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 (O_2 and CO)
- High affinity for hemoglobin (250 times of O_2)
- Transfer is diffusion limited rather than perfusion limited
- Not present in lung normally
- CO diffusion is less affected by other factors

$DLO_2 = DLco \times 1.23$

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 (O_2)
  - Balance nitrogen (N_2)
- 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
0 3 6 9 13 17 21 25 29
0 1 2 3 4 5 6 7 8 9 10

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 O_2 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

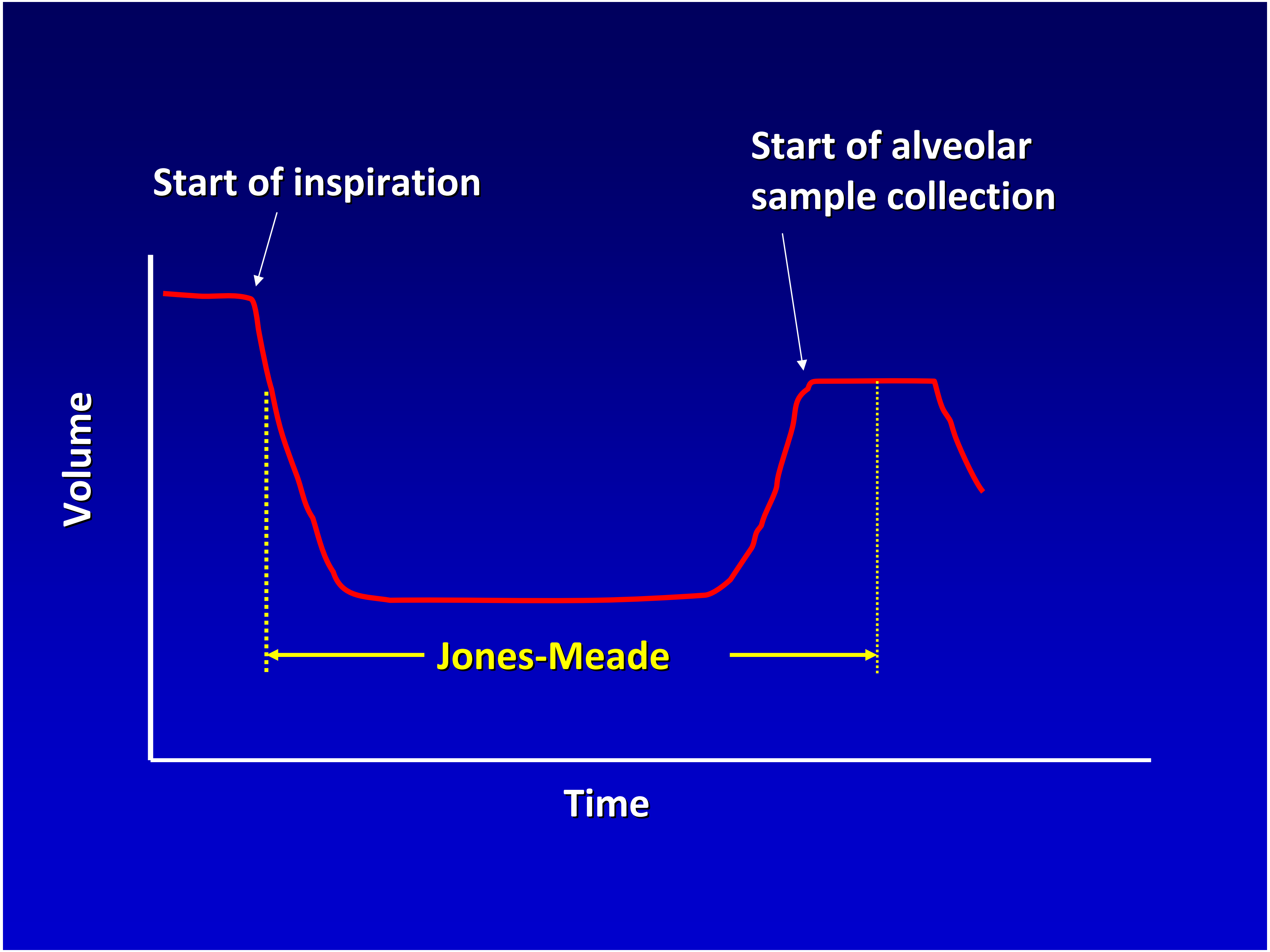
Eur Respir J 2005; 26: 720–735

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
Volume
Jones-Meade
Time

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

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Interval between tests

- Atleast 4 min between tests
- Longer period (~10 min) in obstructive diseases
- Subject should remain seated

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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

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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

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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

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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 Pco_2
- 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 FEV_1
- 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:
  mL (STPD).min^{-1}.$mmHg^{-1}$
- SI units:
  mmol.min^{-1}.kPa^{-1}

Traditional = SI x 3

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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* –

Hb adjusted DLco = measured DLco x

$$\frac{(14.6 \times D_M/V_C) + Hb}{Hb \times (1 + D_M/V_C)}$$

- Clin Sci 1972;42:325-335

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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 x (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
- Kco = DLco/ 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
- Ehnicity: 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
- DL_{CO} increases by 0.31% per mm Hg decrease in PiO_2

Am Rev Respir Dis 1986; 133:676–678

- USA: FiO_2 0.21

  Europe: FiO_2 0.17

  PGI: FiO_2 0.18
- Discontinue suppl. O_2 >10 min before procedure

Subdivisions of total diffusing capacity

- Roughton and Forster equation*

$$1/D_L = 1/D_M + 1/\theta.V_C$$

- Increasing alveolar PO_2 reduces DLco as CO has to compete with O_2 for hemoglobin
- If $1/D_L$ is plotted against $1/\theta$: the slope of line is 1/Vc and the intercept on vertical axis is $1/D_M$

* 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 θVc
  - anemia
  - pulmonary emboli
- Reduced DM
  - 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

Respir Med. 2004 Jun;98(6):567-73

- 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

Med Klin (Munich). 1990 Jun 15;85(6):366-70

- 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

	DLco % predicted
Mild	>60% but <LLN
Moderate	40-60%
Severe	<40%

Eur Respir J 2005; 26: 948–968