Pulmonary function tests other than spirometry

Dr. Selva Vijay S

Dept. of pulmonary medicine

Available in the domain…

Respiratory function	Parameters	Tests
Ventilation	Flow Volume Elastic recoil	✓ Spirometry (post bronchodilator, FV loop, BCT, supine and sitting) ✓ Gas dilution methods (helium dilution & nitrogen washout) ✓ Body plethysmography ✓ Radio graphic methods ✓ Impulse oscillometry ✓ Forced oscillation methods
Diffusion	Transfer factor	✓ DLCo
Others	Exercise	✓ 6 min walk test ✓ Incremental shuttle walk test ✓ Endurance shuttle walk test ✓ CPET
Others	Oxygenation	✓ Pulse oximetry ✓ Arterial blood gas

Murray & Nadel's Textbook of Respiratory Medicine

Why do we need PFT?

- Diagnosis
- Follow up
- Prognostication
- Pre-operative evaluation

Ph.H Quanjer et al., European Respiratory Journal Mar 1993, 6: 16; 5-40

Possible order for undertaking lung function tests in a laboratory

Dynamic studies: spirometry, flow–volume loops, PEF
Static lung volumes
Inhalation of bronchodilator agent (if used)
Diffusing capacity
Repeat dynamic studies (if a bronchodilator was given)

PEF: peak expiratory flow.

M. R. Miller et al, European Respiratory Journal 2005 26: 153-161

Limitations of spirometry

↓

RV-> FRC

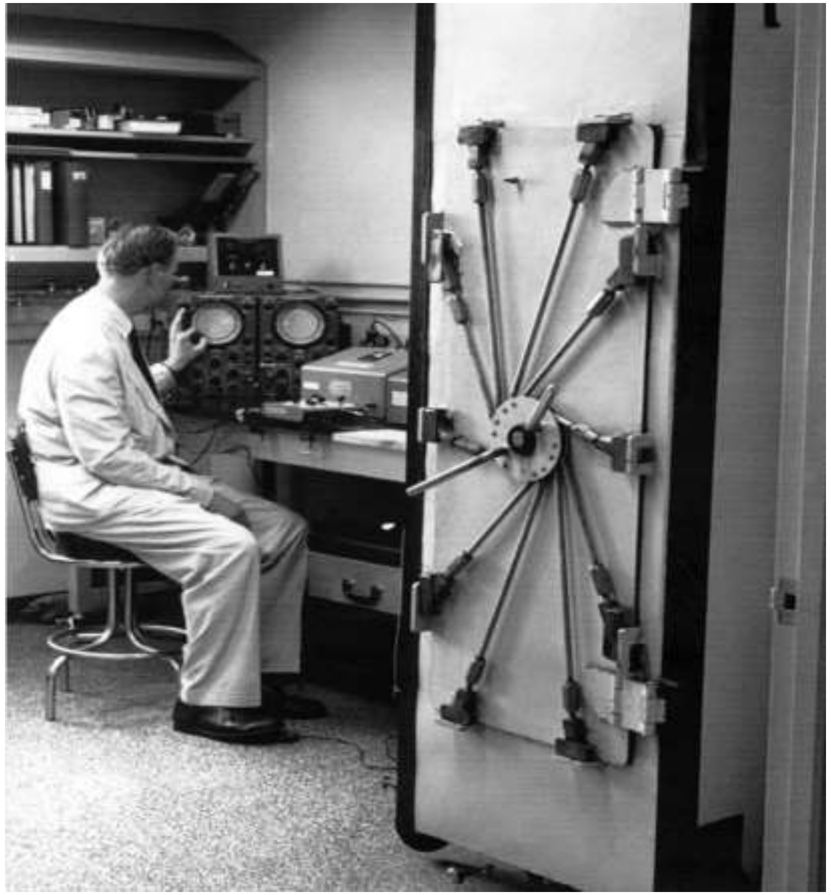
↓

Body plethysmography / body box

↓

FRC/TLC– measured
Rest - spirometry

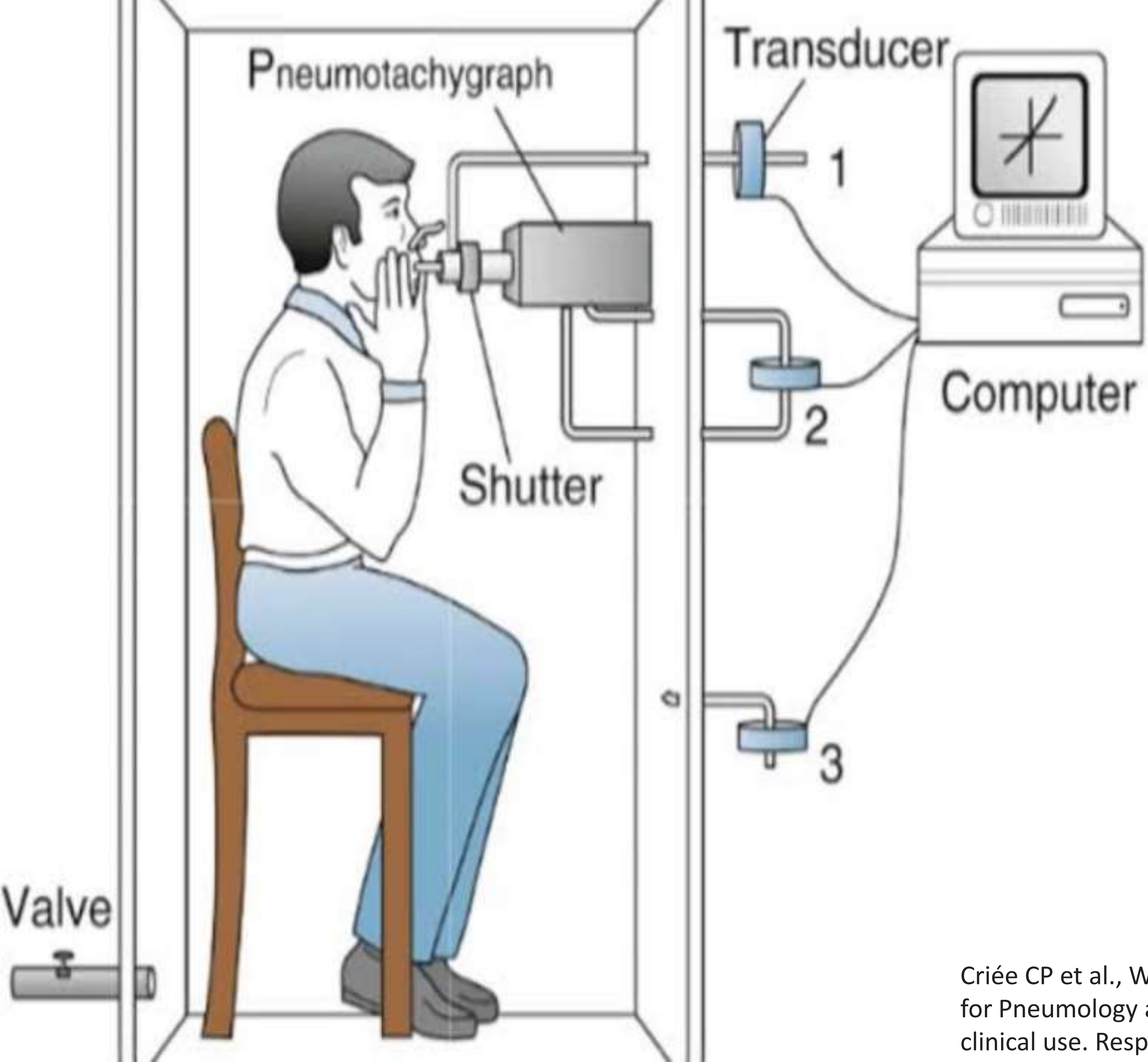
- Arthur Dubois & colleagues - 1953
- Fixed /variable volume
- Common use – fixed volume (Dubois type)
- Boyle's law (PV = constant @ constant temp)
- Lung volume and airway resistance



West JB. The birth of clinical body plethysmography: it was a good week. J Clin Invest. 2004 Oct;114(8):1043-5
Murray & Nadel's Textbook of Respiratory Medicine

When lung volumes should be done?

- Confirm restrictive lung disease
- Subtype restrictive disorders
- Subtype obstructive disorders
- Confirm and quantify hyperinflation
- Complex restrictive disorders



- ✓ Volume constant body box – common use
- ✓ Glass wall
- ✓ 700 -1000 litres - accuracy
- ✓ Controlled leak
- ✓ Shutter mechanism
- ✓ Calibration

Criée CP et al., Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography--its principles and clinical use. Respir Med. 2011 Jul;105(7):959-71

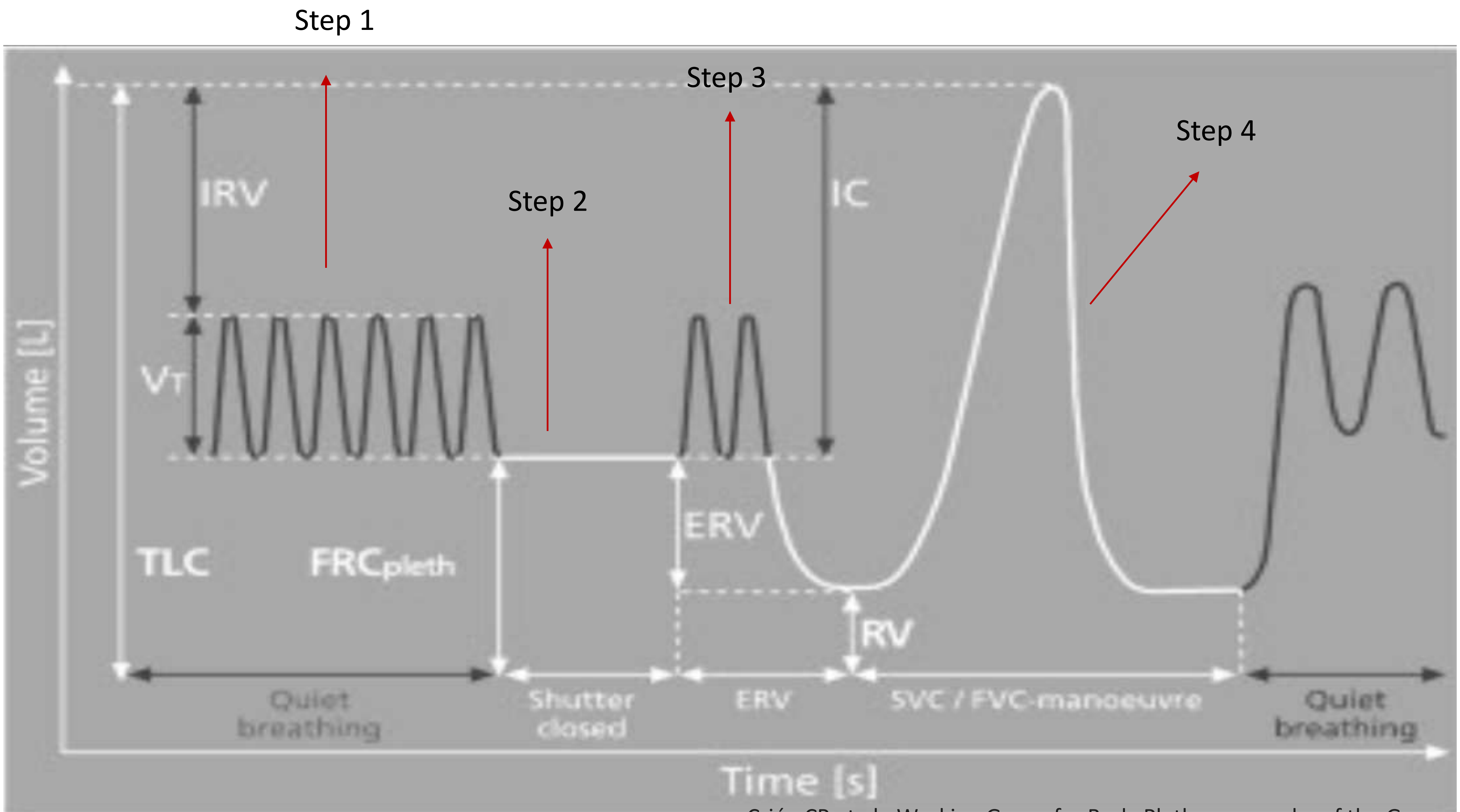
Terminology	Units	Descriptions
Shift volume (delta Vpleth/ delta VL)	ml	Change of volume by which the lung generates positive or negative alveolar pressure
Alveolar pressure (Palv)	Kpa	Mean pressure generated in alveoli
Mouth pressure (Pmouth)	Kpa	Pressure measured at mouth during the shutter manuveur
Box pressure (Pbox)	Kpa	Pressure measured in body plethysmographic box during free breathing or shutter maneuver
Flow rate	L/s	Airflow measured at mouth
Airway resistance (Raw)	Kpa s / L	Flow resistance of airways
Specific airway resistance (sRAW)	Kpa s/L	Airway resistance corrected for lung volumes
Intrathoracic gas volume	TGV	Lung volumes at which shutter is closed

Criée CP et al., Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography--its principles and clinical use. Respir Med. 2011 Jul;105(7):959-71

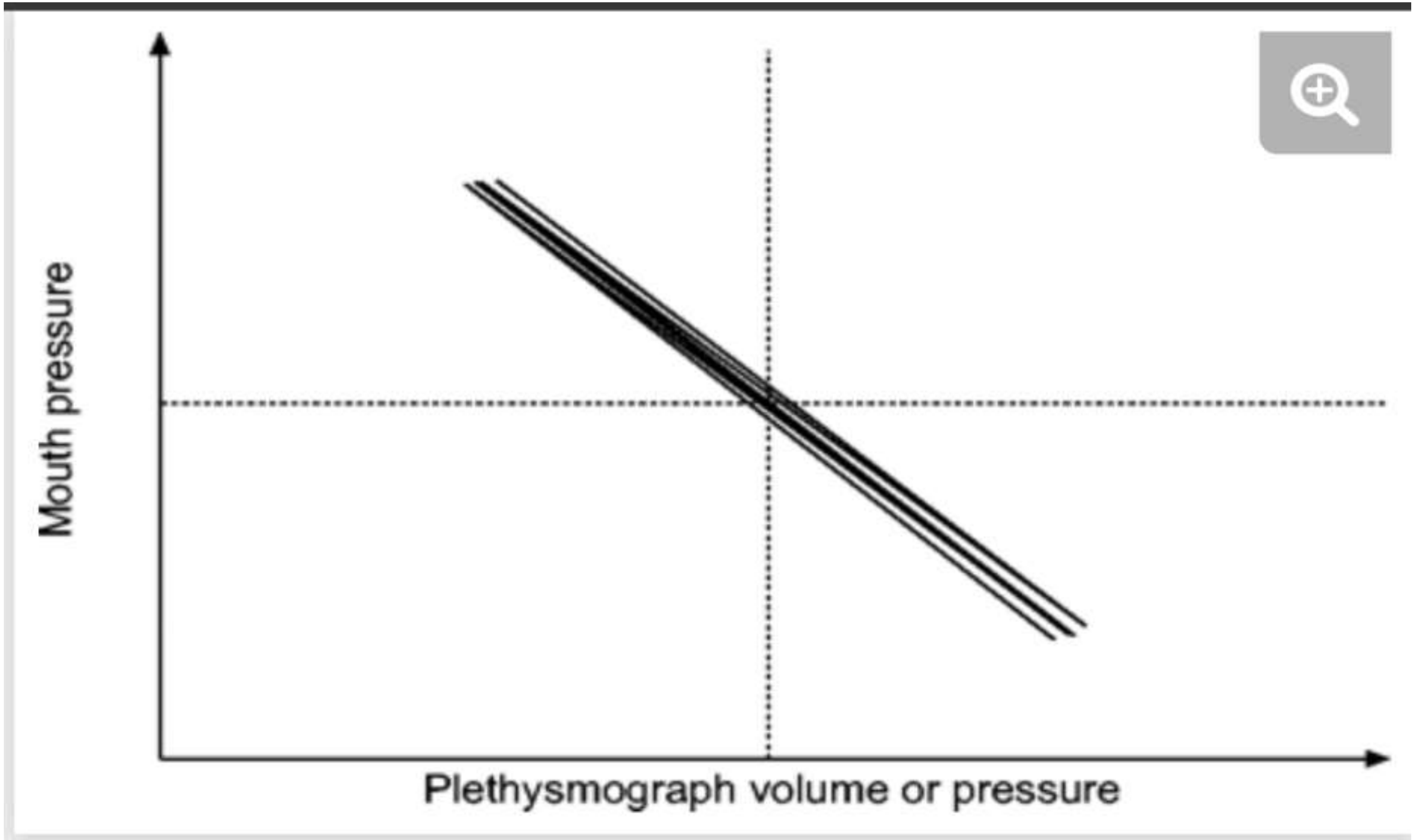
Steps

- Patient breath through the mouth piece with the shutter open as quiet tidal breathing for acclimatisation
- Then close the shutter at FRC and ask the subject to breath in and out gently against the shutter at rate of 0.5 to 1 Hz (30 to 60 breaths/min)
- After 1 to 2 breaths against the shutter, open the shutter and ask the subject to breathe fully out (ERV) and then fully in (IVC) and then breathe normally.
- Release vent, seal box and repeat obtaining 3 technically acceptable traces.

Wanger J et al, Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.



Criée CP et al., Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography--its principles and clinical use. Respir Med. 2011 Jul;105(7):959-71



Wanger J et al, Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.

Assumptions

- Palv is equal to Pao assuming there is no gas flow. High frequency of panting (>1.5Hz) causes to and fro gas flow changes by movement of cheek and pharynx, affecting the FRCpleth measurement
- Pulmonary parenchyma is a elastic structure with gas containing spaces which are freely communicating with each other
- Only thoracic gas undergo compressions and rarefactions. The abdominal gas is considered to be minimal

Coates AL et al, Measurement of lung volumes by plethysmography. Eur Respir J. 1997 Jun;10(6):1415-27.

$$P_1 \times V_1 = P_2 \times V_2$$

$$P_{Alv} \times FRC = (P_{Alv} + \Delta P_{Alv}) X (FRC + \Delta V)$$

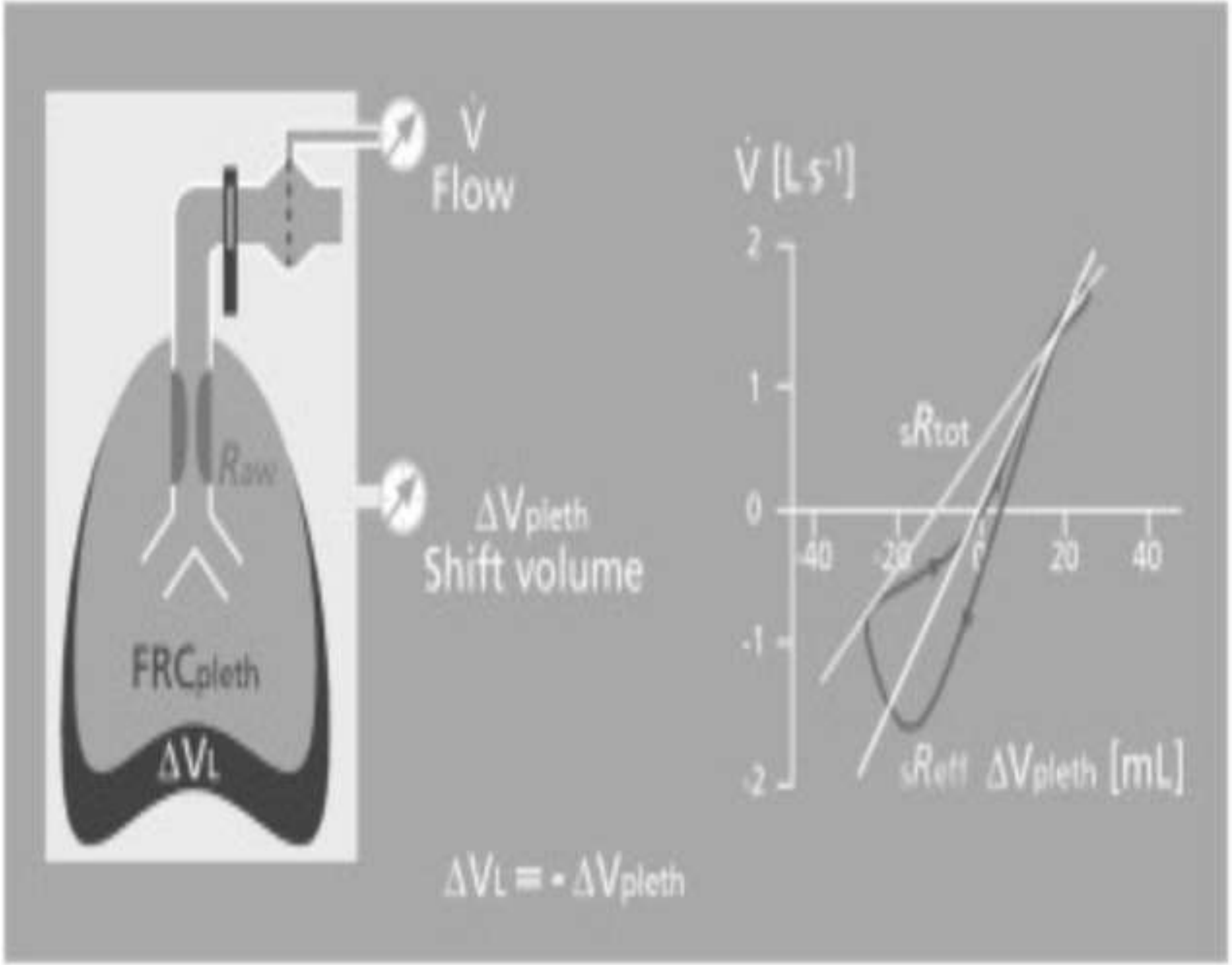
Multiplying out : $P_{Alv} \times FRC = P_{Alv} \times FRC + \Delta V \times P_{Alv} + \Delta P \times FRC + \Delta P \times \Delta V$

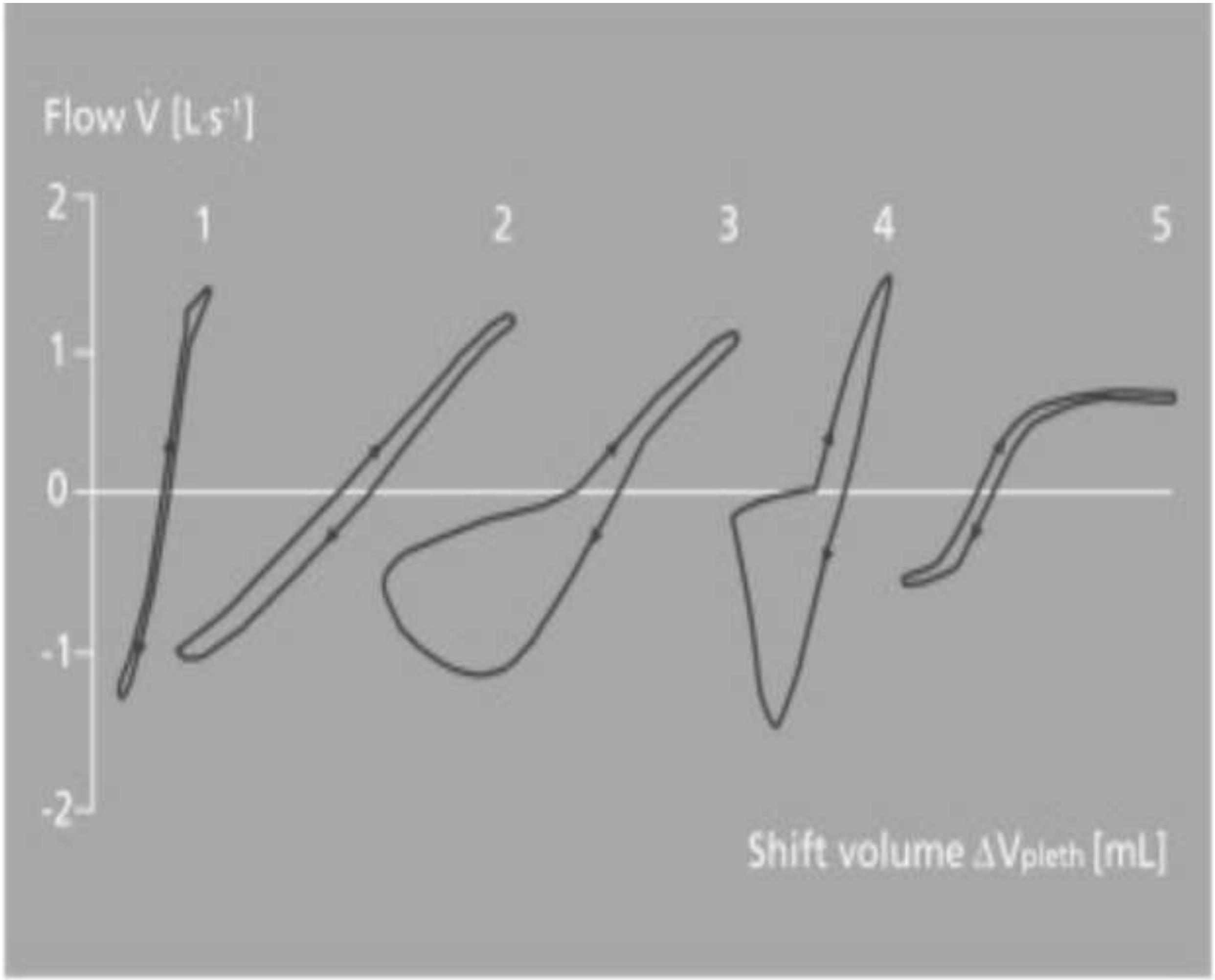
ΔP and ΔV can be omitted since these pressures are negligible in size

The equation can be rearranged making FRC the subject of the equation. Thus:

$$FRC = P_{Alv} \times (\Delta V / \Delta P)$$

Airway resistance





Criée CP et al., Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography--its principles and clinical use. Respir Med. 2011 Jul;105(7):959-71

Not to do in,

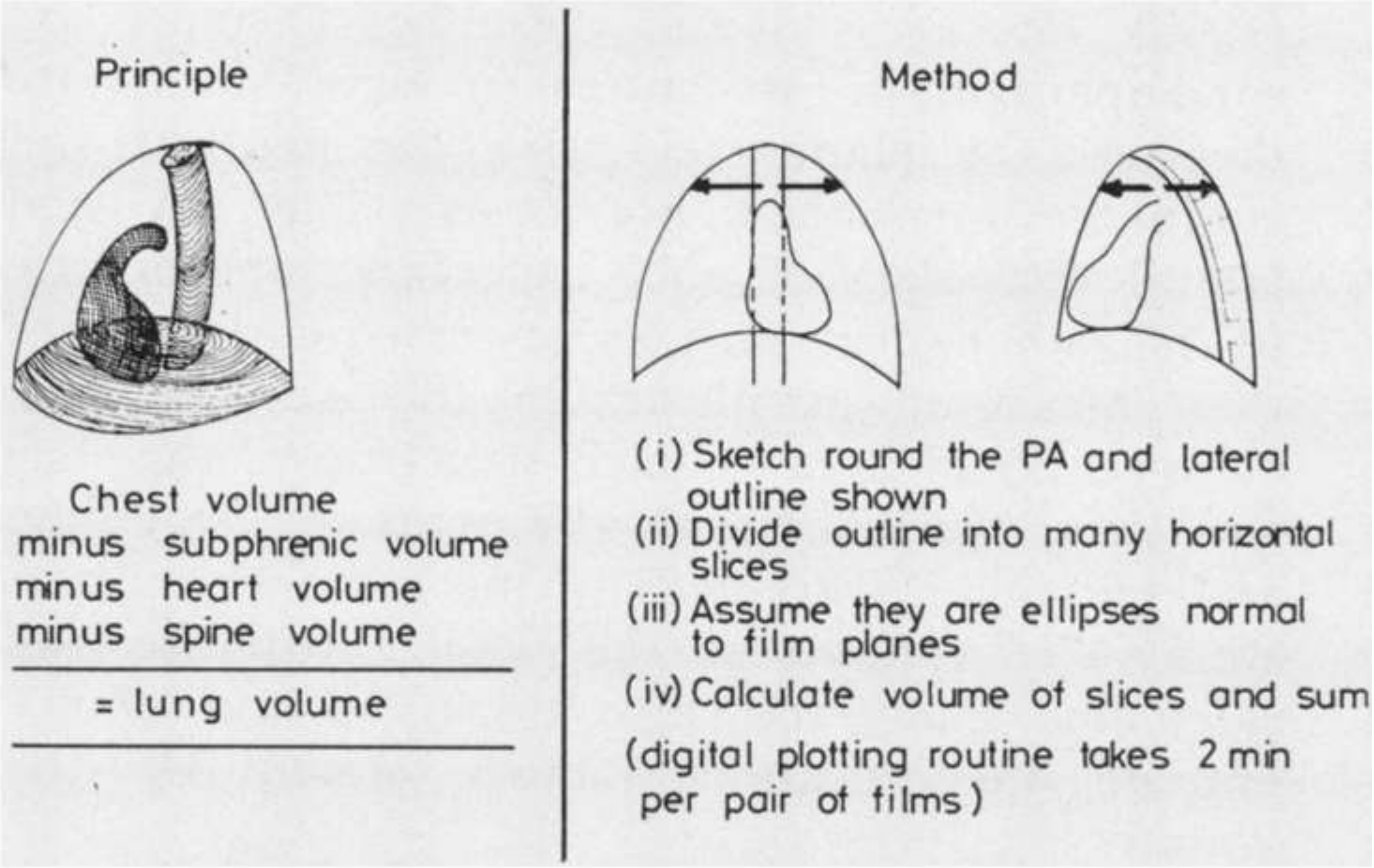
- ✓ Claustrophobia
- ✓ Obesity
- ✓ Obstructive body casts
- ✓ Supplemental oxygen
- ✓ Upper body paralysis
- ✓ Ongoing infusions

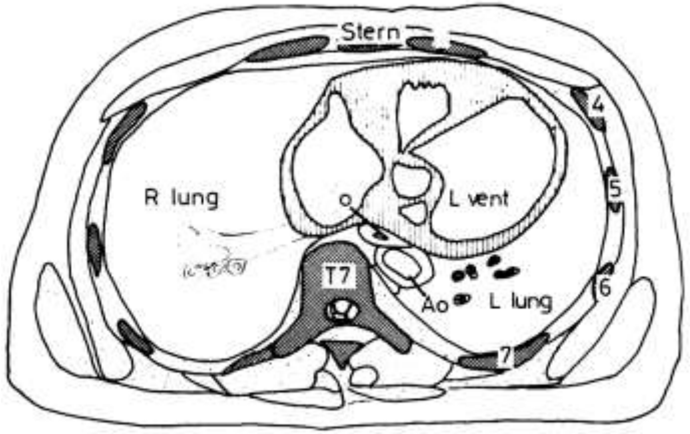
Pitfalls:

- ✓ Excessive TGV, Raw – obstructive lung dx, excessive abdominal gas
- ✓ Incorrect panting – erroneous results
- ✓ Computer measured slopes – inaccuracy

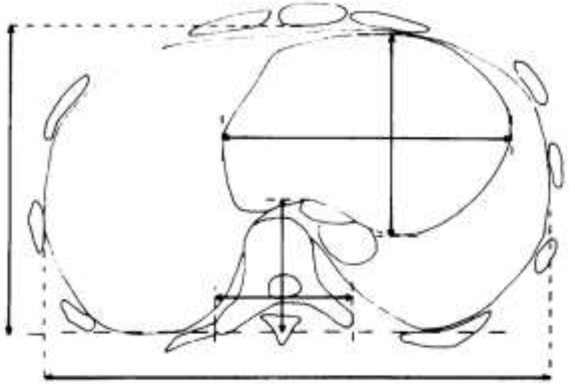
Clayton N. Lung function made easy: assessing lung size. Chron Respir Dis. 2007;4(3):151-7
Cooper BG. An update on contraindications for lung function testing. Thorax. 2011 Aug;66(8):714-23.
AARC GUIDELINE: BODY PLETHYSMOGRAPHY: 2001 REVISION & UPDATE

Lung volumes radiographically!!!





(Adapted from Matsukawa *et al* 1977)



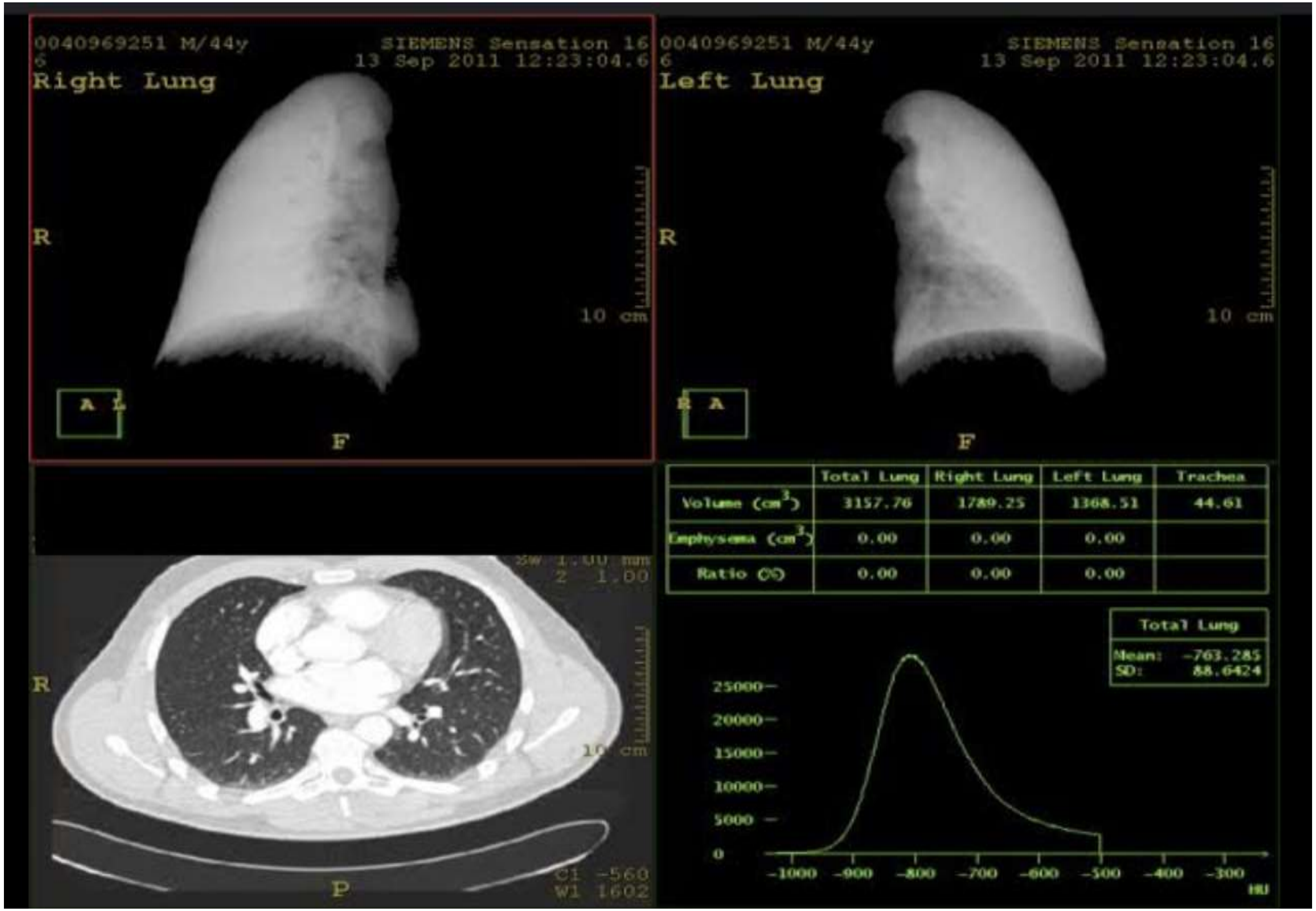
Pierce RJ et.al, Estimation of lung volumes from chest radiographs using shape information. Thorax. 1979 Dec;34(6):726-34.

Table 3 *TLC estimation in 35 normal subjects by three methods**

Chest radiograph	6·93 ± 1·32		
(posture corrected)		0·72 ± 0·37	
Body plethysmograph	6·22 ± 1·18		1·19 ± 0·42
Helium volume	5·74 ± 1·20	0·48 ± 0·29	
(single breath)			

*Results are mean ± 1 SD litres.

Automated lung volumetry



Haas M, Hamm B, Niehues SM. Automated lung volumetry from routine thoracic CT scans: how reliable is the result? Acad Radiol. 2014 May;21(5):633-8.

Population	Intervention and comparator	Outcomes
Cystic fibrosis - 20 patients Observational , prospective, non controlled, single centre pilot study	Dynamic chest radiography vs body plethysmography	@ P < 0.001 Total lung area with TLC Residual lung area with RV Functional residual area with TGV Inspiratory lung area with IC No correlation between Tidal lung area & tidal volume Expiratory reserve lung area & ERV Inspiratory reserve lung area & IRV
Severe COPD patients planned for BLVR – 200 patients Retrospective cohort study Mean – 62 +/-8% FVC 1 S – 29.2 +/- 8.7% RV – 4.54 +/- 1.07 L	Body plethysmography vs gated or non-gated CT	Compared to BP, TLC – 280 +/- 340 ml & 590 +/- 430 ml lower in gated & non-gated CT group RV – 300 +/- 470 ml & 700 +/- 720 ml higher in gated & non-gated group Pearson co-efficient: TLC – G/NG – 0.947/0.917; RV – G/NG – 0.823/0.693; RV/TLC – G/NG – 0.539/0.204

Population	Intervention and comparator	Outcomes
100 asymptomatic volunteers Prospective observational study	CT chest lung volume correlation with PFT CT scans done in supine/sitting/standing posture in breath holding at end inspiration (TLC) and end tidal expiration(FRC) Lobe volumes are also individually measured at different postures (computer aided diagnosis work station)	Correlation coefficient (r) @ 95% CI Inspiratory CT (TLC) @ supine/standing/sitting = 0.831/0.927/0.946. Expiratory CT (FRC) @ supine/standing/sitting = 0.834/0.848/0.811. Total lung volume changes from expiration to inspiration CT (IC) @ supine/standing/sitting = 0.508/0.601/0.625.

Gas dilution methods

- Helium dilution technique
- Nitrogen washout technique

- Law of conservation of mass ($C_1V_1 = C_2V_2$)
- Why helium?? Inert, insoluble, non-toxic, no diffusion in lungs
- Why nitrogen?? Less water soluble

Helium dilution technique

- Closed circuit technique
- Multi-breath helium equilibration method
- Known amount of gas in known volume
- Equipment – spirometer – capacity 7 to 10 L
- Helium concentration – 10% ; oxygen concentration -25 to 30%
- End of test criteria: helium concentration < 0.02%, FRC < 40 ml for 30 seconds
- RV = FRC-ERV; TLC = RV + IVC or FRC + IC
- No standards for reproducibility and repeat ability of the test (3 tests)

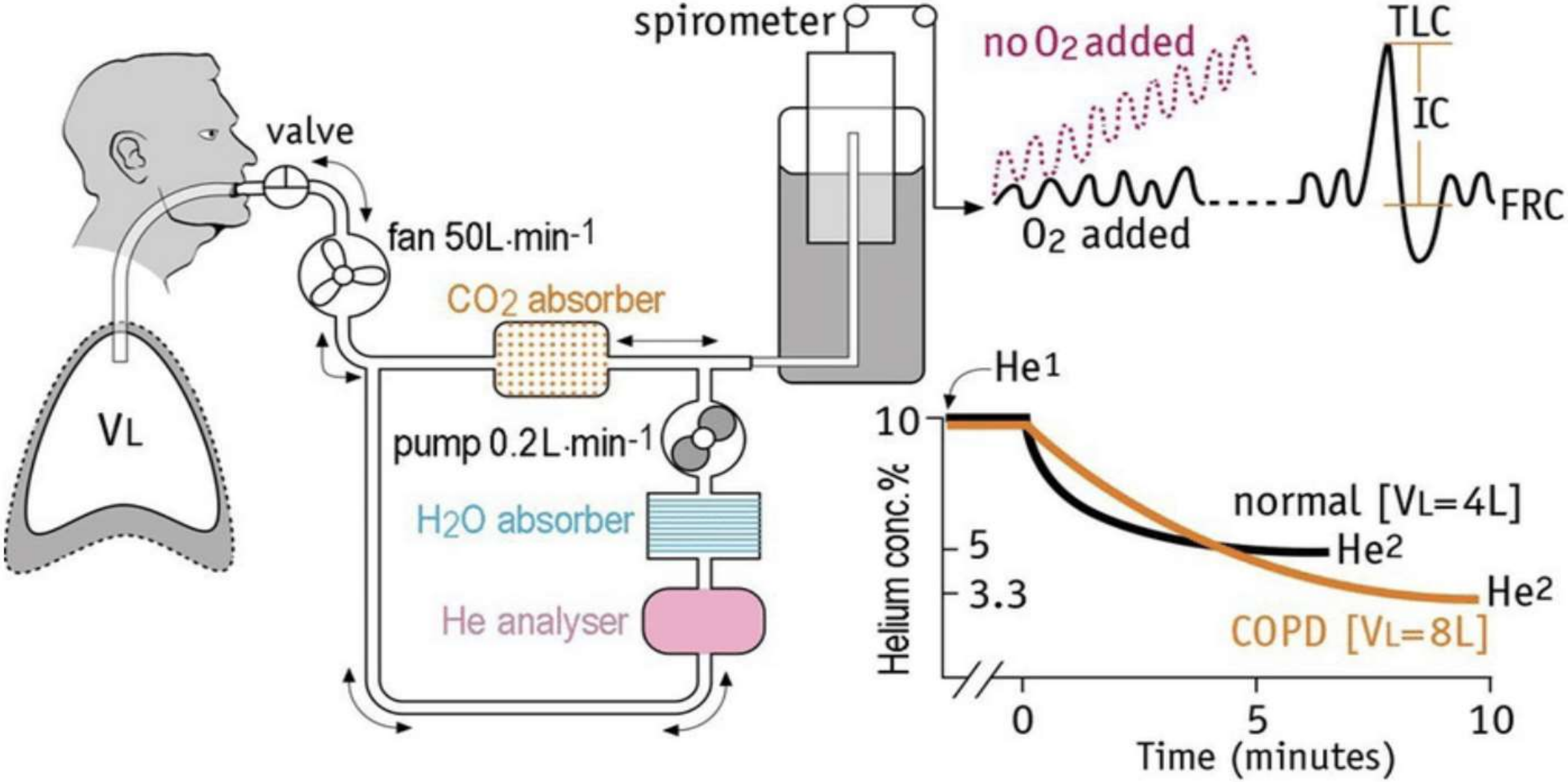
Brown R et al, Multiple breath helium dilution measurement of lung volumes in adults. Eur Respir J. 1998 Jan;11(1):246-55

Steps

- The equipment should be turned on and allowed an adequate warm-up time.
- The equipment should be set up for testing, including calibration, according to manufacturer’s instructions.
- The patient should be asked if he/she has a perforated eardrum (if so, an earplug should be used).
- The patient is seated comfortably, with no need to remove dentures. The procedure is explained, emphasising the need to avoid leaks around the mouthpiece during the test and to use a nose clip.
- The patient breathes for ,30–60 s on the mouthpiece to become accustomed to the apparatus, and to ensure a stable end-tidal expiratory level.
- The patient is turned ‘‘in’’ (i.e. connected to the test gas) at the end of a normal tidal expiration.

Wanger J et al, Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.

- The patient is instructed to breathe regular tidal breaths.
- The O_2 flow is adjusted to compensate for O_2 consumption (significant errors in the calculation of FRC can result if O_2 consumption is not adequately accounted for)
- The helium concentration is noted every 15 s.
- Helium equilibration is considered to be complete when the change in helium concentration is ,0.02% for 30 s. The test rarely exceeds 10 min, even in patients with severe gas-exchange abnormalities.
- Once the helium equilibration is complete, the patient is turned ‘‘out’’ (i.e. disconnected from the test gas) of the system. If the measurements of ERV and IC are to be linked to the FRC measured, it should be ensured that the spirometer has an adequate volume for the full ERV and IVC manoeuvres.
- At least one technically satisfactory measurement should be obtained.



Sylvester KP et al, ARTP statement on pulmonary function testing 2020. BMJ Open Respir Res. 2020 Jul;7(1):e000575.

$$V_{app} \times F_{He1} = (V_{app} + FRC_{He}) \times (F_{He2})$$

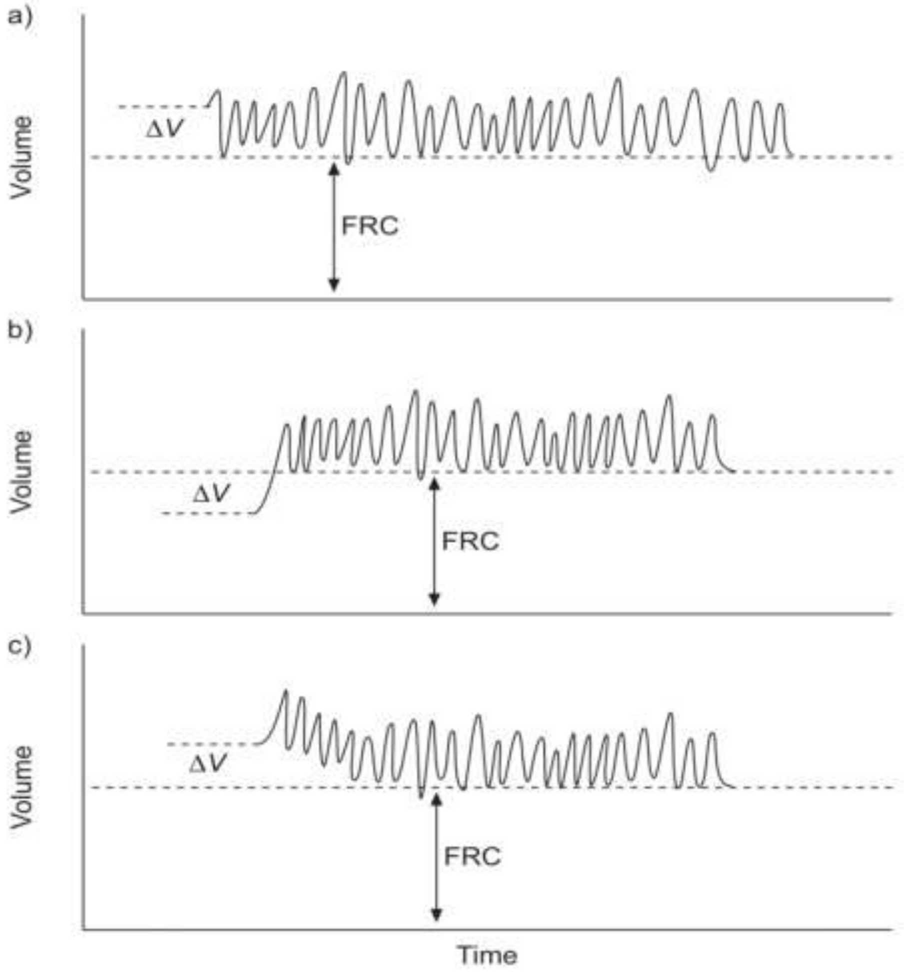
$$FRC_{He} = V_{app}(F_{He1} - F_{He2}) / F_{He2}$$

Vapp – spirometry apparatus of known volume
FHe1 – initial fractional concentration of the helium
FHe2 – final fractional concentration of helium of system
FRChe – lung volume

Wanger J et al, Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.

Limitations

- Helium loss (leaks, swallowed, absorbption,ruptured tympanic mem) – FRC overestimation
- Switch error – over or underestimation of lung volumes
- Underestimate lung volumes in obstructive disorders



Population	Objective	Outcomes
Cohort study, 628 patients(407 +227) Obstructive lung disease patients	Measuring difference in lung volumes by SBHD and WBP and to establish correction equation for SBHD method	TLC: r = 0.701 Delta TLC – depends on severity of obstruction SBHD underestimates TLC in severe OLD
Prospective cohort study including obstructive (20), restrictive(7) and normal(10) subjects	Lung volume measurements by BP, helium dilution and radio graphic methods in respiratory disorders and normal lung	Helium dilution technique underestimate lung volumes in obstructive dx. In all other cases, the lung volumes measured (measured – FRC, ERV, VC; derived – RV, TLC) are similar in all methods

Liu Q et al, Measurement of the Total Lung Volume Using an Adjusted Single-Breath Helium Dilution Method in Patients With Obstructive Lung Disease. Front Med (Lausanne). 2021 Sep 8;8:737360.
Tantucci C et al, Methods for Measuring Lung Volumes: Is There a Better One? Respiration. 2016;91(4):273-80.

Multibreath Nitrogen washout technique

- Open circuit technique
- 5 min – wash out period
- 7 min to perform
- Patient inhale 100% oxygen for short duration until the nitrogen is washed out
- End point : exhaled nitrogen concentration < 1% for 3 successive breaths

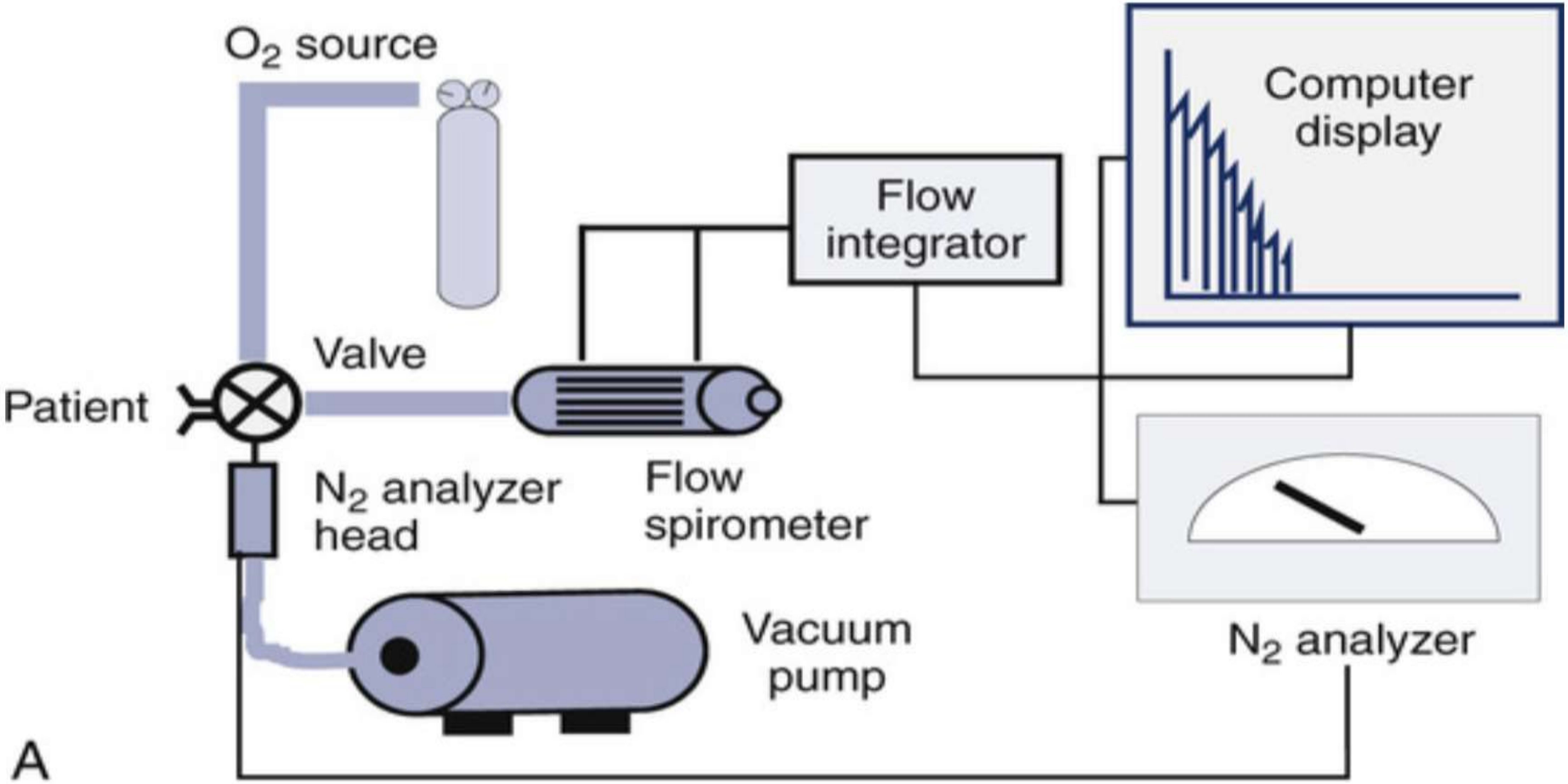
Wanger J et al, Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.

Steps

- The equipment should be turned on and allowed an adequate warm-up time, with calibration as instructed by the manufacturer.
- The patient should be asked if he/she has a perforated eardrum (if so, an earplug should be used)
- The patient is seated comfortably, with no need to remove dentures. The procedure is explained, emphasising the need to avoid leaks around the mouthpiece during the washout and using a nose clip.
- The patient breathes on the mouthpiece for 30–60 s to become accustomed to the apparatus, and to assure a stable end-tidal expiratory level.

Wanger J et al, Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.

- When breathing is stable and consistent with the end-tidal volume being at FRC, the patient is switched into the circuit so that 100% O_2 is inspired instead of room air.
- The N_2 concentration is monitored during the washout. A change in inspired N_2 of >1% or sudden large increases in expiratory N_2 concentrations indicate a leak; hence, the test should be stopped and repeated after a 15-min period of breathing room air.
- The washout is considered to be complete when the N_2 concentration is <1.5% for at least three successive breaths.
- At least one technically satisfactory measurement should be obtained. If additional washouts are performed, a waiting period of 15 min is recommended between trials.


O2 source
Computer display
Flow integrator
Valve
Patient
N2 analyzer head
Flow spirometer
Vacuum pump
N2 analyzer
A

FRC_{N_2} is computed from the following equation:

$$FRC_{N_2} \times F_{N_2}1 = (FRC_{N_2} \times F_{N_2}2 + N_2 \text{ volume washed out}) - (N_2 \text{ volume from tissue})$$

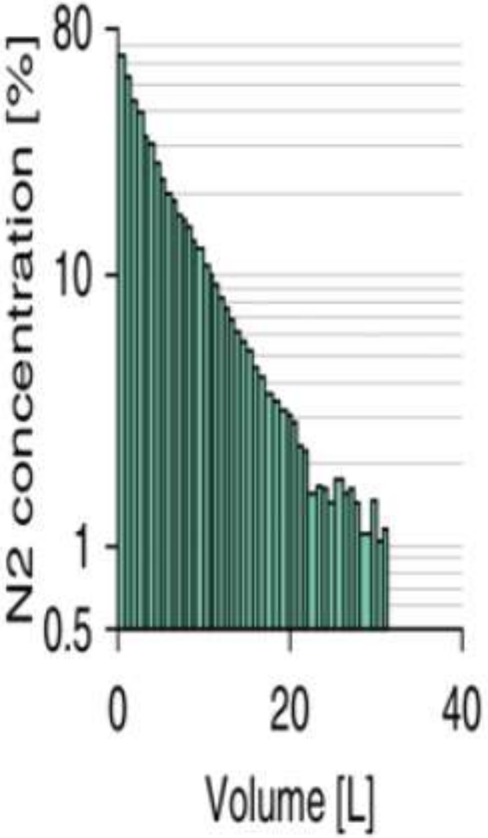
Solving for FRC_{N_2}, this becomes:

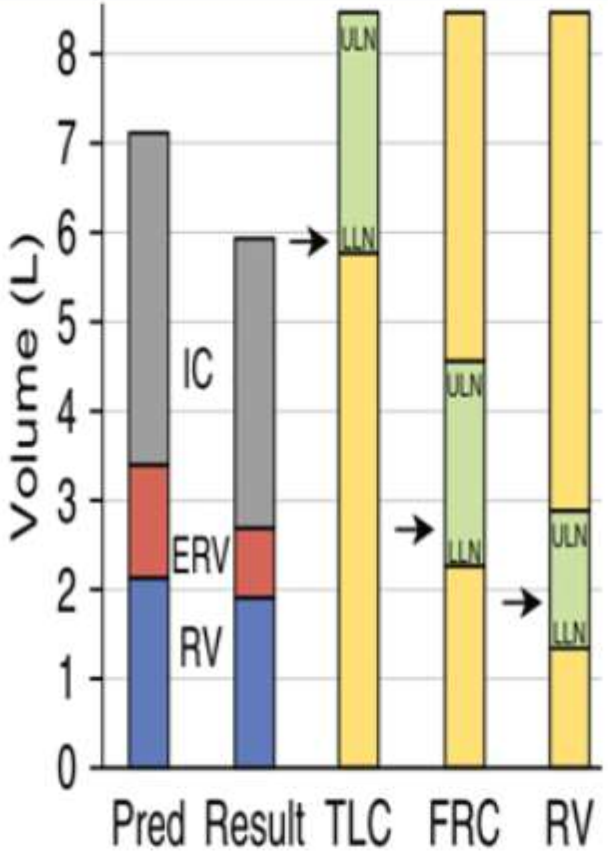
$$FRC_{N_2} = (N_2 \text{ volume washed out} - N_2 \text{ volume from tissue})/(F_{N_2}1 - F_{N_2}2)$$

Wanger J et al, Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep;26(3):511-22.

MULTI-BREATH NITROGEN WASHOUT (Post-Bronchodilator)

	Result	LLN	ULN	z-score	%Pred
TLC mb (L)	**5.95**	5.8	8.5	−1.45	83%
VC (L)	**4.05**	4.0	6.0	−1.61	81%
ICmb (L)	**3.27**				88%
FRC mb (L)	**2.68**	2.2	4.6	−1.03	78%
ERV (L)	**0.78**				61%
RV mb (L)	**1.90**	1.4	2.9	−0.49	89%
RV/TLC (%)	**32%**				
Reference values: Gutierrez 2004; Test quality: QA met					





There are no quality grading systems for lung volume measured by gas dilution methods, radiographic methods and body plethysmography as of now.

Culver BH et al, ATS Committee on Proficiency Standards for Pulmonary Function Laboratories. Recommendations for a Standardized Pulmonary Function Report. An Official American Thoracic Society Technical Statement. Am J Respir Crit Care Med. 2017 Dec 1;196(11):1463-1472..

Limitations

- Nitrogen excreted from tissues impact outcomes
- Leaks overestimate the volumes

Kane M et al, Correcting for tissue nitrogen excretion in multiple breath washout measurements. PLoS One. 2017 Oct 11;12(10):e0185553.

Other uses

- **Lung clearance index (LCI)**

- Assessment of ventilator inhomogenicity
- Early marker of small airway diseases, cystic fibrosis
- Derived from multiple breath wash out technique
- Tracer gas -> nitrogen / SF6
- End tidal tracer gas concentration falls to 1/40th of the starting concentration
- Calculated as cumulative expired volume / functional residual capacity
- Indicates number of breaths turnover required to excrete the tracer gas to predefined end point.
  Increased in airway diseases
- Normal range in adults 5.9 to 7.5 & in children <16 years. 5.3 to 7.3
- No universal standard

Grillo L et al, The reproducibility and responsiveness of the lung clearance index in bronchiectasis. Eur Respir J. 2015 Dec;46(6):1645-53.
Horsley A. Lung clearance index in the assessment of airways disease. Respir Med. 2009 Jun;103(6):793-9.
Horsley AR et al, Lung clearance index is a sensitive, repeatable and practical measure of airways disease in adults with cystic fibrosis. *Thorax* 2008;**63:**135-140.

Lung oscillometry tests

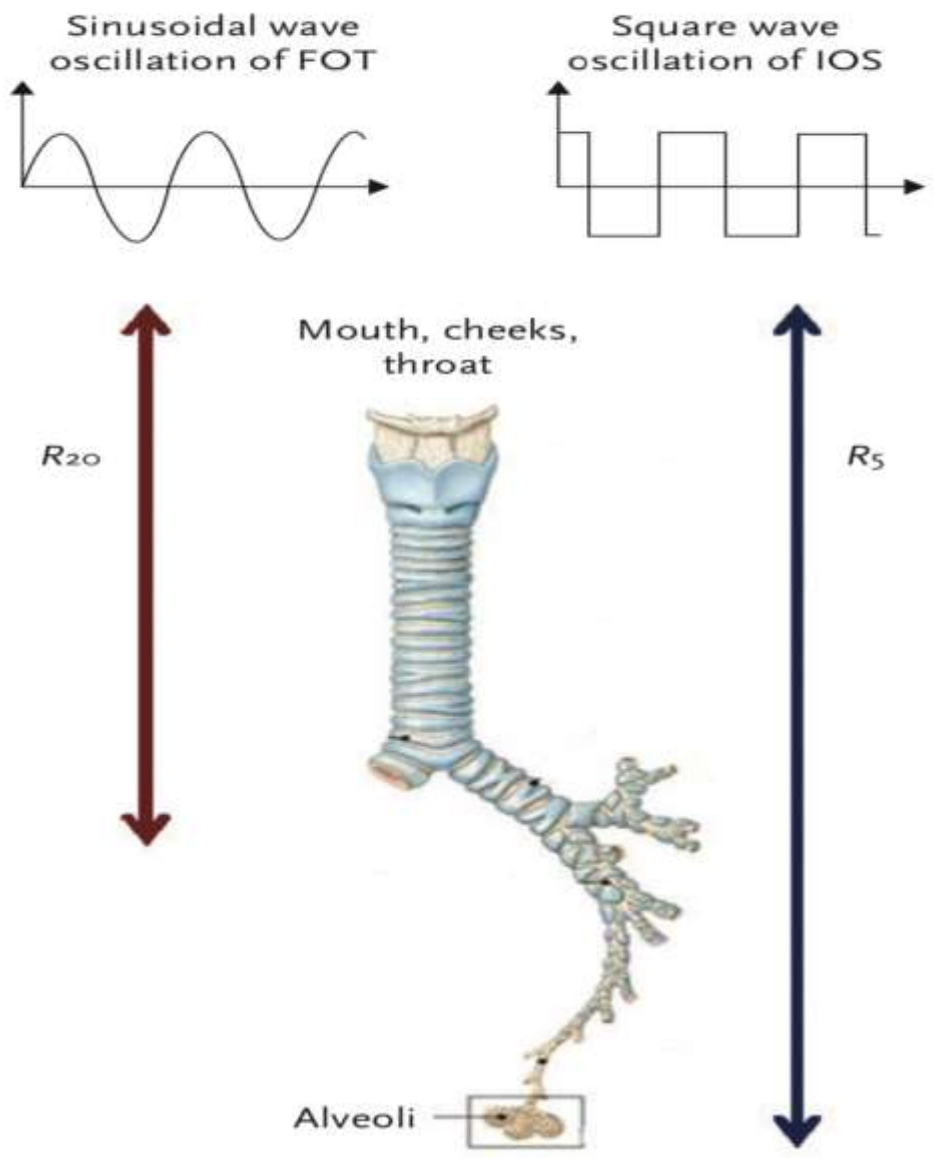
- Dubois et al, in 1956 used sinusoidal wave single sound frequency – forced oscillatory technique

- Michaelson et al, in 1975 used square wave multiple sound frequency – impulse oscillometry

↑

- Sensitivity for peripheral airways pathology

How it works?



- High frequency waves – short distance – larger airways
- Low frequency waves – long distances – deeper in lungs
- Pressure-flow transducer measure inspiratory and expiratory flow and pressure which is separated from breathing pattern by signal filtering
- ZRS = Rrs + Xrs

Characteristics	Spirometry	FOT/IOS
Principle	Flow sensor/volume displacement	Sound waves of single or multiple frequencies as pressure waves into lungs measuring respiratory resistance and reactance
Parameters	Volumes : FEV1, FVC Flows: PEFR, $FEF_{25\text{-}75\%}$	ZRS, RRS, XRS,FRES,AX
Patient co-operation	Yes	Not much
Type of breathing	Forced exhalation	Tidal breathing
Intra-variability	3-5%	5-15%
Airway location sensitivity	Central +, peripheral ++	Central & peripheral +++
Bronchodilator response cut off	12-15% for FEV1	40% for R5 or X5
Bronchoconstrictor response cut off	20% for FEV1	50% for R5
Standardised methodology	Available	
Reference values	Well defined	Not well defined

Brashier B, Salvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulse oscillometry system. Breathe (Sheff). 2015 Mar;11(1):57-65.

Terminology	What is it?	Values
Rrs (respiratory resistance)	Resistance of oropharynx, larynx, trachea, large and small airways, lung and chest wall tissue	cmH2O/L /S or kPa/L/S
R5 (resistance at 5 Hz)	Total airway resistance	
R20 (resistance at 20 Hz)	Large airway resistance	
R5-R20	Small airway resistance	
Zrs	Respiratory impedence. 2 components (respiratory resistance and reactance)	
Xrs (respiratory reactance)	Imaginary, mass-inertive force of moving air column expressed as inertance(I) & Capacitance (C)	cmH2O/L /S or kPa/L/S
C & I	Opposite, dependent on oscillation frequency. Low frequency – small airway capacitance dominate; high frequency – larger airway inertance dominate. Capacitance loss – negative & inertance – positive	
Fres (resonant frequency)	Frequency @ capacitative & inertive pressure are equal. Frequency @ total impedence to airflow is flow resistive	6-11 Hz
Ax (reactance area/Goldman triangle)	Indicative of small airway patency	<0.33 kPa/L

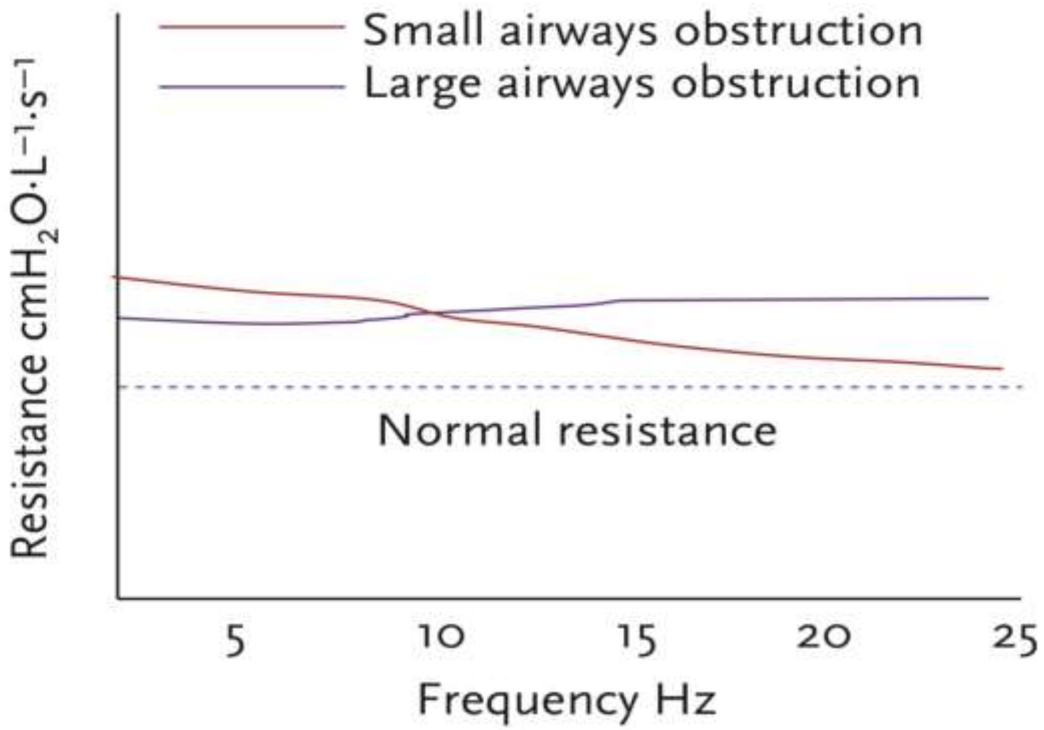


Figure 2
Respiratory resistance versus frequency.

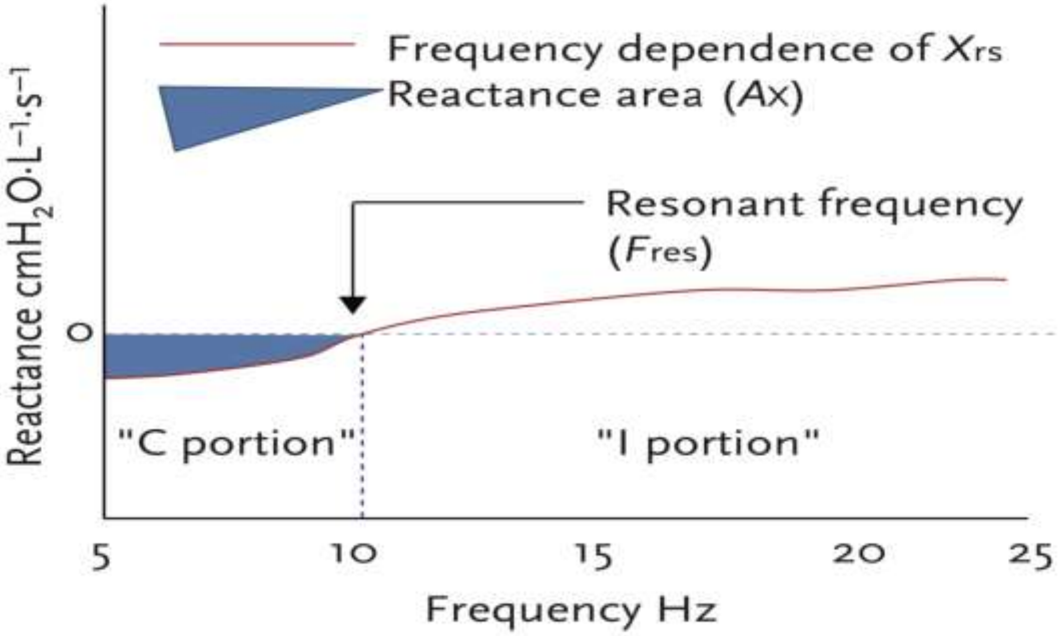
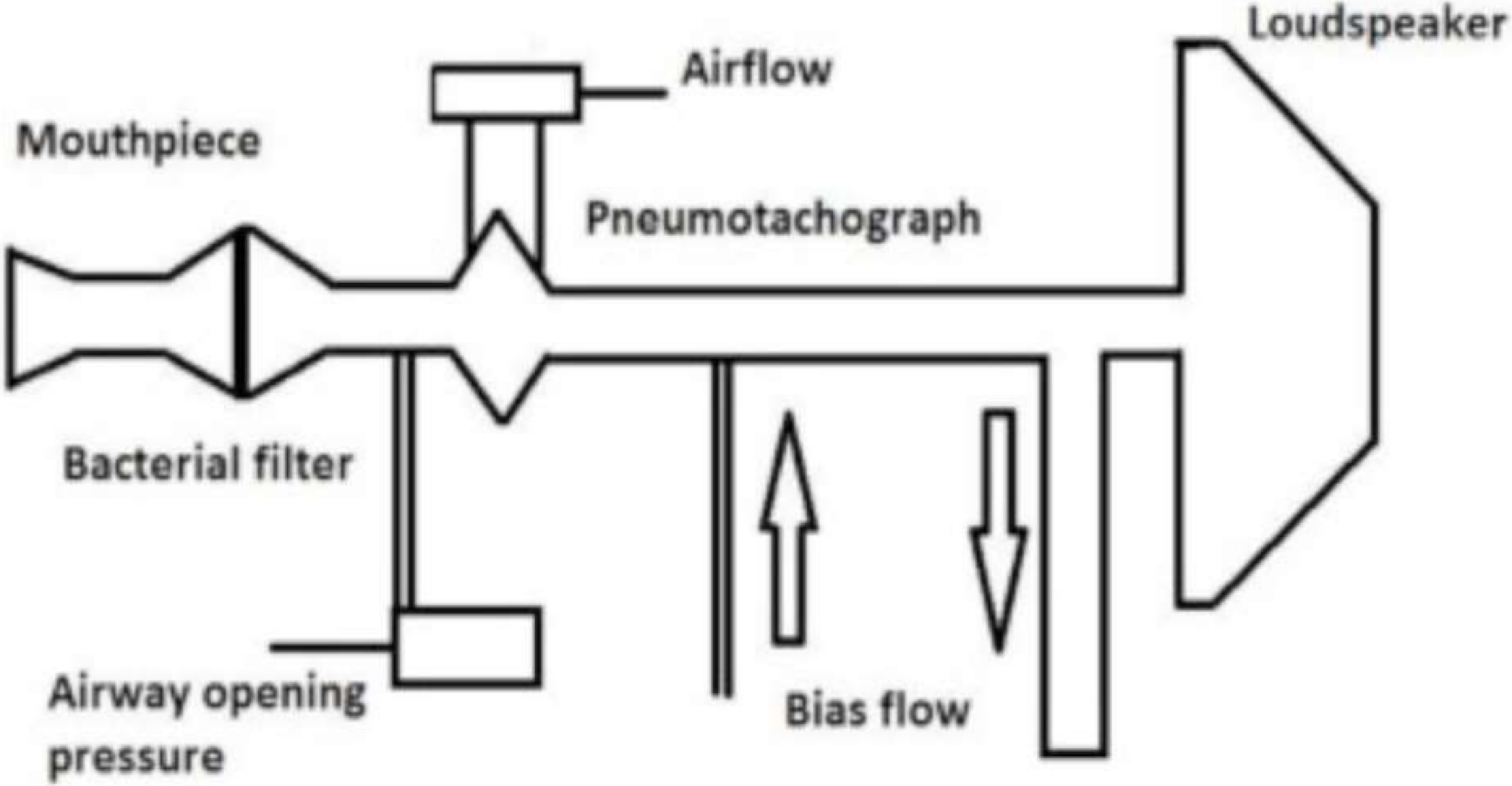


Figure 3
Reactance values in a healthy subject showing the "C" (compliance) and "I" (inertance) portions of reactance, area of reactance (Ax) and resonant frequency (Fres).

Steps

- The IOS instrument should be calibrated and checked every day.
- The procedure should be explained to the patient and the sitting position is preferred. Legs must be kept uncrossed in order to reduce extra-thoracic pressure and a nose clip should be worn.
- The mouthpiece of the FOT/ IOS should be at a comfortable height so that the neck is slightly extended.
- Ensure that there is a tight seal between the mouthpiece and lips to prevent air leak. The cheeks should be held firmly either by the patient with his/her hands or by an assistant who presses the cheeks firmly from behind
- Ask the patient to perform normal tidal breathing in a relaxed state during the FOT/ IOS procedure.
- The recording should be performed for at least 30–45 s. During this period, around 120–150 sound impulses are pushed into the lungs from which the mean reactance and resistance values are determined at frequencies from 5 to 20 Hz.
- A minimum of three such tests should be performed. Care should be taken to ensure reproducible results without any artefacts.


Loudspeaker
Airflow
Mouthpiece
Pneumotachograph
Bacterial filter
Airway opening
pressure
Bias flow

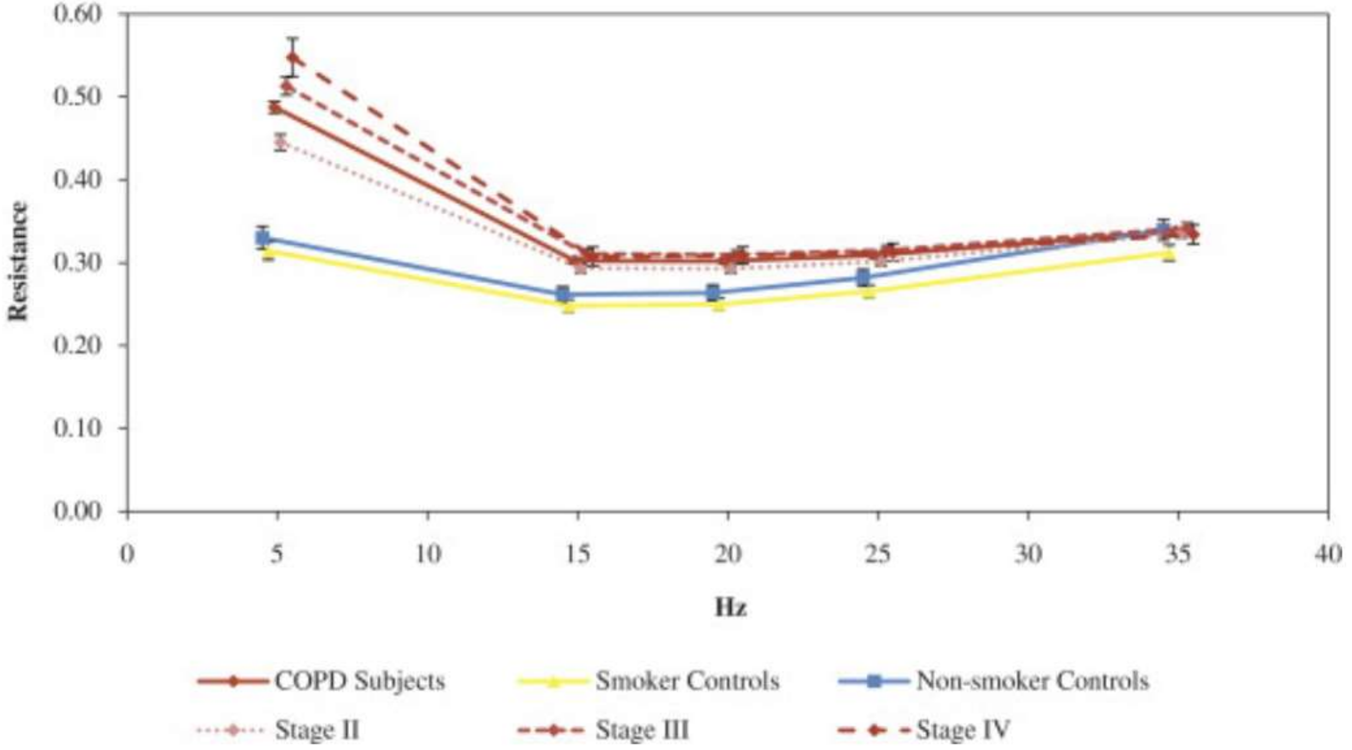
- Spirometry at same setting, performed after oscillometry test
- Coherence – quality control, value between 0 to 1. @ 5 Hz – 0.8 cm H2O & 20 Hz – 0.9 to 1.0
- The CoV of 10% and 15% are current recommendation for quality control in adults & children
- Values by IOS & FOT are different
- ERS task force of international experts recommends that the thresholds for defining a positive bronchodilator response, for both adults and children, are 40% decrease in R5, 50% increase in X5, and 80% decrease in AX
- Age and height in children affect resistance and reactance values
- No satisfactory predicted values for both adults as well as children
- Can be a alternative in subjects who cannot undergo spirometry
- Usefulness in restrictive lung diseases is unclear

Population	Objective & Methodology	Outcomes
70 participants cohort study (Asthma, COPD, healthy pats)	IOS with spirometry in diagnosis of OAD	Statistically significant correlation with decrease in spirometry values with increase in central, peripheral airways resistance & decrease in reactance (more negative). In asthma Sen 100%, spe 83.3% & diagnostic accuracy 96%. In COPD, Sen 83.3%, spe 100% & diagnostic accuracy 84%.
ECLIPSE prospective cohort study (Healthy non-smokers(233) or former smokers(332), COPD pats(2054))	IOS measurements with quantitative CT distribution of emphysema	Respiratory impedence and resistance worsened as severity of COPD increases. Although mean values of impedence, resistance and ct severity increased as severity increased the actual correlation between them was poor (r <0.16)

Mousa et al, Impulse oscillation system versus spirometry in assessment of obstructive airway diseases. The Egyptian Journal of Chest Diseases and Tuberculosis 67(2):p 106-112, Apr–Jun 2018
Crim C et al, ECLIPSE investigators. Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results. Respir Med. 2011 Jul;105(7):1069-78.

Eclipse study

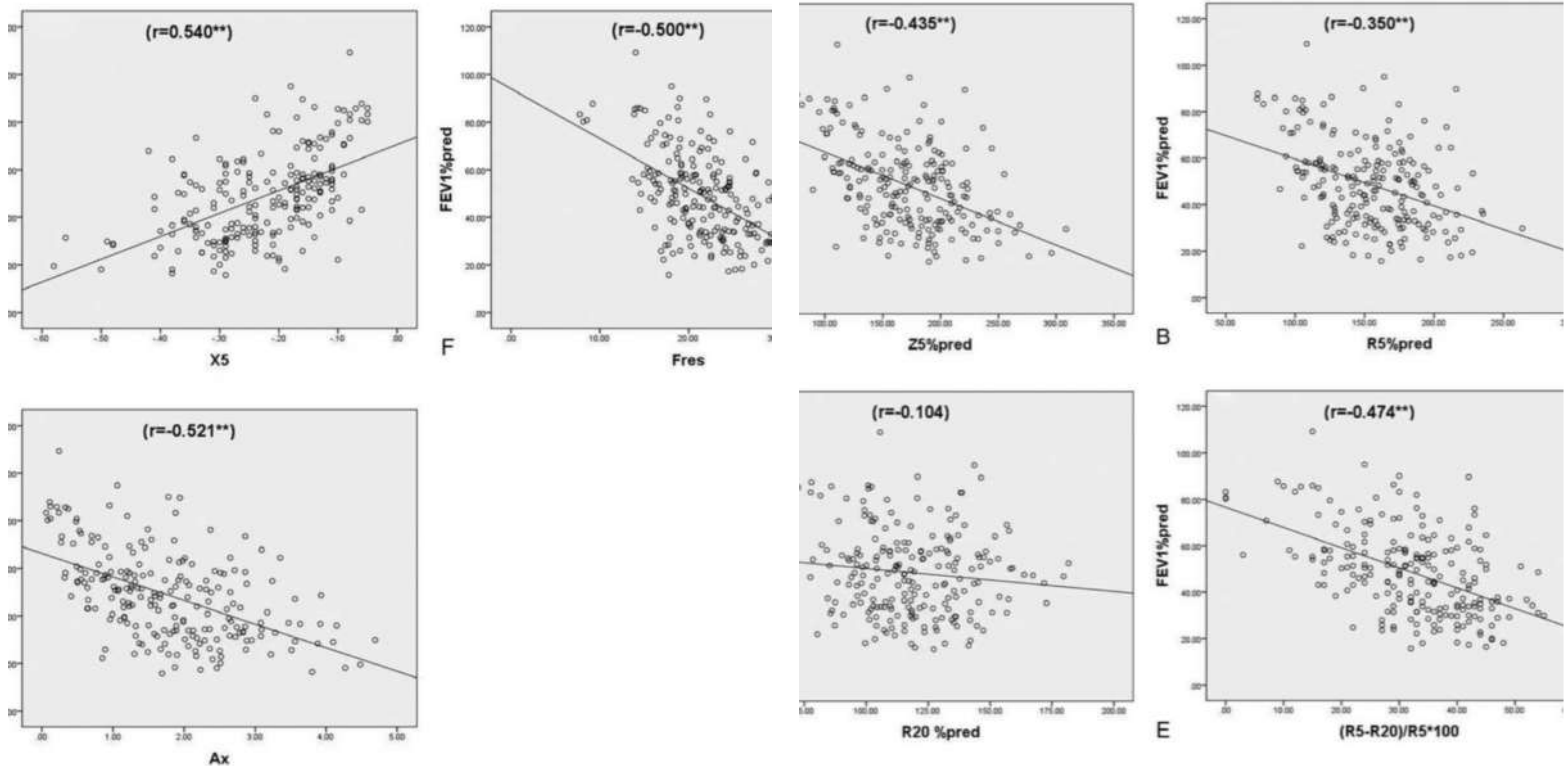
	NSC[a] (*n* = 233)	CS (*n* = 322)	COPD (*n* = 2054)	GOLD 2 (*n* = 915)
R_5 (kPa/L/s)	0.33 (0.10)	0.31 (0.10)	0.49 (0.16)[b]	0.45 (0.14)
R_{20} (kPa/L/s)	0.26 (0.07)	0.25 (0.07)[e]	0.30 (0.08)[b]	0.29 (0.07)
$R_5 - R_{20}$ (kPa/L/s)	0.07 (0.05)	0.06 (0.05)	0.19 (0.10)[b]	0.15 (0.09)
X_5 (kPa/L/s)	−0.10 (0.06)	−0.09 (0.05)	−0.29 (0.17)[b]	−0.21 (0.13)
AX (Hz·kPa/L/s)	0.38 (0.40)	0.34 (0.35)	1.99 (1.46)[b]	1.37 (1.08)
F_{Res} (Hz)	12.4 (3.4)	12.1 (3.2)	20.7 (5.2)[b]	18.3 (4.3)



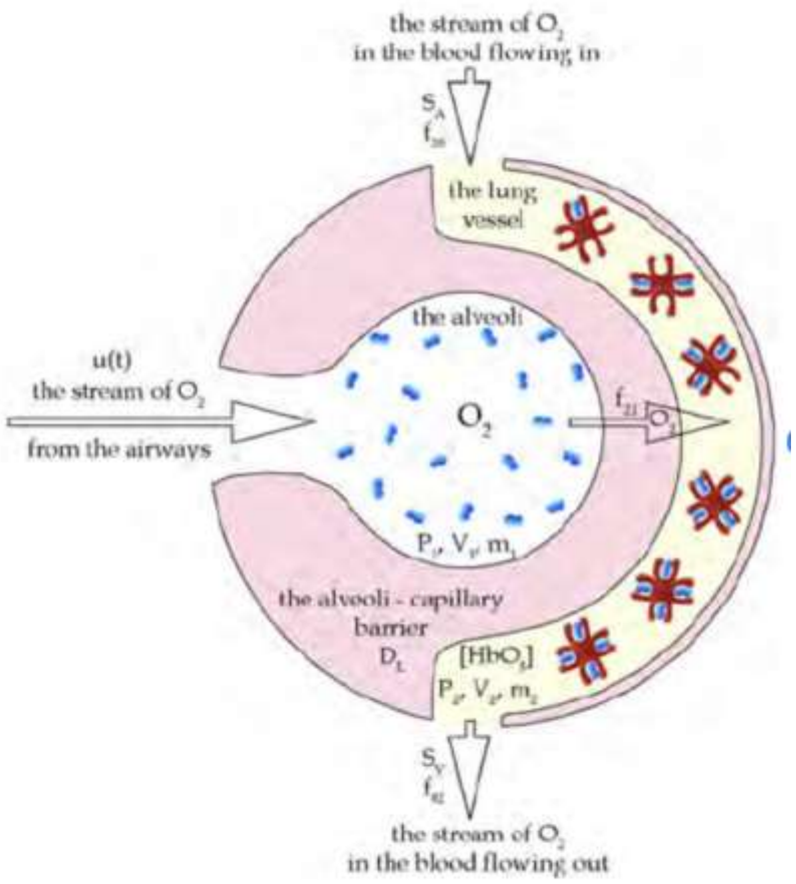
Population	Objective & methodology	Outcomes
Prospective cohort of COPD pats (215)	Assess the IOS parameters in COPD patients with FEV1 < 50% pred	FEV1%pred, MMEF 75%-25%, and residual volume/total lung capacity (RV/TLC) correlated with total respiratory impedance (Z5)%pred, resistance at 5 Hz (R5)-resistance at 20 Hz (R20), R5-R20% R5, R5, R5%pred, frequency response (Fres), reactance area (Ax), and reactance at 5 Hz (X5). Reactance parameters showed a stronger correlation than that of the resistance parameters

Wei X et al,Impulse oscillometry system as an alternative diagnostic method for chronic obstructive pulmonary disease. Medicine (Baltimore). 2017 Nov;96(46):e8543.

Weix et al,


(r=0.540**)
X5
(r=-0.500**)
FEV1%pred
Fres
F
(r=-0.435**)
Z5%pred
(r=-0.350**)
FEV1%pred
R5%pred
B
(r=-0.521**)
Ax
(r=-0.104)
R20 %pred
(r=-0.474**)
FEV1%pred
(R5-R20)/R5*100
E

DLco (diffusion capacity for carbon monoxide) or Transfer factor (TLco)



Structural factors:

Lung gas volume

Thickness and area of alveolar capillary membrane

Volume of Hb in capillaries supplying ventilated alveoli

Functional factors:

Ventilation perfusion ratio

Composition of alveolar gas

Diffusion characteristics of membrane

Concentration and binding properties of Hb in alveolar capillaries

Carbon monoxide and oxygen tension in alveolar capillaries

How carbon monoxide gets transferred?

- Delivery of carbon monoxide to airways and alveolar spaces
- Mixing and diffusion of carbon monoxide in alveolar ducts, air sacs and alveoli
- Transfer of carbon monoxide across gaseous to liquid interface of alveolar membrane
- Diffusion across RBC membrane and within RBC
- Chemical reaction with blood Hb

- Expressed in ml/min/mm Hg or mol/min/kPa under standard temperature, pressure and dry conditions (STPD)
- Conductance property -> 1/Dlco = 1/ Dm + 1/VC(Dm – membrane conductivity, Vc– volume of capillary blood)
- Increase in Vc – exercise, supine position, muller manoeuvres, lung resection – increase Dlco
- Decrease in Vc – Vasava manoeuvre – reduce Dlco
- VA calculated from tracer gas – affected by distribution of ventilation

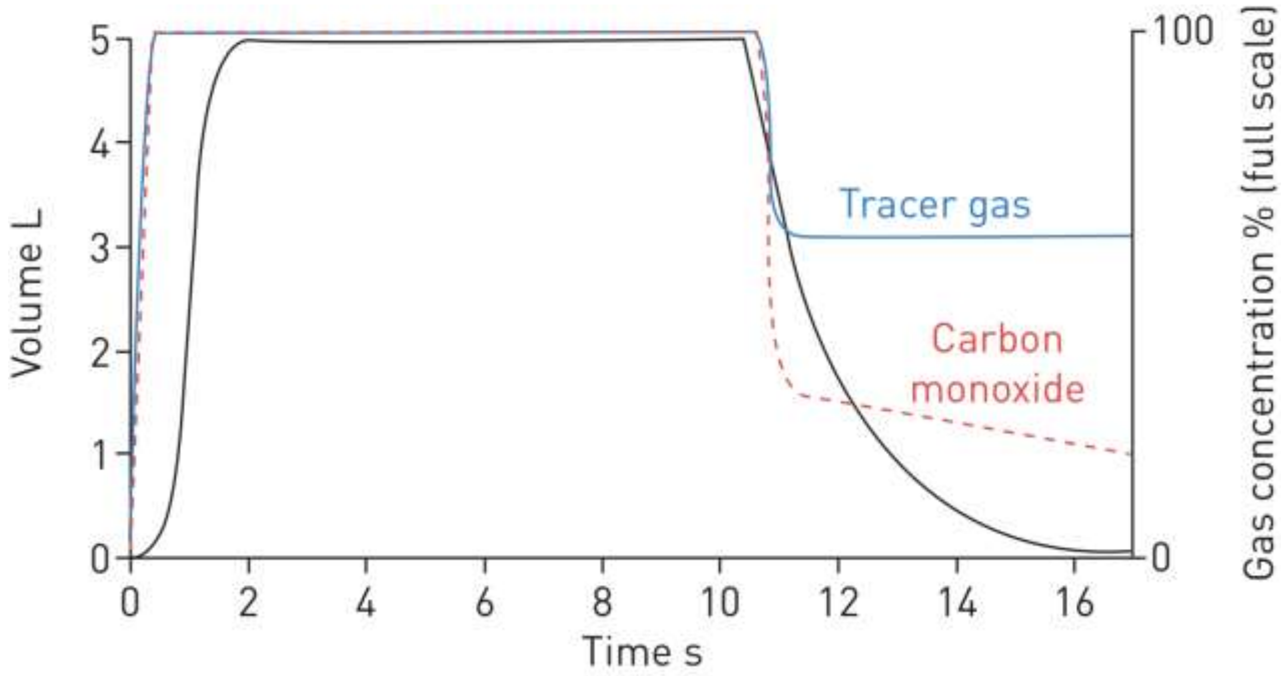
D_{LCO} System	Specification	
	Required	**Recommended**
Rapid gas analyser systems		
Analyser specification		
0–90% response time (see figure 2)	⩽150 ms	
Maximum nonlinearity	±1% of full scale	
Accuracy	Within ±1% of full scale	
Interference from 5% carbon dioxide or 5% water vapour	⩽10 ppm error in [CO]	
Drift for carbon monoxide	⩽10 ppm over 30 s	
Drift for tracer gas	⩽0.5% of full scale over 30 s	
Flow accuracy	Within ±2% over the range of −10 to +10 $L \cdot s^{-1}$	
Volume accuracy (3-L syringe check)	Within ±75 mL	
Barometric pressure sensor accuracy	Within ±2.5%	
Ability to perform a QA check (3-L syringe; ATP mode; inhaling ~2 L test gas)	Calculate total volume (V_A) of 3±0.3 L and D_{LCO} of <0.5 $mL \cdot min^{-1} \cdot mmHg^{-1}$ or <0.166 $mmol \cdot min^{-1} \cdot kPa^{-1}$	
Sample and store data with adequate resolution	Digitise at ⩾100 Hz per channel with ⩾14 bit resolution	Digitise at 1000 Hz
Monitor and report end-expiratory tracer gas and carbon monoxide concentrations (alert operator if washout is incomplete)	Implemented[#]	
Compensate for end-expiratory gas concentrations prior to test gas inhalation in the calculation of V_A and D_{LCO}	Implemented[#]	
Ensure proper alignment of gas concentration signals and the flow signal	Implemented[#]	
Measure anatomic dead-space using the Fowler method (see figure 6)	Implemented[#]	
Display a graph of gas concentration *versus* expired volume to confirm the point of dead-space washout and report the amount of manual adjustment if done (see figure 4)	Implemented[#]	
Measure V_A using all of the tracer gas data from the entire manoeuvre in the mass balance equation	Implemented[#]	
Report the D_{LCO} adjusted for the change in P_{AO_2} due to barometric pressure	Implemented[#]	
Ability to input simulated digital test data and compute D_{LCO}, V_A, TLC, V_D		Calculate values within 2% of actual values
Report the D_{LCO} adjusted for the change in P_{AO_2} due to P_{ACO_2}, if the carbon dioxide concentration signal is available		Implemented[#]

Methods

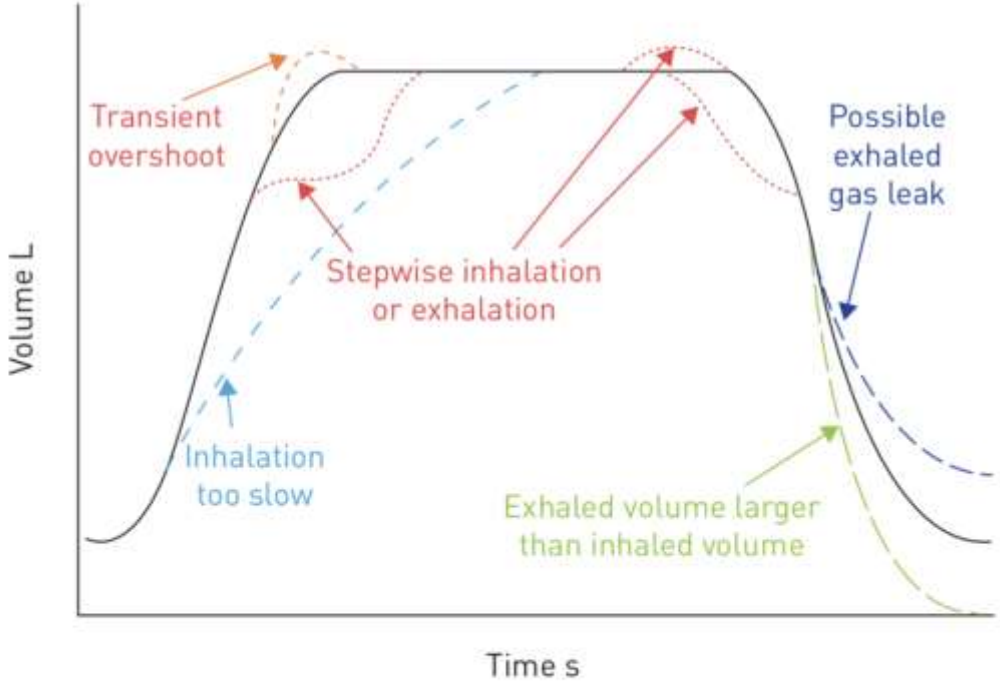
- Single breath method – most commonly used
- Intrabreath method
- Rebreathing technique

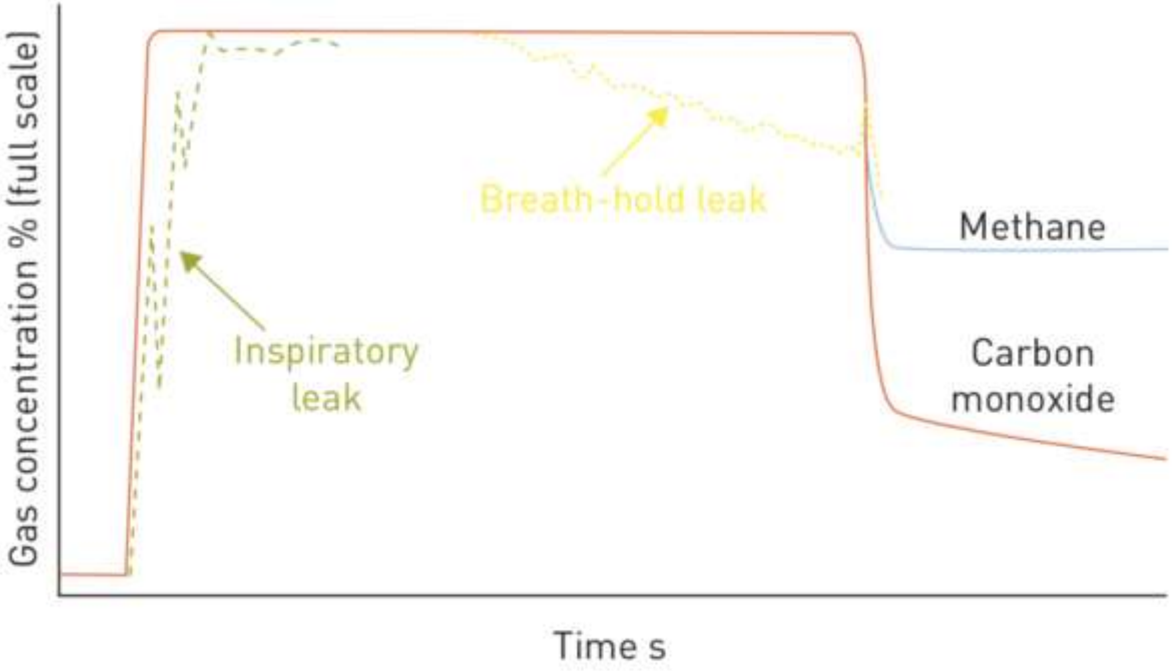
How to perform?

- Non forced exhalation from end TV to RV
- Quick inhalation of vital capacity volume of pre defined mixture of gas (< 4 sec) (CO – 0.3%, He – 10%, O2 – 18 -25%)
- 10 +/- 2 sec breath hold
- Quick unforced exhalation (< 4 sec) with collection of expired gas after washout of dead space



Potential problems!!





Acceptability criteria

- Inspired volume should be > 85%of largest VC and obtained within 4 sec
- A stable breath hold for 10 +/- 2 sec
- No evidence of leaks or Valsalva /muller manoeuvre during breath hold
- Two such acceptable test within inter test interval time of 4 min

Repeatability criteria

- Two acceptable test reports should be within 2ml CO/min / mm Hg or within 10% of the highest value

Precautions during Dlco test

- No more than 5 test be performed in same patient
- 4 min atleast allowed between two test
- Avoid smoking or other sources of carbon monoxide exposure on day of test
- In patients with obstructive lung disease, sufficient time (12 sec) should be given for exhalation to RV
- Inhalation of test gas should be maximal
- Avoid valsalva and muller manoeuvres

Adjustment to measurement of DLco

- Age
- Gender
- Height
- Race
- Hb : every 1 g less 7% dec of Dlco
- Lung volume
- COHb: every 1 % inc, 1% dec Dlco
- PIO2
- Alveolar pCO2
- Body position and exercise

- DLco = Kco * VA ; Kco – rate of uptake by blood & VA – Area of lung for gas exchange

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

- DLco decrease is an independent predictor of mortality

Modi P, Cascella M. Diffusing Capacity Of The Lungs For Carbon Monoxide. 2023 Mar 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
Balasubramanian A, Kolb TM, Damico RL, Hassoun PM, McCormack MC, Mathai SC. Diffusing Capacity Is an Independent Predictor of Outcomes in Pulmonary Hypertension Associated With COPD. Chest. 2020 Aug;158(2):722-734.
Hoeper MM, Meyer K, Rademacher J, Fuge J, Welte T, Olsson KM. Diffusion Capacity and Mortality in Patients With Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction. JACC Heart Fail. 2016 Jun;4(6):441-9.

Whom to perform?

- Differential diagnosis of patients with dyspnea on exertion
- Post BD obstruction in spirometry
- Spirometric restriction
- Early ILD screening
- Pulmonary vascular disease
- Occupational lung disease
- Assess pulmonary side effects of drugs & radiation
- Severity assessment & follow up of ILD & pulmonary vascular diseases

Enright Md P. Office-based DLCO tests help pulmonologists to make important clinical decisions. Respir Investig. 2016 Sep;54(5):305-11.

Increased DLco

- Altitude
- Asthma
- Polycythemia
- Obesity
- Pulmonary haemorrhage
- Left to right shunt
- Mild left heart failure
- Exercise prior to test
- Muller manoeuvre
- Supine position

Low DLco/Normal volumes

- Anemia
- Pulmonary vascular disease
- Early ILD
- Valsalva maneuver

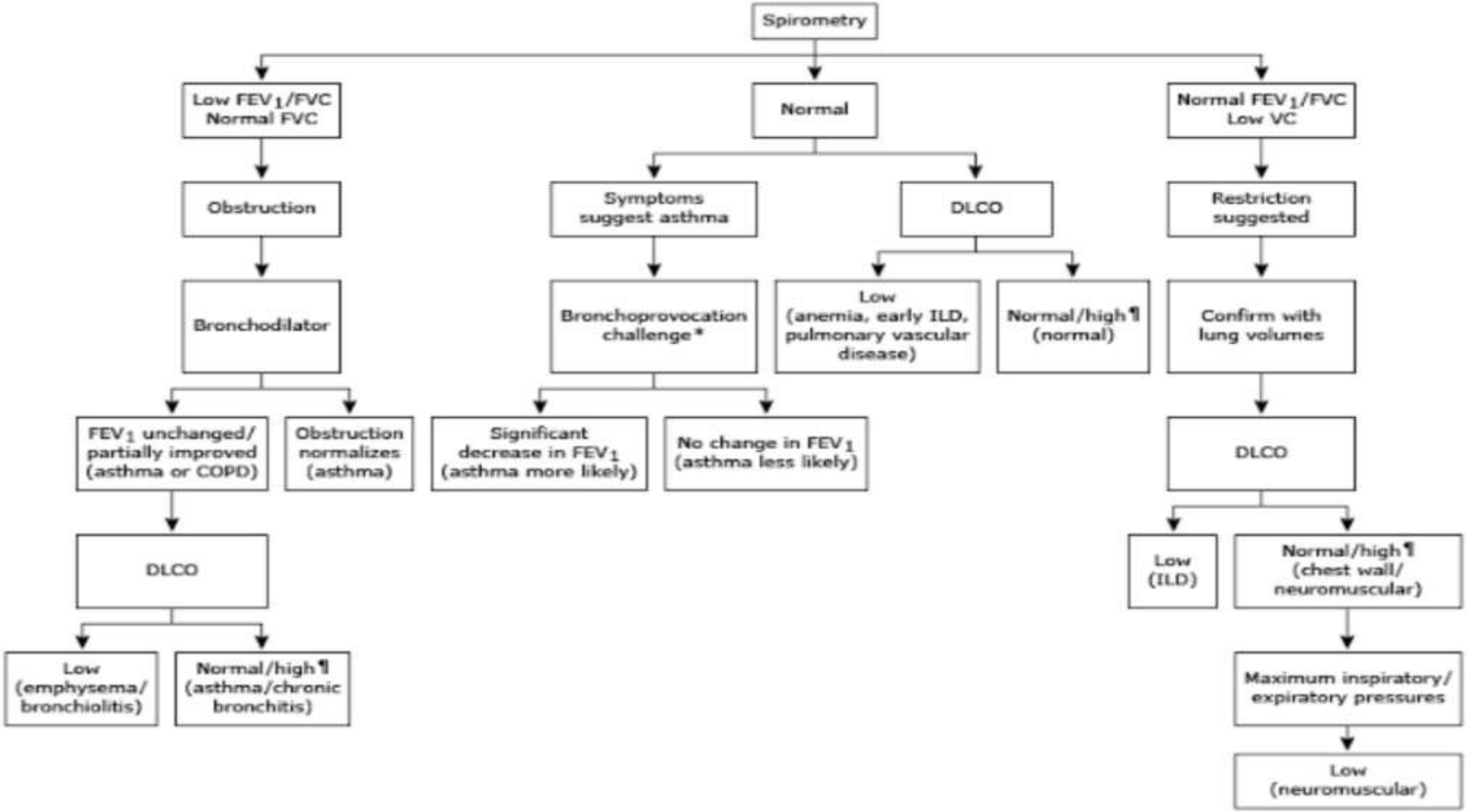
Low DLco with obstruction

- Bronchiolitis
- CPFE
- Cystic fibrosis
- Emphysema
- ILD with COPD
- Sarcoidosis
- Lymphangioleiomyomatosis

Low DLco with restriction

- ILD
- Pneumonitis

Interpretation algorithm



Up-to-date

6 minute walk test

- Objective evaluation of submaximal functional exercise capacity
- In 1960, Balke developed test to assess functional capacity as a 12 minute walk test which was later modified to 6 minute walk test
- Simpler to perform, better tolerated, more reflective of activities of daily living and requires no advance training to technicians
- Assess global & integrated response of all systems (pulmonary, cardiovascular, systemic & peripheral circulation, blood, neuromuscular & muscle metabolism)

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7.

Whom to perform?

- **Pre & post treatment comparisons**

1. Lung transplantation
2. Lung resection
3. Lung volume reduction surgery
4. Pulmonary rehabilitation
5. COPD
6. Pulmonary hypertension
7. Heart failure

- **Functional status**

1. COPD
2. Cystic fibrosis
3. Heart failure
4. Peripheral vascular disease
5. Fibromyalgia

- **Mortality prediction**

1. Heart failure
2. COPD
3. Primary pulmonary hypertension

Whom not to perform?

Absolute

- Unstable angina/MI within 1 month

Relative

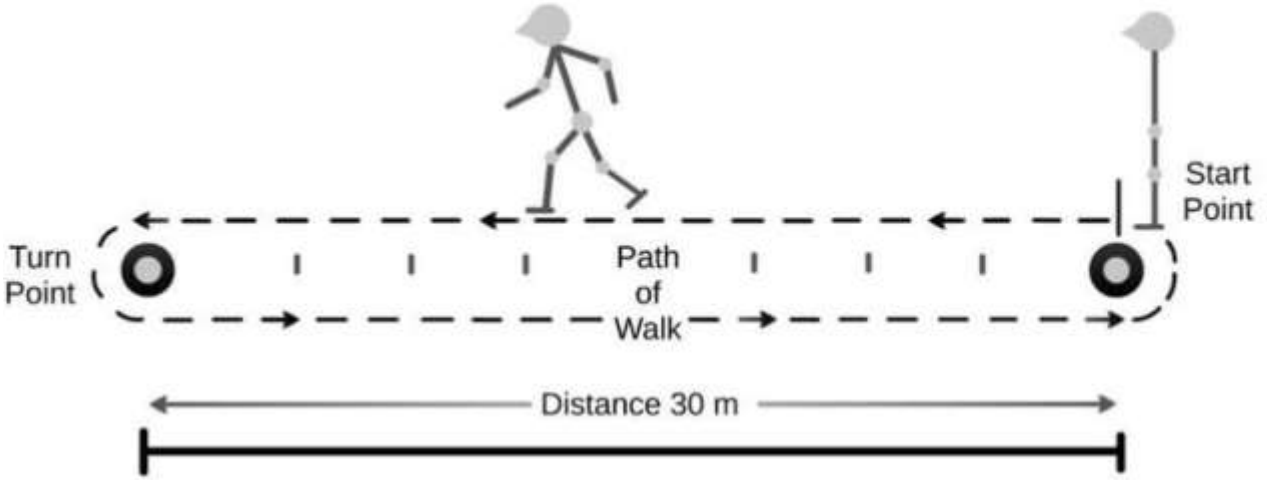
- Resting heart rate >120
- SBP/DBP >180/100 mm Hg

Stable angina controlled on medications is not a contraindication for 6 MWT

Preparation of the patient

- Comfortable clothing
- Appropriate shoes
- Use walking aids if routinely used
- Medical regimen to be continued
- No exercise 2 hours prior to test

Pre-requisites & precautions



- Long, flat, straight , enclosed corridor
- 30 m walking course, length marked every 3 m
- Turn around points marked with cone
- Line denoting starting and ending of 60 m lap marked with bright tape
- Rapid and appropriate response to emergency facility in place
- Oxygen, sublingual nitroglycerin, aspirin & inhalers etc must be available
- Technician should be certified in BLS
- In those on chronic oxygen therapy, oxygen should be given at their standard rate

How do we perform the test?

- Ask the patient rate their dyspnea & fatigue using Borg scale
- Set lap counter to 0 & timer to 6 minutes
- Instruct the patient to walk at own pace in 6 minutes. Patient can slow, stop, rest and resume again
- Start the timer when the patient starts to walk and click lap every time the patient reaches the starting line
- When the test is done, grade the dyspnea & fatigue with Borg scale again
- If pulse oximetry used, measure SpO_2 & pulse rate

Factors affecting 6MWD

Factors Associated with Shorter 6-Minute Walk Distance

- Shorter height (shorter legs)
- Old age
- Higher body weight
- Female gender
- Impaired cognition
- Shorter walking corridor (more turns)
- Chronic obstructive pulmonary disease, asthma, cystic fibrosis, interstitial lung disease
- Angina, myocardial infarction, congestive heart failure, stroke, transient ischemic attack, peripheral vascular disease, ankle-arm index
- Arthritis; ankle, knee, or hip injuries; muscle wasting

Factors Associated with Longer 6-Minute Walk Distance

- Taller height (longer legs)
- Male gender
- High motivation
- Patient has previously performed the test
- Medication for a disabling disease taken just before the test
- Oxygen supplementation

Enright PL. The six-minute walk test. Respir Care. 2003 Aug;48(8):783-5

How to interpret the results?

- Interpreted with the background of factors affecting the results
- Normal healthy subjects – 400 to 700 m
- Low 6MWD is non-specific & non-diagnostic and cause should be evaluated

Enright PL. The six-minute walk test. Respir Care. 2003 Aug;48(8):783-5