anatomical dead space (RGA systems only)
- Single-breath TLC (RGA systems only)
- Test quality grade for acceptable maneuvers
- Reference values source
- Graphs of full maneuver
- Graphs of exhaled gas concentrations versus volume (RGA systems only).
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Age</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson</td>
<td>2008</td>
<td>Australia</td>
<td>45–71 years</td>
<td>498 male/474 female</td>
</tr>
<tr>
<td>Koopman</td>
<td>2011</td>
<td>Netherlands</td>
<td>7–18 years</td>
<td>278 male/265 female</td>
</tr>
<tr>
<td>Garcia-Rio</td>
<td>2012</td>
<td>Spain</td>
<td>65–85 years</td>
<td>169 male/262 female</td>
</tr>
<tr>
<td>Kim</td>
<td>2012</td>
<td>USA and Australia</td>
<td>5–19 years</td>
<td>225 male/254 female</td>
</tr>
<tr>
<td>Thomas</td>
<td>2014</td>
<td>Denmark</td>
<td>5–17 years</td>
<td>male/female (297 total)</td>
</tr>
<tr>
<td>Michailopoulos</td>
<td>2015</td>
<td>Greece</td>
<td>18–91 years</td>
<td>234 male/233 female</td>
</tr>
<tr>
<td>Verbanck</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).
Other Considerations

- New equipment will meet or exceed 2017 standards
- Universal format for output needed
- New standards for interpretation needed
- Ten area identified for further research
Any Questions?

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