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Functional Evaluation in Respiratory Disorders

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1. Introduction

In evaluating the respiratory system, many different tests are used and these can be divided into different categories based on the aspect of lung function they measure. Depending on availability and need, the tests can be complementary and yield results that allow deeper insight into respiratory function to understand disease processes and therapeutic interventions - both medical and surgical.

Categories of Pulmonary Function Tests
a. Airway Function
- Simple spirometry (VC, expiratory reserve volume {ERV}, inspiratory capacity {IC})
- Forced vital capacity (FVC, from which the Forced Expired Volume in the first second is derived- FEV1)
- Maximal inspiratory / expiratory pressures (MIP / MEP)
b. Lung volumes and ventilation
- Function residual capacity (FRC)
- Total lung capacity (TLC)
- Residual Volume (RV)
- RV / TLC ratio
c. Diffusing Capacity Test
- Single breath (breath holding)
d. Blood gases and gas exchange tests
- Blood gas analysis and blood oximetry
- Pulse oximetry
e. Cardiopulmonary exercise tests
- Simple non-invasive tests
- Tests with exhaled gas analyses

Table 1. The categories of pulmonary function testing

1.1 Spirometry & other related tests

Spirometry is a physiological test that measures how an individual inhales or exhales volumes of air as a function of time. The primary signal measured may be volume or time. Spirometry is the pulmonary function test performed most often due to the large number of indications. "It is most often performed as a screening procedure because it may be the first test to indicate the presence of pulmonary disease"(Ruppel, 2009).

Indications for Spirometry

a. Diagnose the presence / absence of lung disease.
   1. History of pulmonary symptoms (dyspnoea, wheezing, cough, phlegm production, orthopnoea)
   2. Physical indicators (decreased breath sounds, chest wall abnormalities)
   3. Abnormal Laboratory findings (Chest x-ray or CT studies)

b. Quantify the extent of known disease on lung function
   1. Pulmonary disease (COPD, Asthma)
   2. Cardiac disease (Cardiac Failure)
   3. Neuromuscular disease (e.g. Guillain-Barrè syndrome)

c. Measure effects of occupational / environmental exposures

d. Determine beneficial / negative effects of therapy

e. Assess risk for surgical procedures
   1. Lung resection
   2. Thoracic procedures
   3. Pulmonary rehabilitation

f. Evaluate disability or impairment

g. Epidemiologic or clinical research involving lung health or disease.

Table 2. List of indications for spirometry (Ruppel, 2009)

> "Spirometry is recommended as the "gold standard" for the diagnosis of obstructive lung disease. However spirometry alone may not be sufficient enough to completely define the extent of disease, therapy response, preoperative risk, or level of impairment (Ruppel,2009)".

In view of the importance of spirometry in aiding an accurate diagnosis and monitoring changes that can be extremely subtle, a good quality spirometer is essential. As the machines become increasingly sophisticated and computerised, it is imperative that they meet the technical specifications so that are accurate and precise. These criteria are quite complex but are well laid out by the American Thoracic Society (ATS- Standardization of Spirometry, 1994 Update). Thus in purchasing or utilising such a device it is crucial that one obtains the manufacturer's guarantee that a reputable testing facility has checked that the spirometer meets and conforms with the ATS recommendations for accuracy and precision. Equally, a well trained pulmonary function technologist who understands the calibration and pitfalls of the testing can be invaluable.

"The two most important measurements of spirometry are (1) **forced vital capacity (FVC)**, which is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration, and the (2) **forced expiratory volume** in one second **(FEV_1)** of an FVC manoeuvre (ATS/ERS,2005)".

Another variable derived from spirometry is the slow **vital capacity (VC)**, which is the volume of gas measured from a slow, complete expiration after a maximal inspiration, without forced or rapid effort. The **Inspiratory capacity (IC)** and **expiratory reserve volume (ERV)** are subdivisions of the VC. The IC is the largest volume of gas that can be inspired from a resting expiratory level. ERV is the largest volume of gas that can be expired from the resting end-expiratory level. IC and ERV are used in the calculation of the **residual volume (RV)** and **total lung capacity (TLC)**. The RV is the volume of gas remaining in the lungs at the end of maximal expiration regardless of the lung volume at which exhalation was started. The TLC is the volume of gas contained in the lungs after maximal inspiration (ATS/ERS,2005).

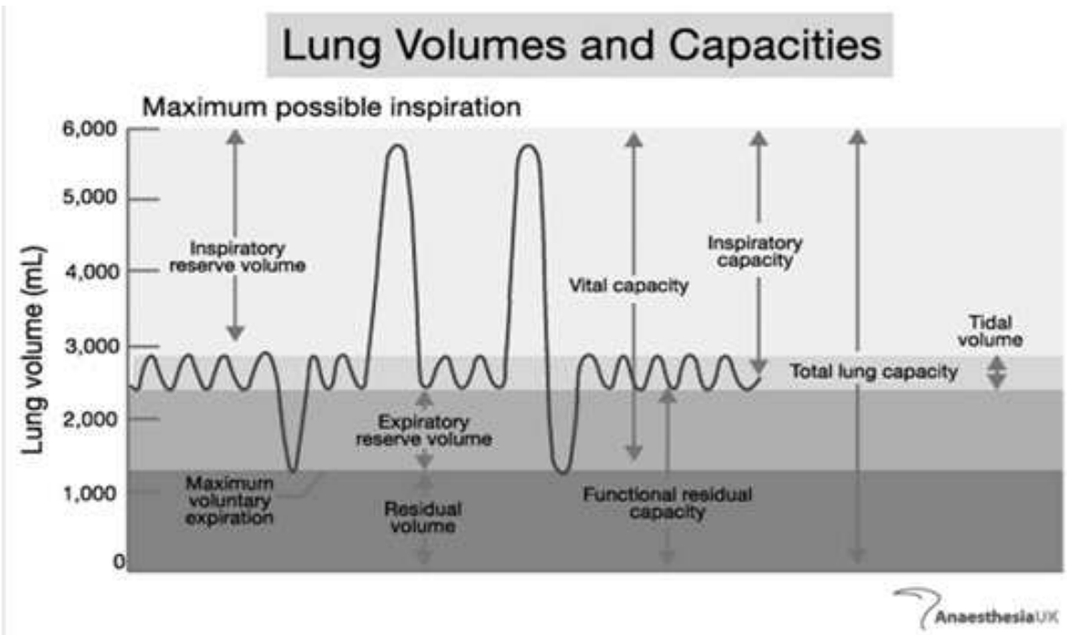


Fig. 1. A schematic presentation of the lung volumes and capacities.

Contraindications to Spirometry
- Myocardial infarction within the last month
- Recent stroke, eye surgery, thoracic / abdominal surgery
- Uncontrolled hypertension
- Known aortic, thoracic, cerebral aneurysm
- Recent pneumothorax
- Relative contraindications: chest, abdominal, facial pain, headache, stress incontinence, dementia, confusion

Table 3. A list of contraindications to spirometry (Ruppel,2009).

2. Flow-volume loop

This procedure is used to measure the FVC, FEV_1 and other forced expiratory flow volumes. This test is dependent on patient effort.

2.1 Significance and pathophysiology

2.1.1 Forced Vital Capacity

The FVC usually equals VC in healthy individuals and should be within 150ml of each other. The FVC and VC may differ if the patient's effort is variable or if significant airway obstruction is present (FEV_1 / FVC is less than 70%). The FVC may be lower than VC in patients with obstructive diseases as forced expiration can cause airway collapse. In these situations a slow VC (SVC) may be more accurate.

Healthy adults can expire their FVC within 4-6 seconds. Healthy children and adolescents may exhale their FVC in less than 4 seconds. Patients with severe obstruction may require 15 seconds or more to exhale completely.

2.1.2 Forced expiratory volume in the first second (FEV_1)

FEV_1 is reported as a volume, although it measures flow over a specific interval. FEV_1 may be reduced in either obstructive or restrictive patterns. The FEV_1 and FEV_1 / FVC ratio are the most standardized indices of obstructive diseases. An obstructive defect is defined best by a reduced ratio.

The severity of an obstructive disease may be gauged by the extent to which FEV_1 is reduced. The ATS / ERS 2005 Task force suggests the following classifications of severity (Ruppel, 2005):

Mild	FEV_1 > 70% predicted
Moderate	FEV_1 = 60% - 69% predicted
Moderately severe	FEV_1 = 50% -59% predicted
Severe	FEV_1 = 35% - 49% predicted
Very severe	FEV_1 < 35% of predicted

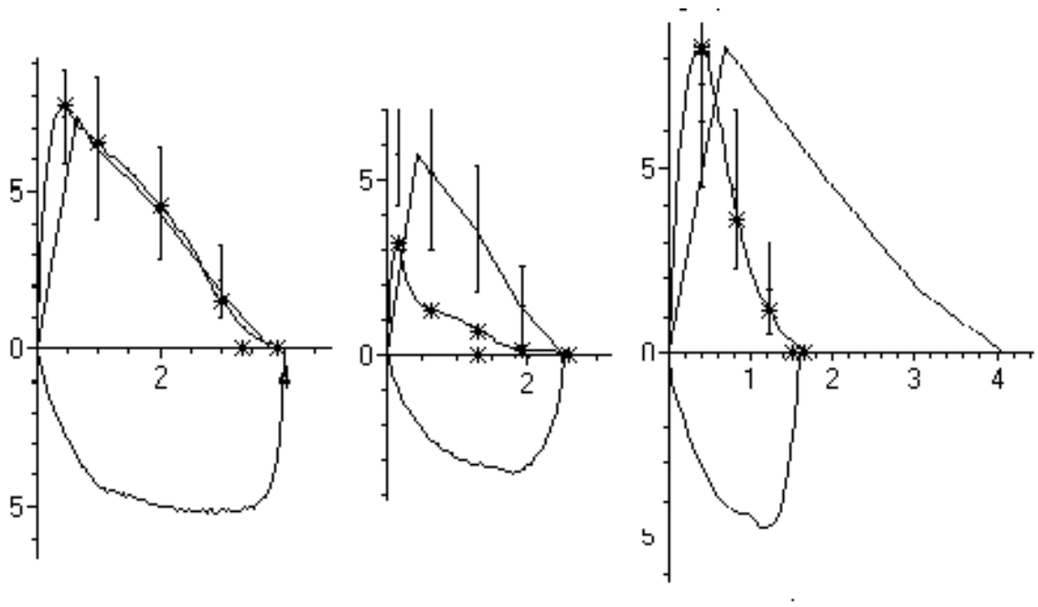
Once the VC is below normal, a concomitant restrictive defect may also be present, and this can be determined by further measurement of volumes, in particular TLC. Restrictive processes such as fibrosis, oedema, and obesity may all cause a decrease in FEV_1. Unlike the pattern seen in obstructive diseases, in which VC is preserved and FEV_1 reduced, in restriction VC and FEV_1 values are proportionally decreased.

The FEV_1 is the most widely used spirometric parameter, particularly for the assessment of airway obstruction. It is also used in conjunction with VC for simple screening, assessment of response to bronchodilators, and detection of exercise-induced bronchospasm.

2.1.3 FEV_1 / FVC ratio

The normal ratio expressed as a percentage for healthy adults is between 75% - 85%. This value can decrease with age, presumably because of gradual loss of lung elasticity. Diagnosis of an obstructive pattern based on spirometry should focus on three primary variables: FVC, FEV_1, and FEV_1 / FVC.

Examples of patterns seen in flow volume loops follow: The actual curve (with asterisks) is usually superimposed on the predicted as derived by the computer based on age, gender, height and ethnicity.



Normal curve Obstructive curve Restrictive curve

2.2 Reversibility testing

This is the determination of reversibility in airflow-limitation with drug administration and is commonly undertaken as part of lung function testing. The choice of drug, dose and mode of delivery is a clinical decision depending on what the clinician wishes to learn from the test. The aim is to determine whether the patient's lung function can be improved with therapy.

The subject first undergoes baseline lung function testing, preferably with no prior drug therapy. According to the ATS/ERS 2005 guidelines, short-acting inhaled drugs should not be used 4hr prior to testing and long-acting β-agonist bronchodilators or oral aminophylline should be stopped 12hr prior to testing. Smoking should be avoided for an hour or more prior to testing as well as throughout the duration of the test procedure.

2.2.1 Procedure (ATS/ERS, 2005)

1. The subject performs 3 acceptable tests, with acceptable repeatability of the two highest FEV_1, FVC and PEF as a baseline.
2. The drug administered (100ug Salbutamol) is inhaled in one breath to TLC from a valved spacer device. The breath is then held for 5-10 s before the subject exhales.
3. Three further doses of Salbutamol (total dose 400ug) are delivered at 30s intervals.
4. Step 1 is repeated 10 – 15 min after administration of a short acting β_2- agonists (and 30 min after short-acting anticholinergic agents).

2.2.2 Determination of reversibility

A positive response to bronchodilator therapy is when either the FVC or the FEV_1 of the post attempt improves by 12% and 200ml from the pre attempt.

1. BD response = $\frac{FEV_1(post) - FEV_1(pre)}{1} \times \frac{100}{1}$

$$2.\ \text{BD response} = \frac{\text{FVC (post)} - \text{FVC (pre)}}{1} \times \frac{100}{1}$$

2.2.3 Clinical significance

Reversibility of airway obstruction is considered significant for increases of greater than 12% and 200ml for either the FEV_1 or FVC. If the sGaw is assessed, an increase of 30%-40% is usually considered as significant. Some patients may show little or even no improvement in FEV_1, but have a significant improvement in their sGaw.

Increases greater than 50% in the FEV_1 may occur in patients with asthma. Patients with chronic obstructive pulmonary diseases may show little improvement in their flows. Failure to show a significant improvement after inhaled bronchodilator therapy does not exclude a response.

It has been erroneously extrapolated that reversibility testing can define a disease; this is not true (Richter & Irusen, 2008). Asthma can be irreversible on spirometry (especially when there is uncontrolled inflammation impairing bronchodilatation) and COPD can be spirometrically reversible in up to 50% of patients. (In this respect, the absolute volume of improvement is more important as it is easy to get a significant percentage change when one starts with a low baseline.)

3. Maximal inspiratory / expiratory pressure (MIP & MEP)

Forced manoeuvres during spirometry require the patient to give a maximal effort, yet it also requires that the patient should have normal muscle function. Muscle function is best assessed by measurement of maximal inspiratory and expiratory pressures. **Maximal inspiratory pressure (MIP)** is the lowest pressure developed during a forceful inspiration against an occluded airway. **Maximal expiratory pressure (MEP)** is the highest pressure that can be developed during a forceful expiratory effort against an occluded airway.

3.1 Significance and pathophysiology

MIP primarily measures inspiratory muscle strength. Healthy adults can generate inspiratory pressures greater than -50cmH_2O in women, and -75 cmH_2O in men (Ruppel, 2009). Decreased MIP is seen in patients with neuromuscular disease or diseases involving the diaphragm, intercostals or accessory muscles. MIP may also be decreased in patients with hyperinflation as in emphysema. MIP is sometimes used to assess patient response to strength training of respiratory muscles. It is also used in the assessment of respiratory muscle function in patients who need ventilatory support.

MEP measures the pressures generated during maximal expiration. Healthy adults can generate MEP values greater than 80 cmH_2O in women and greater than 100 cmH_2O in men (Ruppel, 2009). MEP may be decreased in patients with neuromuscular disorders, particularly those resulting in generalized muscle weakness.

Reduced MEP often accompanies increased RV as seen in emphysema. A low MEP is associated with inability to cough effectively.

Accurate measurement of MIP & MEP depends largely on patient effort. The best efforts should be reproducible within 20% or 10 cmH_2O, whichever is greater. Widely varying pressures for either MIP or MEP should be assessed carefully before interpretation.

4. Body plethysmography

The forces governing maximal airflow are the elastic recoil pressure of the lung and airway resistance upstream from the equal pressure point. **Airway resistance (Raw)** is the pressure difference per unit flow as gas flows into or out of the lungs. Raw is the difference between the mouth pressure and alveolar pressure, divided by flow at the mouth.

Airway conductance (Gaw) is the flow generated per unit of pressure drop across the airways. Gaw is not commonly reported as it changes with lung volume. Instead, specific airway conductance (sGaw), which is Gaw divided by the lung volume at which the measurement was made, is usually reported (Ruppel, 2009).

Spirometry may be performed with the patient in the plethysmograph. The pneumotachometer must be capable of accurately measuring the entire range of gas flows required.

Spirometry, lung volumes, and airway resistance can all be obtained in a single sitting using plethysmography.

4.1 The most common measurements made using a body plethysmograph are:

- Airway resistance (Raw).
- Lung Volumes**:**
  - VC= Volume measured from a maximal inspiration followed by a complete slow expiration.
  - FRC= It is the volume of air left in the lungs at the end of a quiet exhalation
  - IC = Maximal volume of air inspired from a resting expiratory level.
  - ERV= Maximal volume of air expired from a resting expiratory level
  - TGV= Is the absolute volume of gas in the thorax at any point in time and at any level of alveolar pressure
  - RV= Volume of air remaining in the lungs at the end of a maximal expiration.
  - TLC= Volume of gas that the lungs contain after maximal inspiration.
  - RV/TLC (must be in the range 20 – 35% in order to be normal)

4.2 Important derivatives

4.2.1 Thoracic Gas Volume (TGV)

The TGV is a quick and accurate means of measuring lung volumes. It can be used in combination with simple spirometry to derive all lung volume compartments. The plethysmograph's primary advantage is that it measures all gas in the thorax, whether in ventilatory communication with the atmosphere or not.

4.2.1.1 Clinical Significance

Normative data for TGV and pulmonary subdivisions allow definition of restrictive lung disease as distinct from obstructive, in the presence of a reduced VC. Definition of abnormally increased lung volumes in obstructive lung disease is a further appropriate clinical use of whole-body plethysmography. While lung volumes can be measured by gas dilution techniques, it is well known that dilution techniques measure only the volume of ventilated airspaces. Accordingly, when whole-body plethysmography is combined with dilution measures of lung volumes, the volume of trapped gas is estimated by the difference between FRCBox and dilutional FRCGas.

The ratio of FRCBox/FRCGas can be used as an index of gas trapping. This ratio is usually near 1.0 in patients with normal lungs, or even with restriction.
Values greater than 1 indicate gas volumes detectable by the plethysmograph but hidden to the gas techniques. Care must be taken that lung volumes determined by the 2 methods are reliable before the values can be expressed as a ratio. This ratio has been used to evaluate candidates for lung volume reduction surgery (LVRS). Lung volume reduction attempts to directly reduce gas trapping by removal of unperfused lung tissue. Patients with bullous emphysema may have a litre or more difference in TLC (Total Lung Capacity) when the methods are compared.
Some evidence suggests that in severe airway obstruction, FRC may actually be overestimated when the plethysmographic technique is used. This occurs primarily because PMouth may not equal alveolar pressure if the airways are severely obstructed. Rapid panting rates aggravate this inaccuracy.

4.2.2 RAW

Airway resistance (Raw) is the pressure difference per unit flow as gas flows into or out of the lungs. Raw is the difference between mouth pressure and alveolar pressure, divided by flow at the mouth. This pressure difference is caused primarily by the friction of gas molecules in contact with the airways.

4.2.2.1 Clinical Significance

The tracing labelled “(a)” displays a schematic sRaw loop in a normal patient during tidal breathing, which is shown after numerical software compensations to close the sRaw loop. Normal patients manifest a steep linear loop during tidal breathing without hysteresis. In contrast, during voluntary panting efforts, the upper and lower end portions of the loop may become slightly curvilinear.
The curvilinearity is in the form of a very slight "S" shape, analogous to that shown in tracing “(d)”, but much less exaggerated. In normal patients during voluntary panting, the flattening of the sRaw loop at the upper right extremity (mid-inspiration) and at the lower left extremity (mid-expiration) of the loop are only barely visible, depending on the absolute value of flow rates achieved.
Tracing “(b)” is typical of patients with large (central) airway constriction that is relatively uniform (and not a localized stenosis) and without significant small airway obstruction. This might be seen in a patient with mild asthma.
It is well known that expiratory flow limitation and dynamic airway compression may occur during tidal breathing in COPD, and this contributes to the characteristic shape of the sRaw loop in tracing “(c)”.
Tracing “(d)” shows the influence of a fixed or functional stenosis of the upper airways, for example laryngeal abnormality, or paralysis of one vocal cord. This type of "orifice" constriction manifests flow limitation during inspiration, such that, at sufficiently high flows, further increases in driving pressure do not result in any increase in airflow. This reflects localized upper airway obstruction, analogous to that which pertains in the maximal expiratory flow–volume curve. Thus, during forced expiration, when a critical driving pressure for expiratory airflow (intra-pleural pressure for forced expiration) is achieved, further increases in driving pressure do not cause any further increases in flow rate. A similar flow limitation may occur in the extra-thoracic airway during inspiration, as shown in the upper right portion of tracing “(d)”.

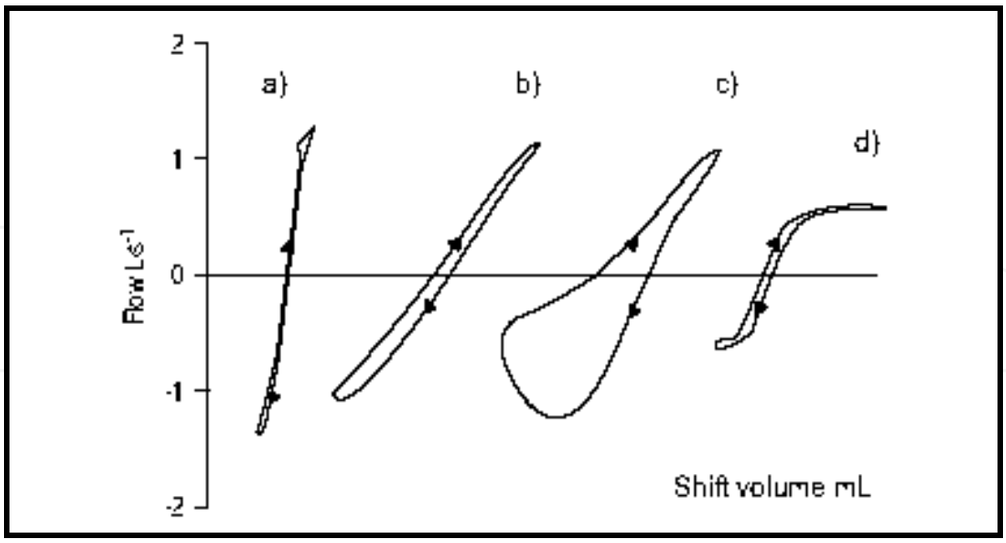


Fig. 2. A schematic presentation of the flow / volume shift measuring Raw

5. Functional Residual Capacity (FRC)

The FRC is the volume of air left in the lungs at the end of a quiet exhalation. There are 2 methods of measuring FRC which are (1) helium dilution and (2) the Nitrogen washout technique.

5.1 Helium dilution

The method for measuring lung volumes is based on the equilibration of gas in the lung with a known volume of gas containing helium. The test gas consists of air with added oxygen of 25–30%, but higher concentrations are acceptable.

5.1.1 Measurement technique (ATS / ERS, 2005)

Specific details of procedures will vary with different types of equipment and degrees of automation, but the basic procedure is as follows.

1. The equipment should be turned on and allowed an adequate warm-up time.
2. The equipment should be set up for testing, including calibration, according to manufacturer's instructions.
3. The patient should be asked if he/she has a perforated eardrum (if so, an earplug should be used).
4. 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.
5. 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.
6. The patient is turned ''in'' (i.e. connected to the test gas) at the end of a normal tidal expiration.
7. The patient is instructed to breathe regular tidal breaths.
8. The O_2 oxygen 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).

9. The helium concentration is noted every 15 s.
10. 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 [9].
11. 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 (fig. 5).
12. At least one technically satisfactory measurement should be obtained. Due to the extra costs and time in making multiple measurements, and the relatively good inter-day variability in adults, two or more measurements of FRCHe need to be made only when necessitated by clinical or research need . If only one measurement of FRCHe is made, caution should be used in the interpretation. For younger children, however, it is recommended that at least two technically satisfactory measurements be performed. If more than one measurement of FRCHe is carried out, the value reported for FRCHe should be the mean of technically acceptable results that agree within 10%.

5.2 Nitrogen washout technique (ATS / ERS, 2005)

This technique is based on washing out the N_2 from the lungs, while the patient breathes 100% O_2. The initial alveolar N_2 concentration and the amount of N_2 washed out can then be used to calculate the lung volume at the start of washout. The technique originally utilized gas collections for a 7-min period, a period deemed adequate for washout of N_2 from the lungs of healthy subjects. The measurement technique should adhere to the following steps:

1. The equipment should be turned on and allowed an adequate warm-up time, with calibration as instructed by the manufacturer.
2. The patient should be asked if he/she has a perforated eardrum (if so, an earplug should be used).
3. The patient is seated comfortably, with no need to remove dentures. The procedure is explained, emphasizing the need to avoid leaks around the mouthpiece during the washout and using a nose clip.
4. 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.
5. 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.
6. 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.
7. The washout is considered to be complete when the N_2 concentration is, 1.5% for at least three successive breaths.
8. At least one technically satisfactory measurement should be obtained. If additional washouts are performed, a waiting period of ≥ 15 min is recommended between trials. In patients with severe obstructive or bullous disease, the time between trials should be ≥ 1 h, if more than one measurement of $FRCN_2$ is made, the value reported for $FRCN_2$ should be the mean of technically acceptable results that agree within 10%. If only one measurement of $FRCN_2$ is made, caution should be used in the interpretation.

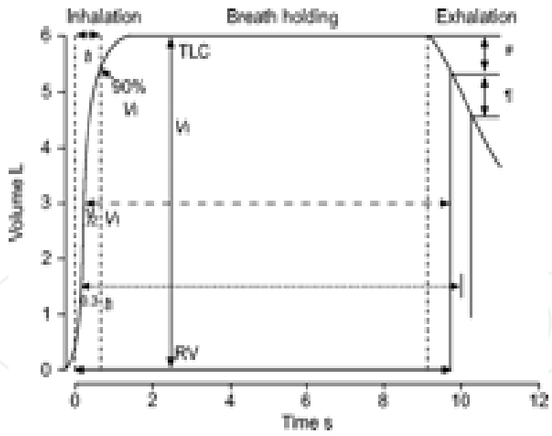


Fig. 3. A schematic presentation of the single breath DLCO manoeuvre

6. Diffusing capacity (DLCO)

6.1 Definition

DLCO measures the transfer of a diffusion-limited gas (CO) across the alveoli capillary membranes. DLCO is reported in millilitres of CO/minute/ml of Mercury at STPD.

6.2 Technique

CO combines with Haemoglobin (Hb) approximately 210 times more readily than O_2. In the presence of normal amounts of Hb and normal ventilator function, the primary limiting factor to diffusion of CO is the status of alveolocapillary membranes.

Diffusing capacity can be affected by factors that change the membrane component, as well as by alterations in Hb and in the capillary blood volume. DLCO is used to assess the gas exchange ability of the lungs, specifically oxygenation of mixed venous blood.

DLCO is used to evaluate pulmonary involvement in systemic diseases such as rheumatoid arthritis. DLCO measurements are often included in the evaluation of patients with obstructive lung disease such as emphysema.

DLCO may be indicated to monitor changes in lung function induced by drugs used to treat cardiac arrhythmias as well as changes caused by chemo and radiation therapy for lung cancer.

Indications for DLCO
a. Evaluate or follow the progress of parenchymal lung diseases
b. Evaluate pulmonary involvement in systemic diseases
c. Evaluate obstructive lung disease - Follow progression of disease - Differentiate types of obstruction - Predict arterial desaturation during exercise in COPD
d. Evaluate cardiovascular diseases
e. Quantify disability associated with interstitial lung disease
f. Evaluate pulmonary haemorrhage, polycythemia, or left to right shunts (Increased DLCO)

Table 4. A list of DLCO indications (Ruppel, 2009)

The most commonly used method is the single-breath or breath-hold technique. The single-breath method is also the most widely standardized.

6.3 Significance and pathophysiology

The expected DLCO value in a healthy patient varies directly with the patient's lung volume. Women have slightly lower normal values, presumably because of smaller normal lung volumes. DLCO values can increase 2-3 times in healthy individuals during exercise in response to increased pulmonary capillary blood flow.

DLCO is often decreased in restrictive lung diseases, particularly those associated with pulmonary fibrosis. Fibrotic changes in the lung parenchyma are associated with asbestosis, berylliosis, and silicosis. Idiopathic pulmonary fibrosis, sarcoidosis, SLE, scleroderma are associated with a decreased DLCO. Inhalation of toxic gases causes alveolitis and a decrease in DLCO values.

A decrease in DLCO is more likely to be related to the loss of lung volume, alveolar surface area, or capillary bed than to thickening of the alveolocapillary membrane. DLCO also decrease when there is a loss of lung tissue or replacement of normal parenchyma by space occupying lesions such as tumours. DLCO may also be reduced in the presence of pulmonary oedema.

Low resting DLCO (less than 50-60 % of predicted) may indicate the need for assessment of oxygenation during exercise. DLCO is directly related to lung volume (V_A) in healthy individuals. DL / V_A relationship can be useful to differentiate whether decreased DLCO is the result of loss of lung volume or from some other causes.

In obstruction, low DLCO without reduction in V_A results in a low ratio. In a purely restrictive process, a decrease in DLCO reflects loss of V_A and the DL / V_A ratio is preserved.

Numerous other physiologic factors can influence the observed DLCO:

- Hb and Hct, COHb
- Alveolar P_{CO2}
- Pulmonary capillary blood volume
- Body position
- Altitude above sea level
- Asthma and obesity

6.4 Interpretive strategies (Ruppel, 2009)

- If DLCO is less than the lower limit of normal (LLN) after appropriate corrections, it's likely that a gas exchange abnormality exists. Evaluate DL / V_A
- If DL / V_A ratio is normal, reduced diffusing capacity is likely related to decreased lung volumes, parenchymal changes, pulmonary vascular disease or pulmonary hypertension. Consider clinical correlation.
- If DL / V_A ratio is decreased, reduced diffusing capacity is likely related to airway obstruction or increased dead space. Compare V_A and TLC; a large difference suggests uneven distribution of ventilation.
- If DLCO is increased after correction of Hb or altitude, consider possible causes of increased pulmonary blood volume, haemorrhage, obesity of left-to-right shunts. Also consider undiagnosed asthma.
- If DLCO is less than 50% of predicted, consider additional tests such as blood gases, exercise desaturation study.

7. Blood gases

Blood gas is the most basic test of lung function. Blood gas analysis is often done in conjunction with pulmonary function studies. Blood is drawn from a peripheral artery without being exposed to air (anaerobically). Blood gas analysis includes measurement of ph, pCO_2, and pO_2.

The same specimen may be used for blood oximetry to measure total Hb, oxyhaemoglobin (O_2Hb), carboxyhaemoglobin (COHb) and methaemoglobin (MetHb). Blood gas is the ideal measurement of pulmonary function because is assesses the two primary functions of the lung – oxygenation and carbon dioxide removal.

7.1 Indications

1. Evaluate adequacy of lung function
2. Determine the need for supplementary oxygen
3. Monitoring of ventilation
4. Document the severity of progression of known pulmonary disease
5. Provide data to correct or corroborate other pulmonary function measurements.

7.2 3 Most important variables in a blood gas result:

1. pH (7.35 – 7.45)
2. pCO_2 (4.67 – 6.00 kPa)
3. pO_2 (10.00 – 13.33 kPa)

7.3 Significance and pathophysiology

pH < 7.35 = Acidemia

pH > 7.45 = Alkalemia

Acid-base disorders arising from lung disease are often related to P_{CO2} and its transport as carbonic acid.

- Acid-base disorders -

	pH	*pCO_2*	*pO_2*
Metabolic acidosis	↓	*N*	↓
Metabolic alkalosis	↑	*N*	↑
Respiratory acidosis	↓	↑	*N*
Respiratory alkalosis	↑	↓	*N*
Compensatory Respiratory acidosis and metabolic alkalosis	*N*	↑	↑
Compensatory Metabolic acidosis and respiratory alkalosis	*N*	↓	↓
Combined Metabolic and Respiratory acidosis	↓	↑	↓
Combined Metabolic and Respiratory alkalosis	↑	↓	↑

Table 5. Three helpful parameters in interpreting a blood-gas result (in the simple uncompensated state- Ruppel, 2009)

pO_2 is the pressure of O_2 dissolved in blood. The amount of Hb and whether it is capable of binding O_2 has only a minimal effect on pO_2. Hypoxemia commonly results from inadequate or abnormal Hb. The severity of impaired oxygenation is indicated by the PaO_2 at rest. PaO_2 is a good index of the lungs 'ability to match pulmonary capillary blood flow with adequate ventilation.

Delivery of O_2 to the tissues however depends on Hb concentration and cardiac output as well as adequate gas transfer in the lungs. Because most O_2 transported is bound to Hb, there must be an adequate supply (12-15 g/dl) of functional Hb.

8. Pulse oximetry

SpO_2 estimates SaO_2 by analyzing absorption of light passing through a capillary bed, either by transmission or reflectance. Pulse oximetry is non-invasive.

8.1 Interfering factors

Motion artefact, shivering, bright ambient lightning, hypotension, low perfusion, hypothermia, vasoconstrictor drugs and dark skin pigmentation can confound.

8.2 Significance and pathophysiology

Most pulse oximeters are capable of accuracy of +/- 2% of actual saturation when SaO_2 is above 90%. Other uses of pulse oximetry are:

- Monitoring of O_2 therapy
- Ventilatory support
- Pulmonary / Cardiac rehabilitation
- Bronchoscopy
- Surgical procedures
- Sleep studies
- Cardiopulmonary exercise testing

Pulse oximetry may not be appropriate in all situations e.g. to evaluate hyperoxemia or acid-base status in a patient, a blood gas analysis is required. Measurement of O_2 delivery, which depends on Hb concentration, cannot be adequately assessed by pulse oximetry.

9. Six minute walk test (6MWT)

This is a simple exercise test used to assess the response to a medical or surgical intervention, but also been used to assess functional capacity as well as to estimate morbidity and mortality. This test doesn't require any sophisticated equipment.

INDICATIONS FOR THE SIX-MINUTE WALK TEST
Pre-treatment and post treatment comparisons
Lung transplantation / Resection
Lung volume reduction surgery
Pulmonary rehabilitation
COPD
Pulmonary hypertension
Heart failure
Cystic fibrosis
Heart failure
Peripheral vascular disease
Predictor of morbidity and mortality

Table 6. A list of indications for a six minute walk test (Ruppel, 2009)

Contraindications
Unstable angina during the previous month
Infarction during the previous month
A resting heart rate of more than 120,
Systolic blood pressure of more than 180 mm Hg,
Diastolic blood pressure of more than 100 mm Hg.

Table 7. A list of the contraindications of a six minute walk test (Ruppel, 2009)

Reasons for immediately stopping a 6MWT include the following:
1. chest pain,
2. intolerable dyspnoea,
3. leg cramps
4. staggering
5. diaphoresis
6. pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope.The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

9.1 Equipment required

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

9.2 Measurements (ATS / ERS 2002)

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation and follow manufacturer's instructions to maximize the signal and to minimize motion artefact. Make sure the readings are stable before recording.

Note pulse regularity and whether the oximeter signal quality is acceptable. The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked. The SpO_2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO_2.

If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected.

5. Have the patient stand and rate their baseline dyspnoea and overall fatigue using the Borg scale
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:
   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation." Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly. "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now or whenever you are ready."

THE BORG SCALE
0 Nothing at all
0.5 Very, very slight (just noticeable)
1 Very slight
2 Slight (light)
3 Moderate
4 Somewhat severe
5 Severe (heavy)
6
7 Very severe
8
9
10 Very, very severe (maximal)

Table 8. The Borg scale

At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale." At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it.
10. Post-test: Record the post walk Borg dyspnoea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

9.3 Interpretation

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent. It is not known whether it is best for clinical purposes to express change in 6MWD as

1. An absolute value,
2. A percentage change, or
3. A change in the percentage of predicted value.

Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

10. Stair climbing

In a setting where corridor length is limited, but a few flights of stairs are available, the stair climb is an ideal test as a primary screening test to decide if a patient can undergo thoracic surgery or needs additional testing e.g. Cardio Pulmonary Exercise Testing.

The stair climb as a test is easy to perform and easy to understand by patients as well as being safe. Minimal equipment and personnel is required. To do the test one instructs the patient to climb the flights of stairs at their fastest pace to a minimum ascent of +/- 20 metre. This climb is timed so as to calculate the speed of ascent, which correlates well with VO_2max measured during cycle ergometry. It was shown that climbing at a speed of ascent of

≥15m/min to an elevation of 20 metres accurately predicted a VO_2max ≥ 20ml/kg/min. (Koegeleneberg, 2009)

11. Cardiopulmonary Exercise Testing (CPET)

Cardiopulmonary exercise testing is used to define work limitations. Cardiopulmonary variables are assessed in relation to the workload. The patterns of change in any particular variable are then compared with the expected normal response. The primary indications for performing this test are dyspnoea and exertion, pain (especially angina) and fatigue. Exercise induces airway narrowing in the majority of patients with asthma. Exercise-induced airway narrowing is called exercise- induced asthma (EIA) and exercise-induced bronchoconstriction (EIB).

Other indications include:

- Evaluation of exercise intolerance of level of fitness
- Exercise evaluation for cardiac or pulmonary rehabilitation
- Assess pre-operative risk, particularly lung resection or reduction.
- Assess disability, particularly related to occupational lung disease
- Evaluate therapeutic interventions such as heart or lung transplantation.

Exercise testing can detect the following:

- Presence and nature of ventilator limitation to work
- Presence and nature of cardiovascular limitations to work
- Extent of conditioning or de-conditioning
- Maximal tolerable workload and safe levels of daily exercise
- Extent of disability for rehabilitation purposes
- O_2 desaturation and appropriate levels of supplemental O2 therapy
- Outcome measurement after a treatment plan.

The preferred modes of exercise are the motor-driven treadmill with adjustable speed and grade or the electromagnetically braked cycle ergometer. Heart rate should be monitored from a three-lead electrocardiographic configuration as a minimum.

Alternatively, a pulse oximeter or other device able to reliably determine heart rate may be used. For those at higher risk for coronary artery disease, a 12- lead ECG configuration is advisable.

11.1 Treadmill protocol (ATS / ERS 1999)

The treadmill speed and gradient are chosen to produce 4–6 min of exercise at near-maximum targets with a total duration of exercise of 6–8 min. For children less than 12 yr of age, the time is usually 6 min; for older children and adults the time is usually 8 min. starting at a low speed and gradient, both are progressively advanced during the first 2–3 min of exercise until the heart rate is 80–90% of the predicted maximum. Ventilation rather than heart rate can be used to monitor exercise intensity. Ventilation should reach 40–60% of the predicted maximum voluntary ventilation (MVV, estimated as FEV1 x 35). The degree of physical fitness and body weight will strongly influence the grade and speed necessary to obtain the desired heart rate. A reasonable procedure is to quickly advance to a rapid, but comfortable, speed and then raise the treadmill slope until the desired heart rate or ventilation is obtained.

For older children and adults 8 min of exercise is usually required to elicit EIB when dry air temperature is inhaled. A treadmill speed greater than 3 mph (about 4.5 km/h) and a gradient greater than 15% or an oxygen consumption of 35 ml/min/kg or greater will usually achieve the target ventilation or heart rate in young healthy subjects. Nomograms have been proposed to predict speed and grade that will elicit the desired heart rate, but they have not been extensively validated. It may be preferable to use nomograms relating oxygen consumption per kilogram to speed and slope of the treadmill.
The test ends when the patient has exercised at the target ventilation or heart rate for at least 4 min. This usually requires a total of 6–8 min of exercise. The test may be terminated by the patient at any time.

11.1.1 Assessing the response

Forced expiratory volume in 1 s (FEV_1) is the primary outcome variable. Spirometry should be performed and evaluated as described earlier. One exception to ATS-recommended techniques for spirometry is allowed. If the only outcome variable to be used is the FEV_1, the duration of the expiration may be limited to 2–3 s. In all cases it is important to vigorously coach the patient to inhale fully even in the presence of chest tightness. Incomplete inhalations will result in false reductions in FEV_1.
If vocal cord dysfunction or other possible causes of central airway obstruction are suspected, full inspiratory and expiratory flow–volume loops should be obtained.
An appropriate post-exercise testing schedule is 5, 10, 15, 20, and 30 min after cessation of exercise. Some investigators include earlier measurements (1 and 3 min post-exercise) because severe EIB can sometimes be present at the cessation of exercise. Early recognition allows it to be dealt with promptly. If the FEV_1 has returned from its nadir to the baseline level or greater, spirometry testing may be terminated at 20 min post exercise. A β-agonist bronchodilator may be administered at any time to reverse the bronchoconstrictive response if the patient experiences appreciable dyspnoea, or if the FEV_1 has not recovered to within 10% of baseline when the patient is ready to leave the laboratory.
The presence of exercise-induced bronchoconstriction is defined by plotting FEV_1 as a percentage of the pre-exercise baseline FEV_1 at each post-exercise interval.
A decrease below 90% of the baseline FEV_1 (i.e., a 10% decrease) is a generally accepted abnormal response. Some authors suggest a value of 15% is more diagnostic of EIB, particularly if exercise has been performed in the field.

12. Bronchial provocation testing

Bronchial challenge testing is used to identify and characterize airway hyper-responsiveness. Challenge test may be performed in patients with symptoms of bronchospasm who have normal pulmonary function studies or uncertain results of bronchodilator studies. It can also be used to assess changes in hyper-reactivity of the airways or to quantify its severity.
Several commonly used provocative agents can be used to assess airway hyper reactivity. These include the following:

- Methacoloine challenge (increase parasympathetic tone in bronchial smooth muscle)
- Histamine challenge (trigger response producing bronchoconstriction)

- Exercise

FEV_1 is the variable most commonly used, although airway resistance and specific conductance can also be measured before and after testing.

12.1 Dosing protocols (ATS /ERS 1999)

1. Two-minute tidal breathing dosing protocol.
2. Five-breath dosimeter protocol.
   a. Set up and check the dosimeter.
   b. Prepare the following five concentrations of methacholine in sterile vials; place them in a holder; and store them in a refrigerator.
   c. Remove the vials from the refrigerator 30 min before testing, so that the contents warm to room temperature before use. Insert 2.0 ml of the first concentration into the nebulizer, using a sterile syringe. The patient is seated throughout the test.
   d. Perform baseline spirometry.
   e. Briefly open the dosimeter solenoid to make sure the nebulizer is nebulising.
   f. Ask the patient to hold the nebulizer upright with the mouthpiece in his/her mouth. Watch the patient during the breathing manoeuvres to ensure that the inhalation and breath hold are correct and that the nebulizer is not tipped.
   g. At end exhalation during tidal breathing (functional residual capacity), instruct the patient to inhale slowly and deeply from the nebulizer. Trigger the dosimeter soon after the inhalation begins; dosimeters may do this automatically. Encourage the patient to continue inhaling slowly (about 5 s to complete the inhalation) and to hold the breath (at total lung capacity, TLC) for another 5 s.
   h. Repeat step g for a total of five inspiratory capacity inhalations. Take no more than a total of 2 min to perform these five inhalations.
   i. Measure the FEV_1 at about 30 and 90 s after the fifth inhalation from the nebulizer. Obtain an acceptable-quality FEV_1 at each time point. This may require repeated attempts. Perform no more than three or four manoeuvres after each dose. It should take no more than 3 min to perform these manoeuvres. To keep the cumulative effect of methacholine relatively constant, the time interval between the commencements of two subsequent concentrations should be kept to 5 min.
   j. At each dose, report the highest FEV_1 from acceptable manoeuvres.
   k. If the FEV_1 falls less than 20%, empty the nebulizer, shake it dry, and trigger the dosimeter once to dry the nebulizer nozzle. Add 2.0 ml of the next higher concentration, and repeat steps g–j.
   l. If the FEV_1 falls more than 20% from baseline (or the highest concentration has been given), give no further methacholine, note signs and symptoms, administer inhaled albuterol, wait 10 min, and repeat the spirometry.

12.2 Interpretive strategies

1. Were there any factors present that could influence the result e.g. failure to withhold bronchodilators ?
2. Respiratory infection? If so interpret cautiously or not at all.
3. Were spirometric efforts repeatable and acceptable before and during the challenge? If not, interpret very cautiously or not at all.

4. For Metacholine or histamine challenge was there a 20% decrease after inhalant of dilatants. Is so, test result is positive.
5. Was there a 20% decrease of FEV1 after inhalation of agonist? If so, test result is likely positive and PC_{20} should be used to categorize the degree of hyper responsiveness.
6. Was there at least 35% decrease in SGaw (Preferably 50%)? If so, test result is likely positive
7. Were there signs of airway hyper reactivity (coughing, wheezing or shortness of breath)? If so, test suggests bronchial hyper responsiveness
8. Were the results borderline? If so, repeat the test.
9. Were symptoms present despite little or no change in FEV_1?
10. Consider additional measurements such as SGaw or related conditions such as vocal cord dysfunction.

13. Conclusion

There are a variety of tests, both simple and sophisticated, that allow greater insights into respiratory disease, functional impairment and suitability for operative intervention. Some of the tests are more complicated to perform and both improvement and deterioration in respiratory status can be subtle. For these reasons strict quality control, in terms of appropriately validated equipment, standardisation and trained and experienced personnel are mandatory. To ensure excellent quality results good patient co-operation is required as well. Disregard for these precautions can lead to diagnostic confusion, misclassification of improvement and deterioration or unnecessary further interventions. These can be costly and also result in needless morbidity and mortality. Thus a full understanding of the tests, their appropriateness and pitfalls can complement patient evaluation and result in greater diagnostic certainty and patient management.

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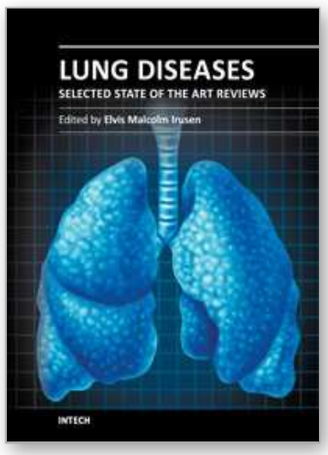

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The developments in molecular medicine are transforming respiratory medicine. Leading clinicians and scientists in the world have brought their knowledge and experience in their contributions to this book. Clinicians and researchers will learn about the most recent advances in a variety of lung diseases that will better enable them to understand respiratory disorders. This treatise presents state of the art essays on airways disease, neoplastic diseases, and pediatric respiratory conditions. Additionally, aspects of immune regulation, respiratory infections, acute lung injury/ARDS, pulmonary edema, functional evaluation in respiratory disorders, and a variety of other conditions are also discussed. The book will be invaluable to clinicians who keep up with the current concepts, improve their diagnostic skills, and understand potential new therapeutic applications in lung diseases, while scientists can contemplate a plethora of new research avenues for exploration.

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