

Smith Seminars
Online Continuing Education
AARC-Approved for 2 CRCE
Pulmonary Function

Objectives

- Understand the purpose and procedures of spirometry
- Recognize obstructive and restrictive lung assessments
- Know the procedure and normal values of carbon monoxide diffusing capacity
- Learn respiratory muscle strength assessment procedures and values
- Have a good understanding of the methacholine challenge testing
- Learn the indications for exhaled nitric oxide measurements

Spirometry

Spirometry assesses the mechanical function of the lung, chest wall, and respiratory muscles by measuring the total volume of air exhaled from total lung capacity (TLC) to the residual volume (RV). This volume, the forced vital capacity (FVC) and the forced expiratory volume in the first second of the forceful exhalation (FEV1) should be repeatable to within 0.15 L upon repeat efforts unless the largest value for either parameter is less than 1 L. Then the expected repeatability is to within 0.1 L of the largest value. The patient is instructed to inhale as much as possible and then exhale rapidly and forcefully for as long as flow can be maintained.

Reduction in the amount of air exhaled forcefully in the first second of the forced exhalation (FEV1) may reflect reduction in the maximum inflation of the lungs (TLC), obstruction of the airways, or respiratory muscle weakness. Airway obstruction is the most common cause of reduction in FEV1. Airflow obstruction may be secondary to bronchospasm, airway inflammation, loss of lung elastic recoil, increased secretions in the airway, or any combination of these causes. Response of FEV1 to inhaled bronchodilators is used to assess the reversibility of airway obstruction.

Spirometry is used to establish baseline lung function, evaluate dyspnea, detect pulmonary disease, monitor effects of therapies used to treat respiratory disease, evaluate respiratory impairment, evaluate operative risk, and examination for occupational-related lung disease.

Relative contraindications for spirometry include hemoptysis of unknown origin, pneumothorax, unstable angina pectoris, recent myocardial infarction, thoracic aneurysms, abdominal aneurysms, cerebral aneurysms, recent eye surgery, recent abdominal or thoracic surgical procedures, and patients with a history of syncope associated with forced exhalation.

Two choices are available with respect to bronchodilator and medication use prior to testing. Patients may withhold oral and inhaled bronchodilators to establish baseline lung function and evaluate maximum bronchodilator response, or they may

continue taking medication as prescribed. If medications are withheld, a risk of exacerbation of bronchial spasm exists.

Interpretation of spirometry results should begin with an assessment of test quality. Failure to meet performance standards can result in unreliable test results. The American Thoracic Society (ATS) defines acceptable spirometry as an expiratory effort that shows minimal hesitation at the start of the forced expiration (extrapolated volume (EV) \leq 5% of the FVC or 0.15 L, whichever is larger); no cough in the first second of forced exhalation; and meets 1 of 3 criteria that define a valid end-of-test: (1) smooth curvilinear rise of the volume-time tracing to a plateau of at least 1-second duration; (2) if a test fails to exhibit an expiratory plateau, a forced expiratory time (FET) of 15 seconds; or (3) when the patient cannot or should not continue forced exhalation for valid medical reasons.

In patients that have significant loss of lung elastic recoil (pulmonary emphysema), spirometry may show negative effort dependence of forced expiratory flow. The effort that has the highest peak expiratory effort may produce a lower FEV1 because of dynamic compression of the larger airways. In this situation, the effort with the highest FEV1 produced by a submaximal effort should not be reported. Although not yet a standard, it appears that selecting only efforts that have a time to peak flow (TPEF) \leq 0.12 seconds helps eliminate this effect.

The 2 largest values for FVC and the 2 largest values for FEV1 in the same testing session should vary by no more than 0.15 L (0.1 L if the largest value is $<$ 1 L). A recent study has shown start-of-test problems (affecting FEV1 measurements) to be relatively uncommon (2% prevalence in one series) and end-of-test problems (affecting FVC quality) being very common (61-84% prevalence). Allowing the patient to relax and push gently after 3-4 seconds of forced exhalation has been shown to greatly enhance the ability of patients with airflow obstruction to satisfy end-of-test criteria.

Inspection of the volume-time tracing aids in identification of early termination of expiration by evaluating the presence of an expiratory plateau. In the absence of an expiratory plateau, a 12- to 15-second expiratory time ensures the quality of the FVC. Inspection of the start of the volume-time tracing can identify a hesitant start, which can result in a falsely low FEV1. Reproducibility of the FVC and the FEV1 helps ensure that the results truly represent the patient's lung function. Attention should be focused on 3 key parameters: FVC, FEV1, and the FEV1/FVC ratio.

Obstructive

Disproportionate reduction in the FEV1 as compared to the FVC (and therefore the FEV1/FVC ratio) is the hallmark of obstructive lung diseases. This physiologic category of lung diseases includes but is not limited to asthma, acute and chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, pneumonia, alpha1-antitrypsin deficiency, and bronchiolitis. The expiratory flow at any given expiratory volume is

reduced. The mechanism responsible for the reduction in airflow can be bronchial spasm, airway inflammation, increased intraluminal secretions, and/or reduction in parenchymal support of the airways due to loss of lung elastic recoil.

When airway obstruction is identified on spirometry, assessing response to inhaled bronchodilators is useful. The ATS has recommended that the threshold for significant response be demonstration of an increase of at least 12% and 0.2 L in either FVC or FEV1 on a spirogram performed 10-15 minutes after inhalation of a therapeutic dose of a bronchodilator. New standards recommend the use of 4 inhalations (100 mcg each, 400 mcg total dose) of albuterol administered through a valved spacer device. When concern about tremor or heart rate exists, lower doses may be used. Response to an anticholinergic drug may be assessed 30 minutes after 4 inhalations (40 mcg each, 160 mcg total dose) of ipratropium bromide. Failure to respond to bronchodilator challenge does not preclude clinical benefit from bronchodilators. A positive response to the bronchodilators may correlate with response to steroid therapy.

Restrictive

Reduction in the FVC with a normal or elevated FEV1/FVC ratio should trigger further diagnostic workup to rule out restrictive lung disease. Because the FEV1 is a fraction of the FVC, it also is reduced, but the FEV1/FVC ratio is preserved at a normal or elevated level. Measuring the TLC and residual volume (RV) can confirm restriction suggested by spirometry.

Measurement by Spirometry

In normal spirometry, FVC, FEV1, and FEV1/FVC ratio are above the lower limit of normal. The lower limit of normal is defined as the result of the mean predicted value (based on the patient's sex, age, and height) minus 1.64 times the standard error of the estimate from the population study on which the reference equation is based. If the lower limit of normal is not available, the FVC and FEV1 should be greater than or equal to 80% of predicted, and the FEV1/FVC ratio should be no more than 8-9 absolute percentage points below the predicted ratio. The ATS has recommended the use of lower limits of normal instead of the 80% of predicted for setting the threshold that defines abnormal test results.

A reduced FVC on spirometry in the absence of a reduced FEV1/FVC ratio suggests a restrictive ventilatory problem. An inappropriately shortened exhalation during spirometry can result in a reduced FVC. Causes of restriction on spirometry include obesity, cardiomegaly, ascites, pregnancy, pleural effusion, pleural tumors, kyphoscoliosis, pulmonary fibrosis, neuromuscular disease, diaphragm weakness or paralysis, space-occupying lesions, lung resection, congestive heart failure, inadequate inspiration or expiration secondary to pain, and severe obstructive lung disease. The severity of reductions in the FVC and/or the FEV1 can be characterized by: Mild: 70-

79% of predicted; moderate: 60-69% of predicted; moderately severe; 50-59%; severe - 35-49% of predicted; Very severe: Less than 35% of predicted.

Small airway obstruction may be present even when the FEV1/FVC is above the lower limit of normal. The mid-flow rate or forced expiratory flow occurring in the middle 50% of the patient's exhaled volume (FEF25-75%) may fall below its lower limit of normal even when the FVC, FEV1, and FEV1/FVC are all normal.

The lower limit of normal for the FEF25-75% can be less than 50% of the mean predicted value, making it important to use the lower limit of normal defined by the 95% confidence limit of the mean predicted value rather than a threshold defined by a fixed percentage of the predicted value. The FEF25-75% is also very dependent on expiratory time. If expiratory times of spirometry efforts vary by more than 10%, comparisons of the FEF25-75% before and after bronchodilator challenge are difficult to interpret. Early termination of expiration shifts the middle 50% of the exhaled volume toward the start of the exhalation, showing a raised FEF25-75%.

Other Assessments

Evaluation of diaphragm strength can be accomplished by measuring the vital capacity in an upright or sitting position followed by a measurement made in the supine position. A reduction in the vital capacity to less than 90% of the upright vital capacity suggests diaphragm weakness or paralysis. Interpreting an increased reduction in vital capacity in the supine position as diaphragm dysfunction should be made cautiously if the patient is obese with a body mass index (BMI) greater than 45 kg/m². Studies reporting the normal reduction of the vital capacity of less than 10% from upright to supine were conducted with individuals who were not obese. Slightly greater reductions in obese individuals in a supine position may not indicate diaphragm dysfunction, but rather an increase in the resistance to diaphragm function.

The configuration of the flow-volume curve of a properly performed spirometry test can be used to demonstrate various abnormalities of the larger central airways (larynx, trachea, right and left mainstem bronchi). Three patterns of flow-volume abnormalities can be detected: (1) variable intrathoracic obstructions, (2) variable extrathoracic obstructions, and (3) fixed upper airway obstructions. Reproducing these findings on every effort is important because spurious non-reproducible reductions in inspiratory flow are not uncommon after completion of forced expirations in subjects without upper airway obstruction. Examples of variable intrathoracic obstruction include localized tumors of the lower trachea or mainstem bronchus, tracheomalacia, and airway changes associated with polychondritis.

Variable upper airway obstructions demonstrate flow reductions that vary with the phase of forced respirations. Variable intrathoracic obstructions demonstrate reduction of airflow during forced expirations with preservation of a normal inspiratory flow configuration. This is observed as a plateau across a broad volume range on the

expired flow limb of the flow-volume curve. The reduction in airflow results from a narrowing of the airway inside the thorax, in part because of a narrowing or collapse of the airway secondary to extraluminal pressures exceeding intraluminal pressures during expiration.

Variable extrathoracic obstructions demonstrate reduction of inspired flows during forced inspirations with preservation of expiratory flows. Again, the major cause of the reduced flow during inspiration is airway narrowing secondary to extraluminal pressures exceeding intraluminal pressures during inspiration. Causes of this type of upper airway obstruction include unilateral and bilateral vocal cord paralysis, vocal cord adhesions, vocal cord constriction, laryngeal edema, and upper airway narrowing associated with obstructive sleep apnea.

Fixed upper airway obstructions demonstrate plateaus of flow during both forced inspiration and forced expiration. Causes of fixed upper airway obstruction include goiters, endotracheal neoplasm, stenosis of both main bronchi, post-intubation stenosis, and performance of the test through a tracheostomy tube or other fixed orifice device.

Preoperative Assessment

While no single test can effectively predict intraoperative and postoperative morbidity and mortality from pulmonary complications, the FEV1 obtained from good quality spirometry is a useful tool. When the FEV1 is greater than 2 L or 50% of predicted, major complications are rare.

Operative risk is heavily dependent on the surgical site, with chest surgery having the highest risk for postoperative complications, followed by upper and lower abdominal sites. Patient-related factors associated with increased operative risk for pulmonary complications include preexisting pulmonary disease, cardiovascular disease, pulmonary hypertension, dyspnea upon exertion, heavy smoking history, respiratory infection, cough (particularly productive cough), advanced age (>70 years), malnutrition, general debilitation, obesity, and prolonged surgery.

Assessment for lung surgery typically involves prediction of a postoperative FEV1 by using the preoperative FEV1. In a borderline case, consideration of the contribution of the remaining portions can be assessed by a perfusion scan. The relative percentage of perfusion (Q) of the remaining lung or lung segments usually is proportional to its contribution to ventilation and can be used to estimate postoperative function as shown in the following equation: Postoperative FEV1 = Preoperative FEV1 X Q% of the remaining lung.

For example, if the preoperative FEV1 is 1.6 L and the lung to be resected demonstrates 40% perfusion, the postoperative FEV1 would be $1.6 \times 0.6 = 0.96$ L. An estimated postoperative FEV1 of less than 0.8 L often is associated with chronic respiratory failure and may indicate an unacceptable degree of operative risk. Arterial

blood gases (ABGs) and cardiopulmonary exercise testing may help evaluate operative risk in patients who have a preoperative FEV1 below 2 L or 50% of predicted.

Technical Considerations

The American Thoracic Society (ATS) has published guidelines for a standardized technique that includes spirometer performance standards. A reasonable end-point for the maneuver in the absence of true flow cessation, such as airway obstruction is present, is 15 seconds. Patients often discontinue the forced exhalation prematurely because of the discomfort of prolonged forced exhalation. A modified technique, the patient exhales with maximum force for 3 seconds followed by continued relaxed exhalation, has been shown to enhance the patient's ability to sustain expiration, thus yielding a larger FVC in patients with airflow obstruction.

Lung Volumes Determination

Lung volumes determinations are used in the evaluation of suspected restrictive lung disease and the evaluation of hyperinflation. Inability to follow instructions is a contraindication. Patients with claustrophobia may not tolerate being closed into a confined space (body plethysmograph).

Use of supplemental oxygen just prior to a nitrogen washout test may cause underestimation of FRC unless the initial exhaled nitrogen is considered in the calculations. Duplicate measurements of FRC by either gas dilution technique should be delayed until a post-test interval is equivalent to 1.5 times the equilibration time to eliminate the effects of residual oxygen or helium.

Lung volumes provide useful information that confirms the presence of restrictive lung disease suggested by a low vital capacity on a spirometry test. Hyperinflation, elevation of the RV and TLC can be demonstrated by this test. The test is dependent first on an accurate measurement of the volume of gas in the lungs at a resting end-expiration, known as the FRC, which represents the balance of the elastic recoil properties of the lung and the chest wall.

FRC can be measured by 1 of 3 techniques, inert gas dilution, nitrogen washout, or whole-body plethysmography. Both gas dilution techniques are subject to error by leak at the mouthpiece or nose clip or, occasionally, even small leaks from the eardrum. When measured by whole-body plethysmography, resting end-expiratory volume is known as the FRC_{pleth} and will include the volume of gas contained in non-communicating spaces such as blebs or bullae that the FRC measured by gas dilution techniques will not measure. Body plethysmography allows multiple determinations of lung volumes to be made rapidly.

When measured by inert gas dilution or nitrogen washout, premature termination of the procedure before adequate demonstration of equilibrium or washout results in underestimation of FRC, RV, and TLC. Repeat measurements should allow a recovery

period of 1.5-times the wash-in or wash-out time to prevent residual helium or oxygen from affecting the new measurement. Body plethysmography is performed rapidly, allowing multiple determinations in minutes. Ideally, each measurement of lung subdivisions should be linked to each FRC or intrathoracic gas volume (ITGV) measurement (patient should remain on the mouthpiece).

Two types of errors are known to occur with body plethysmography techniques. One involves the underestimation of mouth pressure swings during respiratory efforts when the airway is occluded. The assumption that when no airflow is present the mouth pressures accurately reflect alveolar pressure has been shown to be not true when respiratory efforts occur at a frequency of greater than 1 Hz (respiratory rate of 60 breaths per minute). FRCpleth is overestimated if the frequency of the respiratory effort is not kept between 0.5 and 1.0 Hz (30-60 breaths per minute) during shutter closure.

The second type of measurement error using body plethysmography involves trying to pace the patient's tidal breathing before shutter closure. The ideal respiratory rate during shutter closure is far in excess of the patient's resting respiratory rate and will cause dynamic hyperinflation when the shutter is open. Patients should breathe at a relaxed spontaneous respiratory rate without coaching before shutter closure.

Test Results

FRC or ITGV is expressed in liters. This is the volume of gas in the lungs at the end of an average resting expiration. It is comprised of the expiratory reserve volume (ERV), the volume of gas that can be voluntarily exhaled beyond the FRC or ITGV, and the RV. The TLC then can be calculated by adding the RV to the vital capacity (VC). RV also is expressed as a fraction of the TLC, the RV/TLC ratio. The expected repeatability of 3 repeated same-session measurements of FRC is $\pm 5\%$. The standards for expected repeatability of other parameters (RV, IC, TLC) have not been set, but the expected repeatability of the VC is the same as FVC, ≤ 0.15 L difference between the 2 largest.

Interpretation

Obstructive lung diseases, particularly emphysema, result in an increase in the RV and RV/TLC ratio. In severe emphysema, particularly bullous emphysema, the TLC can show a marked increase. Bronchial spasm, airway inflammation, excessive secretions in the airway, and loss of lung elastic recoil increase airways resistance. This results in an insidious progressive increase in the end-expiratory lung volume that results in chronic hyperinflation (elevated RV, TLC, and RV/TLC ratio). Other pulmonary causes of increased RV include pulmonary vascular congestion and mitral stenosis. Extra-pulmonary causes of increased RV include expiratory muscle weakness as observed in spinal cord injuries and myopathies.

A reduced TLC is the hallmark of restrictive lung disease. An isolated reduction of the residual volume may be an early sign of restrictive lung disease. Pulmonary processes that can reduce the TLC include interstitial lung disease, atelectasis, pneumothorax, pneumonectomy, consolidation, edema, and fibrosis. Extra-pulmonary causes of restriction include obesity, respiratory muscle weakness, thoracic deformities, and disease of the pleura.

Diffusing Capacity of the Lung for Carbon Monoxide

Carbon monoxide diffusing capacity (DLCO) is the rate of uptake of carbon monoxide (CO) per driving pressure of alveolar CO. Carbon monoxide (CO) diffusing capacity (DLCO) provides an objective measurement of lung function. It is defined as the lung's ability to take up an inhaled nonreactive test gas, such as carbon monoxide (CO), which binds to hemoglobin. CO will bind to hemoglobin with such a high affinity; virtually all of the CO will reach the alveolar space. This will cause the carbon monoxide to cross the alveolar air-blood barrier, and thus reaching a red cell that will bind to hemoglobin, and will be removed with the exhaled gas.

Inability to follow instructions is a contraindication to a DLCO test. Patients should be alert, oriented, able to exhale completely and inhale to total lung capacity, able to maintain an airtight seal on a mouthpiece, and able to hold a large breath for 10 seconds.

Patient should refrain from smoking for several hours before the test. Alcohol vapors can affect the accuracy of some fuel cell types of CO analyzers, and alcoholic beverages should be withheld for 8 hours.

DLCO, also known as the transfer factor of the lung for CO (TLCO), is a measurement of the ease of transfer for CO molecules from alveolar gas to the hemoglobin of the red blood cells in the pulmonary circulation. It often is helpful for evaluating the presence of possible parenchymal lung disease when spirometry and/or lung volume determinations suggest a reduced vital capacity, RV, and/or TLC.

Most pulmonary laboratories in the United States perform this test by the single-breath technique (DLCO SB) because it is quicker to perform and more reproducible than other techniques. In the single-breath technique, the subject exhales to RV and then inspires the test gas (10% helium, 0.3% CO, 21% oxygen, and balance nitrogen) briskly to TLC. This vital capacity size breath is held for 10 seconds and then exhaled into a sample bag after an initial discard of 0.5-0.75 L to account for dead space.

The sample (0.5-1 L) then is analyzed for helium and CO. The helium dilution of the vital capacity breath of test gas by the patient's RV provides both a means to estimate the initial alveolar concentration of CO and to estimate the patient's TLC. The rate of diffusion of the CO can be estimated by the change from this initial alveolar level to that of the expired grab sample. This change in the CO concentration is then multiplied by the single-breath estimate of TLC to calculate the diffusing capacity.

Abnormal hemoglobin (Hb) levels can affect the diffusing capacity and, if known, should be used to mathematically correct the measured diffusing capacity to normal Hb.

Adjusted DLCO (adolescent males and men): Hb adjusted DLCO (DLCOc) = measured DLCO $([10.22 + \text{Hb g/dL}]/[1.7 \text{ Hb}])$. Hb adjusted DLCO (children <15 y and women): Hb adjusted DLCO (DLCOc) = measured DLCO $([9.38 + \text{Hb g/dL}]/[1.7 \text{ Hb}])$. The measured DLCO also can be adjusted for elevated levels of carboxyhemoglobin, as follows:

Carboxyhemoglobin-adjusted DLCO (DLCOc) = measured DLCO $(1 + [\% \text{CO Hb}/100])$.

The diffusing capacity is a measure of the conductance of the CO molecule from the alveolar gas to Hb in the pulmonary capillary blood. The transfer of the CO molecule is limited by both perfusion and diffusion. CO (and oxygen) must pass through the alveolar epithelium, tissue interstitium, capillary endothelium, blood plasma, and red cell membrane and cytoplasm before attaching to the Hb molecule.

Test Results

Reported parameters typically include the DLCO (mL/min/mm Hg) and the diffusing capacity of lung/alveolar volume (DL/VA), the average inspiratory vital capacity (IVC) of 2 reproducible measurements and the average calculated alveolar volume (VA), and Hb-corrected and carboxyhemoglobin-corrected values.

Interpretation

Because the DLCO is directly proportional to VA (the single-breath dilutional estimate of TLC), nonpulmonary processes that reduce the TLC cause reductions in the DLCO. If VA can be assessed accurately, these reductions produce a normal or elevated DL/VA ratio. Examples of this include lung resection, thoracic cage abnormalities (kyphoscoliosis), and small lungs. DLCO is reduced in pulmonary emphysema; however, because of the poor distribution of the inspired test gas, the VA may grossly underestimate the TLC, and the resultant DL/VA may be normal. A reduced DLCO and a reduced DL/VA ratio suggest a true interstitial disease such as pulmonary fibrosis or pulmonary vascular disease. Recent studies have shown that, in normal patients, the DL/VA is increased to above normal levels when the DLCO test is performed at volumes less than the TLC. This suggests that a low DLCO and a normal DL/VA may be a function of an inappropriately low predicted value for DL/VA when TLC is reduced.

The pattern of a low DLCO and a normal DL/VA may not be sufficient to rule out the presence of parenchymal disease. Studies advocate the volume correction of the predicted value for DLCO by using the measured VA to "correct" the predicted DLCO for low or high lung volumes. Studies demonstrating the nonlinearity of the relationship between lung volume and DLCO are sufficiently convincing that the practice of interpreting a low DLCO and a normal DL/VA as normal should not be performed. The degree of severity of reduction in the diffusing capacity can be assigned according to

the following scheme: less than the lower limit of normal (LLN) but greater than 60% of predicted is mild, between 40 and 60% of predicted is moderate, and less than 40% is severe.

Non-perfusion of ventilated alveoli, such as in pulmonary vascular disease, produces reduction of both the DLCO and the DL/VA. Anemia produces a virtual reduction in pulmonary capillary blood volume that causes a reduction in DLCO that can be adjusted mathematically for the reduced Hb. The DLCO may be reduced temporarily in a variety of disorders such as pneumonia, interstitial infiltrative disorders, and alveolar proteinosis. The importance of obtaining an inspiratory vital capacity (IVC) greater than 90% of the best measured VC from the day of the test cannot be overemphasized. Inability to achieve an IVC of greater than or equal to 90% of the largest VC measured that day must be noted on the report.

Respiratory Muscle Strength Assessment

Maximum inspiratory pressures (MIP), maximum expiratory pressures (MEP), negative inspiratory force (NIF), respiratory pressures, and maximum respiratory pressures are used to measure muscle strength. Assessing respiratory muscle strength allows for assessment ventilatory failure, restrictive lung disease, and respiratory muscle strength. There are no contraindications for performance of the assessment. Patients must be able to follow directions. Determinations of respiratory muscle pressures are a quick and noninvasive means of assessing respiratory muscle strength.

MIP: Patients breathe through a flanged mouthpiece with nose clips in place. Patients are instructed to exhale to RV. At RV, a valve or shutter is closed and the patient is coached to inhale as forcefully as possible. Maximum pull should be maintained for 1-2 seconds. A standardized leak must be present in the measurement system to eliminate significant overstatement of MIP by allowing the cheek muscles to contribute to the measured pressures. Initial maximum negative pressures that cannot be maintained for 1 full second are ignored.

MEP: Patients breathe through a flanged mouthpiece with nose clips in place. Patients are instructed to inhale to TLC. At TLC, a valve or shutter is closed and the patient is coached to exhale as forcefully as possible. Maximum push should be maintained for 1-2 seconds. Initial maximum positive pressures that cannot be maintained for 1 full second are ignored.

A new procedure, measurement of sniff nasal-inspiratory force (SNIF) has been shown to have promising utility in predicting mortality in patients with amyotrophic lateral sclerosis (ALS). A standardized device is not commercially available. A polyethylene catheter ending in a plug is attached to a pressure transducer, and the plug end is inserted into a nostril. The contralateral nostril is occluded, and the patient is instructed to exhale to FRC, then close the mouth and take a deep sniff or a maximal inspiratory

effort. Both nostrils are tested, and the highest of 6 recorded pressures sustained for at least 1 second is reported.

Tests Results

Maximal inspiratory mouth pressure (P_Imax), maximal expiratory mouth pressure (P_Emax), and SNIF are reported in centimeters of water pressure.

Interpretation

As many as 10 efforts are needed before consistency (2 measurements within 10% of the highest measured pressure) is achieved in some patients. When respiratory muscle fatigue or neuromuscular disease is present, fatigue may set in before consistency is achieved. Adequate rest between efforts is important.

The range of normal values is broad, suggesting wide variations in respiratory muscle strength among normal values. This makes interpretation of low values difficult. Initial values should be compared to the lower limit of normal values for the patient's age.

In general, a P_Imax of less than -80 cm water pressure and a P_Emax of greater than +80 cm water pressure excludes important weakness of the respiratory muscles. Patients with a P_Emax less than 50 cm water pressure may have difficulty generating sufficient cough to clear respiratory secretions.

In patients with ALS, a SNIF pressure less than 40 cm water was associated with a hazard risk for death of 9.1 (confidence interval [CI], 4-20.8) and the median mortality was 6 ± 0.3 months (95% CI, 2.5-8.5 mo).

Technical Problems

All tests are dependent on effort and technique. Good instruction, vigorous coaching, and adequate rest between efforts are essential. Maximum values should be reproducible within the greater of 10% or 5 cm water pressure. A controlled leak (1 mm diameter, 15 mm length) must be part of the system to prevent erroneously high MIP readings resulting from the use of cheek muscles. This leak is not needed for MEP or SNIF pressure measurements.

Methacholine Challenge Testing

Methacholine challenge is also called Mecholyl challenge or bronchial provocation test. Indications are to diagnose asthma, confirm diagnosis of asthma, document severity of hyperresponsiveness, and follow changes in hyperresponsiveness. Absolute contraindications include FEV₁ less than 1.5 L in adults, less than 1 L in children, recent severe acute asthma, myocardial infarction or cerebral vascular accident within 3 months, and arterial aneurysm. Relative contraindications include moderate baseline airway obstruction, spirometry-induced

bronchoconstriction, recent upper respiratory tract infection (URI), exacerbation of asthma, hypertension, pregnancy, and epilepsy.

In preparations for the test, the medications not to be taken by the patient before a methacholine challenge test for the specified period of time include: Short-acting beta agonists (6 h), long-acting beta agonists (36 h), oral beta agonists (24 h), short-acting methylxanthines (12 h), long-acting methylxanthines (48 h), anticholinergics (6 h), cromolyn sodium (24 h), and antihistamines (72 h). The withholding of oral or inhaled steroids before methacholine has not been shown to be necessary but may have an impact. The appropriateness of the methacholine challenge test in a patient who requires oral steroids should be considered.

Test

The following list shows the most common schedule of methacholine dosing in use in the United States today. Some labs begin with the lowest strength methacholine solution immediately after baseline; others advocate the use of a diluent stage between baseline and methacholine. This allows identification of a small percentage of individuals who exhibit significant bronchoconstriction in response to the diluent itself, suggestion, or repeated spirometry efforts. Abbreviated protocols that start with higher concentrations of methacholine should be used cautiously, if at all.

Methacholine challenge schedule: After establishing baseline spirometry measurements, the patient inhales 5 breaths of saline or diluent aerosol and then 5 breaths of each of the following strengths of aerosolized methacholine in solution: 0.0625 mg/mL, 0.25 mg/mL, 1 mg/mL, 4 mg/mL, and 16 mg/mL.

An alternative longer (10-stage) dosing schedule that may yield a more precise assessment of airway hyperreactivity calls for the patient to inhale 5 breaths of methacholine aerosol in the following strengths: 0.031 mg/mL, 0.0625 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL, and 16 mg/mL.

The following dosing schedule is approved by the US Food and Drug Administration and also may be used, although the ATS guidelines for methacholine challenge testing recommend 1 of the 2 schedules outlined above because the dosing steps are more even: 0.025 mg/mL, 0.25 mg/mL, 2.5 mg/mL, 10 mg/mL, and 25 mg/mL.

Methacholine aerosol is delivered in a standardized fashion by using a dosimeter, a device that applies a 0.6-second burst of compressed air to the nebulizer at the start of the inhalation from FRC to TLC. Subjects should hold their breath for 5 seconds. Spirometry is performed 30-90 seconds after the end of the last breath of each stage of the challenge. Symptoms volunteered by the subject are recorded. The challenge is discontinued when a fall in FEV1 of greater than 20% is observed upon repeat efforts or a final cumulative dose of 188.64 cumulative dose units is received.

Administration of a bronchodilator should immediately follow the final post-methacholine assessment.

Test Results

Results are presented as both a table of spirometry parameters for each stage of the challenge and as a dose-response curve plotting the fall in FEV₁ against the methacholine concentration. The reporting of the PC₂₀ (provocative concentration in mg/mL causing a 20% fall in FEV₁ from baseline) is the usual method of expressing the results of a positive test.

Interpretation

A 20% fall in FEV₁ generally is considered a positive test. The American Thoracic Society recommends the use of a 35% fall specific airway conductance (SGaw) to denote the presence of airway hyperreactivity when technically good spirometry cannot be obtained. It has been suggested that a significant subset of patients will exhibit a 35% fall in SGaw when the FEV₁ remains greater than 80% of its baseline value. This may represent a subset of patients that has widespread small airway changes.

One scheme for using the PC₂₀ FEV₁ to characterize the severity of clinical hyperreactivity has been used. PC₂₀ FEV₁ severity is assessed as follows: 0.03-0.124 is considered severe, 0.125-1.99 is considered moderate, 2.00-7.99 is considered mild, and 8-25 is considered an increased hyperresponsive reaction (however, clinically significant disease is not common).

Technical Problems

False non-reproducible falls should not be considered valid. Continuation of the challenge beyond 25 mg/mL has little clinical value because responses of some healthy patients who are non-asthmatic begin at this level.

Failure to demonstrate bronchial hyperreactivity does not totally exclude asthma, particularly asthma triggered by occupational exposure to chemicals such as methylene diisocyanate or toluene diisocyanate.

Nonspecific bronchial hyperreactivity is characteristic of asthma but can persist for some months after a viral respiratory illness. Nonspecific bronchial hyperreactivity also can be found in chronic obstructive pulmonary disease, cystic fibrosis, and bronchiectasis.

Cardiopulmonary Stress Testing

Cardiopulmonary exercise (CPX) test is used for evaluation of dyspnea that is out of proportion to findings on static pulmonary function tests, preoperative evaluation of operative risk when lung function is compromised or removal of lung segments is contemplated, evaluation of disability, identification of exercise-induced asthma, and evaluation of therapy.

Absolute contraindications include unstable angina, aortic stenosis, uncontrolled hypertension, uncontrolled asthma, hypoxemia (SaO₂ <85% at rest), and febrile illness.

Relative contraindications include hypertension, cardiac disease, epilepsy, and locomotor disorder (inability to exercise).

Patient Preparations

Perform calibration of the volume-measuring device and gas analyzers. Patients should avoid eating a heavy meal 1-2 hours before the test. Patients should wear loose comfortable clothing and athletic shoes. If exercise-induced bronchoconstriction is considered, withhold medications as with the methacholine challenge. ECG electrodes/leads are applied. Adjustment of the seat height on a bicycle ergometer is made to permit near-full leg extension when one pedal is at its lowest position (slight bend at knee). Airtight fitting of a low dead-space mask or mouthpiece/nose clips is applied. Apply and correctly position a blood pressure cuff. A pulse oximeter probe is applied securely. Insertion of an indwelling arterial canula for arterial blood sampling is optional.

Test

The cardiopulmonary exercise test is a means of measuring the integrated response of the pulmonary, cardiovascular, and muscular systems to a steadily increasing workload. The test may be performed on a bicycle ergometer or treadmill. Resting measurements are made for 3-5 minutes. Three minutes of unloaded cycling is performed as a warm-up period. The workload is incremented at a rate designed to allow reaching maximum work capacity in 8-12 minutes. The test continues to a point of symptom limitation (severe dyspnea, chest pain, faintness, pallor, inability to continue pedaling or walking) or discontinuation by medical staff for one of the following conditions: significant ECG abnormalities, fall in systolic or diastolic blood pressure (BP) greater than 20 mm Hg below resting value, rise in systolic BP to greater than 250 mm Hg, rise in diastolic BP to greater than 120 mm Hg, severe oxygen desaturation (<80%), or achievement of maximum predicted heart rate.

Determining the proper rate of workload incrementation: The workload incrementation rate should be chosen to produce a test of 8-12 minutes in length. If the workload incrementation is too high, the test will be too brief. In this circumstance, the patient should be allowed to recover and should be retested. If the workload incrementation is too small, fatigue may prevent a valid second test.

Wasserman's method for estimating the workload increment size for cycle ergometry:

Estimate the unloaded oxygen consumption per minute (VO₂): Unloaded VO₂ (mL/min) = 150 + (6 X weight [kg])

Estimate the peak VO₂: Peak VO₂ (mL/min) = (height [cm] – age [y]) X 20 for sedentary men or peak VO₂ (mL/min) = (height [cm] – age [y]) X 14 for sedentary women

Estimate the work rate increment: Work rate increment (watts/min) = (peak VO₂ (mL/min) – unloaded VO₂ (mL/min))/100

Patients with significant reductions in the predicted VEmax (FEV1 below 50% of predicted) should use an increment of 10 watts/min or less. Patients with severe obstruction resulting in pre-exercise maximum voluntary ventilation (MVV) of less than 40 L/min should use a 5-watt/min incrementation rate.

Test Results

The following parameters are measured or calculated on a breath-by-breath basis: minute ventilation (VE, LPM), tidal volume (VT, mL/breath), respiratory rate (RR, mL/breath), oxygen uptake (VO₂, mL/min and mL/min/kg), carbon dioxide production (VCO₂, mL/min), respiratory exchange ratio (RER, VCO₂ -to-VO₂), SpO₂, heart rate (HR, beats/min), oxygen pulse (mL VO₂/min/heartbeat), and BP (mm Hg). If ABG determinations are obtained, discrete values for the ratio of dead space to tidal volume (VD/VT) and alveolar to arterial oxygen gradient (A-aO₂) can be calculated for that interval of exercise.

Interpretation

The assessment of a normal work capacity is made by evaluation of the peak oxygen uptake (VO₂ peak). The normal value for oxygen uptake is based on sex, age, and weight.

The predicted peak VO₂ is determined by the patient's age and sex. This value can be further refined for sedentary individuals by a 3-step process that adjusts the predicted value up or down based on a comparison of the patient's weight and their ideal body weight:

Sedentary men: Calculate the cycle factor, cycle factor = $50.72 - (0.372 \times \text{age})$.

Step 1: Measure the man's weight (W [kg]) and height (H [cm]) in light clothes and without shoes, and record his age (A [y]).

Step 2: Calculate his normal (predicted) W in kg, normal (predicted) $W = (0.79 \times H) - 60.7$.

Step 3A: If his actual W equals his normal W, the formula is predicted peak VO₂ (mL/min) = actual W X cycle factor.

Step 3B: If his actual W is less than his normal W, the formula is predicted peak VO₂ (mL/min) = $[(\text{normal } W + \text{actual } W)/2] \times \text{cycle factor}$.

Step 3C: If his actual W exceeds his normal W, the formula is predicted peak VO₂ (mL/min) = $(\text{normal } W \times \text{cycle factor}) + [6 \times (\text{actual } W - \text{normal } W)]$.

Step 4: If a treadmill is used rather than cycle, multiply predicted VO₂ by 1.11.

Sedentary women: Calculate the cycle factor, cycle factor = $22.78 - (0.17 \times \text{age})$

Step 1: Measure her weight (W [kg]) and height (H [cm]) in light clothes and without shoes, and record age (A [y]).

Step 2: Calculate her normal (predicted) W in kg, normal (predicted) $W = (0.65 \times H) - 42.8$.

Step 3A: If her actual W equals her normal W, the formula is predicted peak VO_2 (mL/min) = (actual W + 43) X cycle factor.

Step 3B: If her actual W is less than her normal W, the formula is predicted peak VO_2 (mL/min) = [(normal W + actual W + 86)/2] X cycle factor.

Step 3C: If her actual W exceeds her normal W, the formula is predicted peak VO_2 (mL/min) = [(normal W + 43) X cycle factor] + [6 x (actual W – normal W)].

Step 4: If a treadmill is used rather than a cycle, multiply her predicted VO_2 by 1.11.

A normal CPX test demonstrates a normal peak VO_2 , the peak HR at or below the predicted maximum HR, and demonstration of ventilatory reserve (peak ventilation/predicted maximum ventilation <65-70%). When the VO_2 peak is low, the peak HR is compared to the predicted maximum HR to determine cardiovascular reserve. A ratio of HR peak to HR predicted maximum that approaches or exceeds 1 indicates a clear cardiovascular limitation to exercise.

The peak expired volume (minute ventilation, VE) is compared to the larger of a pretest MVV or FEV1 multiplied by 40 to determine the pulmonary reserve. A ratio of VE peak to VE predicted maximum that approaches or exceeds 1 is a clear indication of pulmonary limitation. A VO_2 peak below 15 mL/min/kg often is used as an indication of disability. Pulmonary limitation also may cause significant oxygen desaturation due to the reduction of the transit time of the pulmonary capillary blood to a point where diffusion limitation can occur. In the absence of cardiovascular or pulmonary limitation, peripheral circulatory or skeletal muscle limitation may exist. This must be distinguished from poor effort or malingering.

The anaerobic threshold is defined as the workload (expressed as VO_2) in which blood lactate levels rise significantly, indicating that a significant fraction of the work is being accomplished by anaerobic metabolic sources. The establishment of the anaerobic threshold may have clinical importance, particularly when the evaluation seeks to determine the presence of an occupational disability.

Identifying the anaerobic threshold noninvasively: The noninvasive determination of the anaerobic threshold can be accomplished by analyzing time averaged (20- to 30-s intervals) plots of parameters measured or calculated during the CPX test. Two methods can be used, the V-slope method and the ventilatory equivalent method. Both methods allow determination of the same physiologic event, the increased production of carbon dioxide by isocapnic buffering of lactic acid produced by anaerobic metabolism and yield comparable estimations.

V-slope method: The V-slope method of determining the anaerobic threshold makes use of the fact that carbon dioxide production (VCO_2) plotted against oxygen consumption (VO_2) shows a slope of slightly less than 1 for work below the anaerobic

threshold. A line of best fit for points obtained from the start of exercise is drawn through this plot to obtain the initial slope (S1). When this slope changes to a steeper slope (S2), it indicates an increase in carbon dioxide production from the isocapnic buffering of lactic acid. The intersection of S1 and S2 mark the anaerobic threshold, typically reported as either the absolute value of the oxygen uptake (VO_2 , mL/min) at that point or as the percentage of the predicted peak VO_2 .

Ventilatory equivalent method: The ventilatory equivalent method of determining the anaerobic threshold makes use of the derived values known as the ventilatory equivalents for oxygen and carbon dioxide. Carbon dioxide production (VCO_2) and oxygen consumption (VO_2) divided into the minute ventilation (VE , L/min) are known as the ventilatory equivalents for carbon dioxide (VE/VCO_2) and oxygen (VE/VO_2). When time averaged (20- to 30-s intervals) plots of VE/VO_2 and VE/VCO_2 are plotted against time, the point at which the VE/VO_2 is seen to increase without a simultaneous increase in the VE/VCO_2 marks the anaerobic threshold.

Exhaled Nitric Oxide

The transition from the first description of exhaled nitric oxide in humans in 1991 to the notion of using the exhaled nitric oxide as a clinical marker of disease activity in asthma has been rapid. In 2005, the ATS and the European Respiratory Society (ERS) published their recommendations for a standard technique of measurement.

Measurement of exhaled nitric oxide offers an easy, noninvasive alternative to direct sampling of the lower airways by sputum induction, lavage, or biopsy. The fractional concentration of exhaled nitric oxide (FE NO) in asthma may have the utility of helping make the diagnosis, monitoring the patient's compliance with prescribed medications, and predicting pending exacerbations.

Procedure

Clinical instruments for the measurement of exhaled nitric oxide typically measure "online" (patient exhales directly into the measuring device) rather than "offline" (exhaled breath is collected into a sample bag for later measurement). Offline measurements may have utility in epidemiology and research.

Online devices typically use a flow limiter to keep the sample flowing at a fixed flow range, typically 50 mL/s. The standardization of the measurement technique has allowed the development of normal ranges and standard interpretation schemes for online measurements.

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