

ATS/ERS Statement on Respiratory Muscle Testing

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Introduction

Over the last 25 years, great efforts have been made to develop techniques to assess respiratory muscle function. Research output in this area has progressively increased, with the number of peer reviewed articles published on respiratory muscle function having increased remarkably during the 1995–2000 period compared with 1980–1985.

This official joint statement represents the work of an expert ATS/ERS committee, which reviewed the merits of currently known techniques available to evaluate respiratory muscle function. The statement consists of 10 sections, each addressing a major aspect of muscle function or a particular field of application. Each section addresses the rationale for the techniques,

their scientific basis, the equipment required, and, when pertinent, provides values obtained in healthy subjects or in patients. Some of the techniques reviewed in this statement have thus far been used primarily in clinical research and their full potential has not yet been established; however, they are mentioned for the purpose of stimulating their further development.

Through continued efforts in the area of respiratory muscle testing, it is anticipated that there will be further enhancement of diagnostic and treatment capabilities in specialties such as intensive care, sleep medicine, pediatrics, neurology, rehabilitation, sports medicine, speech therapy, and respiratory medicine.

1. Tests of Overall Respiratory Function

Routine measurements of respiratory function, that is, volumes, flows, and indices of gas exchange, are nonspecific in relation to diagnosis but give useful indirect information about respiratory muscle performance. On occasion, the presence of respiratory muscle dysfunction is first suspected from the pattern of conventional respiratory function tests. More frequently, they are of use in assessing the severity, functional consequences, and progress of patients with recognized muscle weakness.

STATIC LUNG VOLUMES

Rationale and Scientific Basis

The most frequently noted abnormality of lung volumes in patients with respiratory muscle weakness is a reduction in vital capacity (VC). The pattern of abnormality of other subdivisions of lung volume is less consistent. Residual volume (RV) is usually normal or increased, the latter particularly with marked expiratory weakness (1). Consequently, total lung capacity (TLC) is less markedly reduced than VC, and the RV/TLC and FRC/TLC ratios are often increased without necessarily implying airway obstruction.

The VC is limited by weakness of both the inspiratory muscles, preventing full inflation, and expiratory muscles, inhibiting full expiration. In addition to the direct effect of loss of muscle force, reductions in compliance of both the lungs (2) and chest wall (3) also contribute to the reduction of VC in patients with chronic respiratory muscle weakness. In severe weakness, the TLC and VC relate more closely to lung compliance than to the distending force (4, 5) (Figure 1). The mechanism of reduced lung compliance is unclear. Contrary to earlier suggestions, it is probably not simply due to widespread microatelectasis (6). Static lung volumes may also be affected in some patients by coexistent lung or airway disease. Vital capacity, thus, reflects the combined effect of weakness and the static mechanical load on the respiratory muscles.

In mild respiratory muscle weakness, VC is less sensitive than maximum respiratory pressures. However, the curvilinear relation between VC and maximum inspiratory pressure (5) (Figure 2) implies that, in more advanced disease, marked reductions in VC can occur with relatively small changes in maximum pressures.

In patients with isolated or disproportionate bilateral diaphragmatic weakness or paralysis, the VC shows a marked fall in the supine compared with the erect posture because of the action of gravitational forces on the abdominal contents. In some patients, this postural fall may exceed 50%. In most normal subjects, VC in the supine position is 5–10% less than when upright (7) and a fall of 30% or more is generally associated with severe diaphragmatic weakness (8).

Methodology and Equipment

Recommendations and requirements for the measurement of VC and other lung volumes are covered in detail elsewhere (9, 10).

Advantages

VC has excellent standardization, high reproducibility and well-established reference values. It is easily performed, widely available, and economical. It is quite sensitive for assessing progress in moderate to severe respiratory muscle weakness. The rate of decline has been shown to predict survival in both amyotrophic lateral sclerosis (11) and Duchenne muscular dystrophy (12).

Disadvantages

VC has poor specificity for the diagnosis of respiratory muscle weakness. In mild weakness, it is generally less sensitive to changes than are maximum pressures (13).

Applications

Serial measurements of VC should be routine in monitoring progress of patients with acute and chronic respiratory muscle weakness.

Measurement of postural change of VC gives a simple index of weakness of the diaphragm relative to the other inspiratory muscles.

DYNAMIC SPIROMETRY AND MAXIMUM FLOW

Rationale and Scientific Basis

Airway resistance is normal in uncomplicated respiratory muscle weakness (14). Airway function may appear to be supernormal when volume-corrected indices such as FEV_1/VC or specific airway conductance are used (2).

The maximum expiratory and maximum inspiratory flow–volume curves characteristically show a reduction in those flows that are most effort dependent, that is, maximum expiratory flow at large lung volumes (including peak expiratory flow) and maximum inspiratory flow at all lung volumes (2, 5) (Figure 3). The descending limb of the maximum expiratory flow–volume curve may suggest supernormal expiratory flow when this is related to absolute volume (2, 3). With severe expiratory weakness, an abrupt fall in maximum expiratory flow is seen immediately before RV is reached (1). In health the FEV_1 is usually less than the forced inspiratory volume in 1 second. Reversal of this ratio is seen with upper (extrathoracic) airway obstruction, as well as in respiratory muscle weakness, and may give a pointer to these diagnoses during routine testing.

The effect of coughing can be visualized on the maximum expiratory flow–volume curve in healthy subjects as a transient flow exceeding the maximum achieved during forced expiration. The absence of such supramaximal flow transients during coughing presumably results in impaired clearance of airway secretions and is associated with more severe expiratory muscle weakness (15). Even with quadriplegia, however, some patients can generate an active positive pleural pressure in expiration (16). This can allow them to achieve the pressure required for flow limitation through most of expiration so that FEV_1 may still be reliable as an index of airway function. Impaired maximal flow in some neuromuscular diseases may also reflect poor coordination of the respiratory muscles rather than decreased force per se.

Oscillations of maximum expiratory and/or inspiratory flow—the so-called sawtooth appearance—are seen particularly when the upper airway muscles are weak and in patients with extrapyramidal disorders (17) (Figure 4).

Methodology and Equipment

Recommendations and requirements for maximum flow–volume curves are covered in detail elsewhere (9, 10).

Advantages

Maximum flow–volume curves are easily performed, widely available, and economical. Peak expiratory flow can be obtained with simple portable devices.

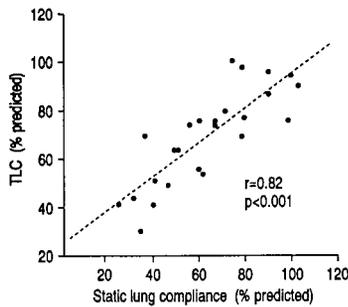


Figure 1. Relation between static lung compliance and total lung capacity in 25 patients with chronic respiratory muscle weakness of varying severity. Dashed line is regression line. Reprinted by permission from Reference 5.

Disadvantages

Intersubject variability is greater than for VC. Reference values for $\dot{V}_{E\max}$ at standard percentages of FVC may present problems of interpretation.

Applications

Visual inspection may suggest the likelihood of weakness.

The sawtooth appearance in an appropriate context may suggest weakness or dyscoordination of upper airway muscles. However, this appearance is nonspecific and is seen also in some subjects with obstructive sleep apnea, nonapneic snoring, and thermal injury of the upper airway.

MAXIMUM VOLUNTARY VENTILATION

Rationale and Scientific Basis

The maximum voluntary ventilation was formerly recommended as a more specific test for muscle weakness than volume measurements but, in practice, the proportionate reduction is usually similar to that of VC (18, 19). Disproportionate reductions may be seen in Parkinson's disease (20), in which the ability to perform frequent alternating movements is impaired.

Methodology and Equipment

Recommendations and requirements are covered elsewhere (10).

Advantages

No advantages are perceived in most situations.

Disadvantages

The test depends on motivation and is tiring for the subject.

Applications

Maximum voluntary ventilation is not generally recommended for patients with known or suspected respiratory muscle weakness but may be helpful in the assessment and monitoring of patients with extrapyramidal disorders.

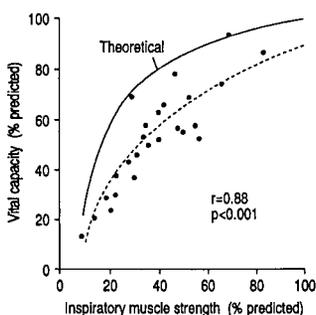


Figure 2. Curvilinear relation of maximum static inspiratory pressure (inspiratory muscle strength) to vital capacity in 25 patients with chronic weakness of varying severity. Dashed line and statistics relate to logarithmic regression. Solid line represents relationship calculated from a standard maximal static pressure–volume diagram assuming normal elastic properties of the respiratory system. The greater than expected reduction in VC is due to reduced compliance of the lungs and chest wall. Reprinted by permission from Reference 5.

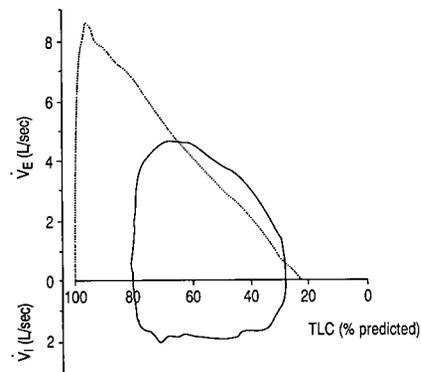


Figure 3. Schematic maximum expiratory and inspiratory flow–volume curves in a patient with severe respiratory muscle weakness (solid line) compared with predicted (dotted line). Volume is expressed in absolute terms (i.e., percent predicted). Note marked reductions in FVC, $\dot{V}_{E\max}$ at higher volumes, and $\dot{V}_{I\max}$ at all volumes. Note also the blunted contour of the expiratory curve and the abrupt cessation of $\dot{V}_{E\max}$ at RV. In the midvolume range, $\dot{V}_{E\max}$ exceeds that predicted for the absolute lung volume.

ARTERIAL BLOOD GASES: AWAKE

Rationale and Scientific Basis

In chronic muscle weakness, even when quite severe, P_{aO_2} and the alveolar–arterial P_{O_2} difference are usually only mildly abnormal (2, 21). In acute muscle weakness, P_{aO_2} may be more markedly reduced, but the picture may be complicated by atelectasis or respiratory infection (22).

With mild weakness, P_{aCO_2} is usually less than normal (19, 22), implying alveolar hyperventilation. In the absence of primary pulmonary disease, daytime hypercapnia is unlikely unless respiratory muscle strength is reduced to < 40% of predicted and VC is reduced to < 50% of predicted (19) (Figures 5 and 6). Elevation of venous bicarbonate concentration occasionally gives an important clue to otherwise unsuspected hypercapnia. Patients with muscle weakness are less able than normal subjects to compensate for minor changes in respiratory function. If hypercapnia is established or incipient, even minor infections may cause a further rise in P_{aCO_2} , as also may injudicious use of sedative drugs or uncontrolled oxygen.

Advantages

Arterial blood gases assess the major functional consequence of respiratory muscle weakness. In patients with Duchenne muscular dystrophy, hypercapnia has been shown to predict shorter survival (12).

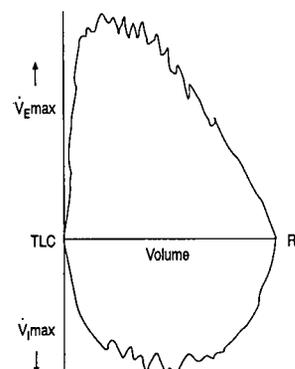


Figure 4. Maximum expiratory and inspiratory flow–volume curves, showing "sawtooth" oscillations of flow.

Disadvantages

Definitely abnormal arterial blood gases usually imply late and severe impairment of respiratory muscles and therefore their measurement is neither sensitive nor specific. Daytime values may underestimate the severity of abnormal gas exchange.

Applications

Measurement of arterial blood gases is routinely performed to assess the consequences of respiratory muscle weakness.

MEASUREMENTS DURING SLEEP

Rationale and Scientific Basis

Patients with moderate or severe respiratory muscle weakness characteristically show dips in oxygen saturation (Sa_{O_2}) related to periods of rapid eye movement (REM) sleep (23, 24) (Figure 7). The episodic desaturation is usually due to hypopnea and less often to apnea and is associated particularly with phasic REM sleep, when brief periods of rapid, irregular eye movements are accompanied by reduced activity of skeletal muscles (24) (Figure 8). The hypopneas and/or apneas may appear to be either "central" (Figure 8) or "obstructive," or sometimes a mixture of both. The precise pattern of such events depends on the relative activation of the respiratory pump and upper airway dilator muscles (24). Obstructive apneas are more likely in weak patients who are also overweight (25). In patients with severe respiratory muscle weakness, some apneas that appear to be central may in fact be obstructive, incorrect classification being due to failure of external sensors to detect chest wall movements of reduced amplitude (26).

Hypercapnia in patients with slowly progressive weakness probably develops first during sleep. Continuous monitoring during sleep (e.g., with a transcutaneous P_{CO_2} electrode) shows a gradual rise in P_{CO_2} during REM sleep (23) (Figure 7). Consequently, Pa_{CO_2} measured shortly after waking is more likely to be elevated than values obtained later in the day. Symptoms of nocturnal hypoventilation include morning headaches, daytime sleepiness, and lack of energy. Similar symptoms can also result from sleep disruption associated with frequent apneas and hypopneas, even in the absence of persistent hypercapnia. Daytime somnolence is particularly common in patients with myotonic dystrophy. However, even though sleep hypopnea and apnea are frequently found in this condition, they appear not to explain the sleepiness of most patients with myotonic dystrophy (27).

The timescale of progression from nocturnal to persistent diurnal hypercapnia in patients with chronic respiratory muscle weakness is not known.

Methodology

Polysomnographic techniques are described in detail elsewhere (28). To assess whether upper airway narrowing is a contributing

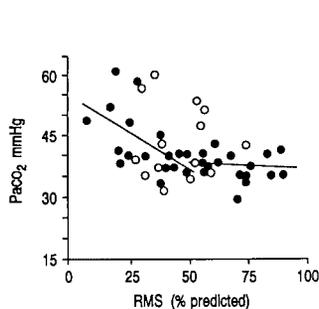


Figure 5. Relation of daytime Pa_{CO_2} to "respiratory muscle strength" (RMS = arithmetic mean of P_{imax} and P_{emax}) in 33 patients with "uncomplicated" chronic myopathy (closed circles, regression lines) and 14 patients with myopathy plus chronic lung disease (open circles). Note that in uncomplicated myopathy, Pa_{CO_2} is reduced (< 40 mm Hg) in most patients with mild weakness and is likely to be elevated only when RMS $< 40\%$ predicted. Reprinted by permission from Reference 19.

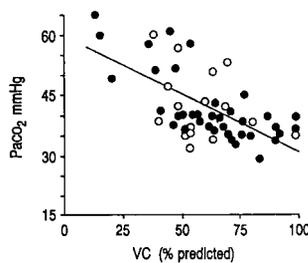


Figure 6. Relation of daytime Pa_{CO_2} to VC in 37 patients with uncomplicated chronic myopathy (closed circles, regression line) and 16 with myopathy plus chronic lung disease (open circles). Reprinted by permission from Reference 19.

cause of apneas or hypopneas may require use of a supraglottic or esophageal pressure sensor. Interpretation of recordings obtained by inductance plethysmography or other devices that measure rib cage and abdominal expansion is problematic in patients with quadriplegic or diaphragm paralysis. It is essential to check the polarity of the tracings and to compare phase relations awake and asleep.

Reliability of the devices for monitoring P_{CO_2} in sleep is currently doubtful and requires more study.

Advantages

Overnight oximetry is simple to perform.

Nocturnal measurements are more sensitive for detection of abnormal pulmonary gas exchange than daytime blood gases.

Disadvantages

Polysomnography is labor-intensive and relatively expensive. Current evidence suggests that nocturnal hypoxemia is a less good prognostic indicator than either vital capacity or awake Pa_{CO_2} (12, 29).

Applications

The role of sleep measurements in patients with respiratory muscle weakness is currently uncertain. Polysomnography may be useful in patients with daytime sleepiness and suspected nocturnal hypoventilation, perhaps especially if awake Pa_{CO_2} is borderline or only mildly elevated.

Marked REM-related desaturation is seen occasionally in patients with relatively normal daytime Sa_{O_2} (26). More typically, however, the severity of nocturnal desaturation is predictable from daytime measurements, with more marked desaturation in patients with lower daytime Pa_{O_2} , higher Pa_{CO_2} , and lower VC (23) (Figure 9).

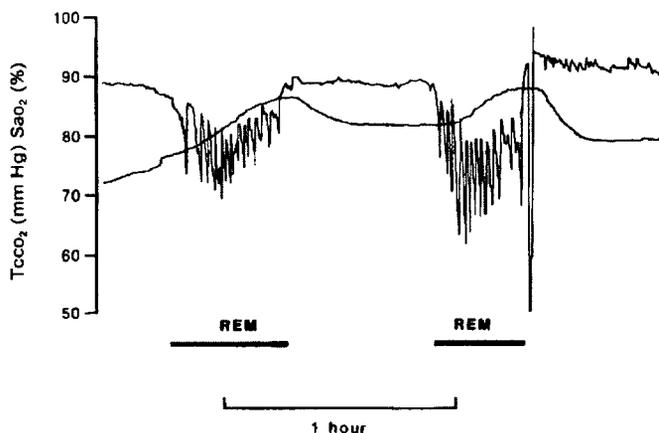


Figure 7. Section of sleep recording of Sa_{O_2} and transcutaneous P_{CO_2} ($TcCO_2$) in a patient with chronic myopathy, showing mild desaturation (Sa_{O_2} 90%) in non-REM sleep and frequent periodic dips in Sa_{O_2} in REM sleep. The P_{CO_2} shows progressive elevation during REM periods. Reprinted by permission from Reference 23.

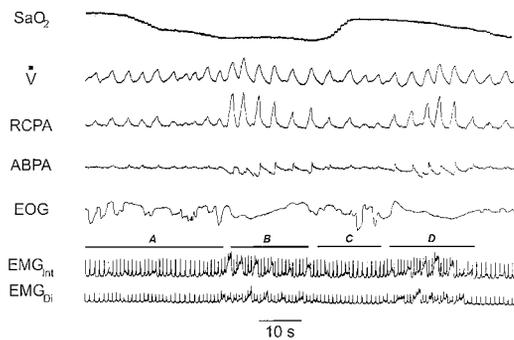


Figure 8. Brief (~ 2 minute) polysomnographic recording in REM sleep in a patient with chronic myopathy. The signals are as follows: SaO_2 , airflow (\dot{V}), posteroanterior motion of rib cage (RCPA) and abdomen (ABPA) are electro-oculogram (EOG), and integrated surface electromyograms from inspiratory intercostals (EMG_{int}) and diaphragm (EMG_{di}) (the ECG is superimposed on EMG signals). A–D, Periods of REM sleep. During periods A and C, marked irregular eye movements (“phasic” REM) are accompanied by reduced EMG activity and consequently reduced motion and flow with subsequent desaturation; rib cage and abdominal motion remain in phase, indicating central hypopneas. During periods B and D, eye movements are relatively quiescent and EMG activity increases with consequent increased motion and flow and subsequent recovery of SaO_2 (increasing SaO_2 during period C reflects the increased ventilation in period B). Reprinted by permission from Reference 24.

Sleep studies should be performed in all patients for whom nocturnal ventilatory support is being considered. On occasion, the finding of frequent hypopneas and/or apneas that are predominantly obstructive will suggest a trial of treatment with nasal continuous positive airway pressure. More frequently, however, in patients with respiratory muscle weakness, bilevel pressure support or another method of noninvasive intermittent positive pressure ventilation will be the treatment of choice. Because there is no evidence that treatment of abnormalities of gas exchange per se during sleep is beneficial, currently there is no indication for widespread application of polysomnography in the absence of relevant symptoms.

TESTS OF RESPIRATORY CONTROL

Rationale and Scientific Basis

The respiratory control system may be considered to have three functional components: (1) sensory receptors that provide information about the status of the respiratory system (only chemoreceptors that measure arterial PCO_2 , PO_2 , and pH are usually considered or tested, but there are many other sensory inputs of importance); (2) the central integrating circuits; and (3) the motor output to the respiratory muscles. The tests available are stimulus response tests, in which a receptor is stimulated and the motor output or a downstream mechanical effect of motor output, is measured. It is important to recognize that these tests are generally unable to separate the three functional components of the control system.

Minute ventilation and arterial PCO_2 are maintained at normal levels even with quite marked weakness of the respiratory muscles, implying that the control system compensates for the weakness by driving the respiratory muscles harder than normal. The mechanism by which the control system identifies muscle weakness and adjusts its motor output is unknown. The increased motor output is difficult to appreciate because it succeeds in generating only normal pressures, volumes, and flows. It is most readily apparent when accessory muscles or abdominal muscles are more active than normal during quiet breathing.

If phasic contraction of scalenes, sternocleidomastoids, pectoral muscles, or abdominal muscles can be palpated, it is safe to conclude that respiratory motor output is above normal.

When respiratory muscles are chronically severely weak and arterial PCO_2 begins to rise, two explanations are possible. The muscles may be so weak that they cannot continually generate sufficient alveolar ventilation. Otherwise, an abnormality of the ventilatory control system may be allowing the PCO_2 to rise even though the muscles themselves are quite capable of keeping it normal. A gradual shift in the PCO_2 “set point” of the controller does seem to occur in some patients with muscle disease, as it does in some cases of sleep apnea and chronic obstructive pulmonary disease.

Laboratory tests of overall respiration that have been used to try to assess the control system include inhalation of hypercapnic or hypoxic gas mixtures to stimulate chemoreceptors, with measurements of ventilation or occlusion pressure to assess motor output, and sleep studies to monitor behavior of the control system during sleep.

In patients with weak muscles, interpretation of slopes of conventional ventilatory curves is clouded for several reasons.

- The output of the controller is abnormally high when ventilation is normal. The controller may therefore be on the nonlinear part of its normal response curve.
- The high motor neuron output cannot be measured directly and its mechanical effect (e.g., ventilation) is reduced in the presence of weakness.
- The response will become flat if ventilation nears the limit of respiratory muscle endurance and that limit may be only a short distance above resting ventilation.

Abnormal central control of respiration is well documented in bulbar poliomyelitis and other conditions affecting the central nervous system, presumably because of direct involvement of medullary respiratory centers. It has been suggested that certain muscle diseases are also associated with primary abnormalities of central respiratory control; these conditions include myotonic dystrophy, acid maltase deficiency, and other congenital myopathies. Impaired ventilatory responses to CO_2 and/or hypoxia have frequently been described, but in many cases, respiratory muscle function was assessed inadequately. In myotonic dystrophy it has been shown that the relations between hypercapnia and both maximum respiratory pressures and VC are similar to those in nonmyotonic diseases (30).

Occlusion pressure is the pressure generated in the airway (and by inference the pressure generated in the pleural space) by contraction of inspiratory muscles when the airway has been occluded at end expiration. It was introduced to separate hypoventilation due to high pulmonary resistance or elastance from hypoventilation due to a failure of the respiratory pump apparatus (i.e., the muscles, passive components of the chest wall, and the control system) (31, 32). Occlusion pressure amplitude does not directly assess either the degree of muscle weakness or the degree of neuronal adjustment to the weakness. $P_{0.1}$ is the pressure generated in the first 100 milliseconds of inspiration against an occluded airway. Its timing is such that it is not influenced by the conscious response to occlusion and as an index of ventilatory drive it has the advantage over ventilation of being independent of the mechanical properties of the lung (31). It is, however, dependent on the contractile state and function of the respiratory muscles and consequently on the lung volume at which it is measured. For example, because of the length–tension relationship of the muscles, a reduced value for a given neural output would be expected with pulmonary hyperinflation and an elevated FRC. On the other

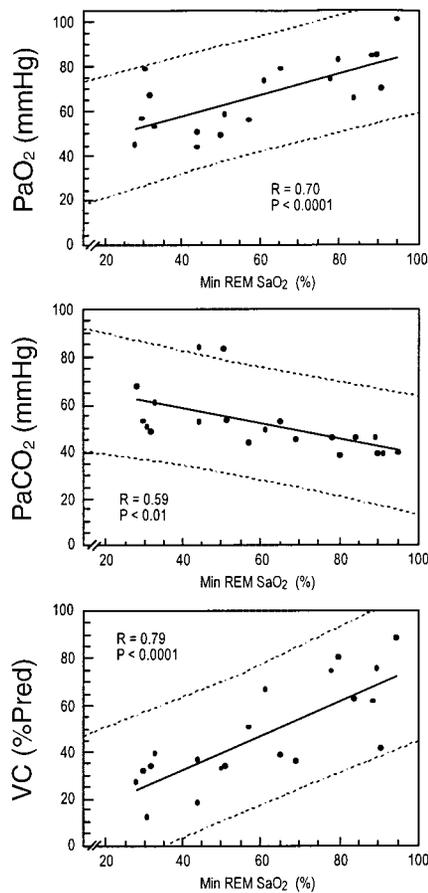


Figure 9. Relation of sleep hypoxemia to daytime blood gases and VC in 20 patients with chronic myopathy (regression line [solid line] \pm 95% confidence limits [dashed lines]). The abscissa in each panel shows the nadir SaO_2 in REM sleep. More severe REM desaturation occurs with lower awake PaO_2 (top panel), higher awake $PaCO_2$ (middle panel), and lower VC (lower panel). Reprinted by permission from Reference 23.

hand, if inspiration starts below equilibrium lung volume the value of $P_{0.1}$ recorded depends on relaxation of the *expiratory* muscles.

Values of $P_{0.1}$ are around 1 cm H_2O in normal subjects at rest, around 3 cm H_2O in patients with stable chronic obstructive pulmonary disease, and may be 10 cm H_2O or more in acute respiratory failure due to chronic obstructive pulmonary disease or acute respiratory distress syndrome. Such values reflect a high ventilatory drive consequent on a greatly increased mechanical load. Some, although not all, studies have suggested that in patients with chronic obstructive pulmonary disease receiving ventilatory support values greater than 4–6 cm H_2O are associated with failure to wean (33).

In patients with weak muscles, resting $P_{0.1}$ tends to be normal or slightly increased (34). In the model of acute respiratory muscle weakness provided by partial curarization of healthy subjects, the slope of $P_{0.1}$ response to CO_2 is increased even though the ventilatory response is reduced (35). However, in patients with chronic weakness the ventilatory and $P_{0.1}$ slopes are both diminished (even though resting $P_{0.1}$ is normal or increased). Hence, a reduced response in such individuals does not necessarily imply impaired ventilatory drive (30).

Methodology and Equipment

For assessment of ventilatory responses to hypercapnia or hypoxia (36), the subject inhales a gas mixture that causes a

change in either arterial PO_2 or PCO_2 . A plot of PO_2 (or PCO_2) against ventilation (or, for PO_2 response the algebraic constants describing a hyperbola) are compared with normal values. The induced change in blood gases may be continuous (rebreathing methods) or a few discrete points (steady state methods). Usually PCO_2 is held constant while PO_2 is changed and vice versa. Standard methods are available for measuring ventilatory responses during rebreathing (37, 38).

Steady state or quasi-steady state tests (39) are done simply by having the subject inhale a prepared mixture of gases, usually for 5 minutes (40). Judgments about the safety of inducing hypoxemia or acidosis are made clinically for individual patients. In chronically hypoxemic patients, transient responses to inhalation of pure oxygen may be useful and are safe (40).

For the measurement of $P_{0.1}$, it is essential to close the airway exactly at the point of zero flow. This is usually done by separating the inspiratory and expiratory lines with one-way valves and then closing the inspiratory line while the subject is exhaling. Conscious subjects must be unable to anticipate occlusions, which must be done silently and unexpectedly. Obstruction can be simply performed by inflating a balloon within the lumen of the inspired line or by closing a valve. A sensitive transducer and timer are used to record pressure at 0.1 second.

Advantages

A completely flat ventilatory response may identify defective chemoreceptor or brainstem function, but lesser abnormalities are difficult to interpret.

Occlusion pressure ($P_{0.1}$) is relatively easy to measure. Marked discrepancies between occlusion pressure and minute ventilation point to a lung disease causing substantial increase in airway resistance or lung elastance. Usually, however, such a problem is clinically evident and better evaluated by spirometry.

Disadvantages

Indices of ventilatory control have a wide normal range and are subject to overinterpretation.

Occlusion pressures in general, and $P_{0.1}$ in particular, are difficult to interpret without additional measurements of mechanics and control events through the whole respiratory cycle, which are usually not available. $P_{0.1}$ is a valid index of neural output only at FRC. Breath-to-breath scatter in the data requires averaging of many breaths to obtain precise results. The theoretical issues regarding measurement and interpretation have been reviewed (41).

Clinical Applications

These tests are seldom used in routine clinical assessment of stable patients. In acute respiratory failure, mouth occlusion pressure during unstimulated breathing may be of value in assessing respiratory drive and the likelihood of successful weaning.

Occlusion pressure has no proven clinical value in respiratory muscle disease but may occasionally be helpful by pointing to an unsuspected mechanical problem.

If a patient is known to have a mixed problem of muscle weakness and a lung disease (e.g., polymyositis plus interstitial pulmonary fibrosis) and the response of the controller to CO_2 or O_2 is being studied, $P_{0.1}$ can be measured in conjunction with ventilation as the response and may be a more reliable way of comparing the result with normal values.

CARBON MONOXIDE TRANSFER

Rationale and Scientific Basis

Single-breath CO diffusing capacity (transfer factor) (DL_{CO}) in patients with muscle weakness is usually normal or mildly

reduced. Reduction is due to inability to achieve full distension of the lungs at TLC and consequent failure to expose all the alveolar surface to carbon monoxide. As with other extrapulmonary causes of lung volume restriction, the transfer coefficient (K_{CO}) is often supernormal.

Advantages

The measurement is easily performed and well standardized.

Disadvantages

A reduced DL_{CO} is a nonspecific finding (but if accompanied by elevation of K_{CO} it suggests extrapulmonary volume restriction). Any effects of respiratory muscle weakness on the measurements are indirect.

Clinical Applications

The pattern of normal or mildly reduced DL_{CO} and raised K_{CO} directs attention to extrapulmonary conditions, that is, respiratory muscle weakness, pleural disease or rib cage abnormalities. Otherwise, the main role of measurement of CO uptake is in the recognition or exclusion of coexistent lung disease.

EXERCISE TESTING

In many patients with muscle weakness, exercise is limited, and therefore, maximum oxygen consumption is reduced because of weakness of the leg muscles rather than cardiorespiratory factors. The limited available data suggest that the relation of workload to oxygen consumption is normal, as also are indices of submaximal exercise performance (42).

Advantages

Formal testing allows confirmation and quantification of exercise incapacity and may aid elucidation of its mechanism.

Disadvantages

Exercise is limited by weakness of nonrespiratory muscles in many patients with neuromuscular disease. Exercise testing is poorly standardized in this patient population.

Clinical Applications

Exercise testing may help determine the main factor(s) limiting exercise capacity, especially if related or coexistent cardiac or pulmonary disease is present or suspected.

CONCLUSION

This Section of the Statement has explored the usefulness of analyzing the results of pulmonary function tests to infer alterations in respiratory muscle function. Some such inferences are as follows:

1. Respiratory muscle weakness reduces VC.
2. Expiratory muscle weakness can increase RV.
3. Reduction in chest wall and lung compliance, as a consequence of muscle weakness, reduces lung volumes, notably VC.
4. A fall in VC in the supine position, compared with when upright, suggests severe diaphragm weakness or paralysis.
5. With respiratory muscle weakness the maximal expiratory and inspiratory flow-volume loops show a reduction in effort-dependent flows (peak flows) and a sharp fall in end-expiratory flow.
6. Reduced maximal flows in neuromuscular disease may reflect poor respiratory muscle coordination.
7. Maximum inspiratory and expiratory flow-volume curves showing sawtooth oscillations are seen when the upper

airway muscles are weak and also in patients with extrapyramidal disorders (e.g., Parkinson's disease).

8. Pa_{O_2} and Pa_{CO_2} are affected by muscle weakness. Mild weakness causes slight hypoxemia and hypocapnia; severe weakness causes hypercapnia, but only when strength is < 40% predicted. A raised bicarbonate level may suggest muscle weakness.
9. Respiratory muscle weakness may cause desaturation and hypercapnia during REM sleep.
10. CO transfer (DL_{CO}) in patients with muscle weakness is normal or mildly reduced but, as with other causes of extrapulmonary lung volume restriction, the transfer coefficient (K_{CO}) is often raised.

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2. Tests of Respiratory Muscle Strength

PRESSURE MEASUREMENTS

Muscles have two functions: to develop force and to shorten. In the respiratory system, force is usually estimated as pressure and shortening as lung volume change or displacement of chest wall structures. Thus, quantitative characterization of the respiratory muscles has usually relied on measurements of volumes, displacements, pressures, and the rates of change of these variables with time.

Several important considerations have to be kept in mind:

1. Pressures at a given point are usually measured as a difference from barometric pressure.
2. Pressures measured at a point are taken to be representative of the pressure in that space. Differences in pressure at different locations in normal subjects can arise from two causes: gravity and shear stress (1). Gravity causes vertical pressure gradients related to the density of the contents of the space. In the thorax this gradient is $0.2 \text{ cm H}_2\text{O} \cdot \text{cm}^{-1}$ height and is related to lung density. In the abdomen, this gradient is nearly $1 \text{ cm H}_2\text{O} \cdot \text{cm}^{-1}$ height. Pressure fluctuations are usually little affected by gravitational gradients. Deformation of shape-stable organs can cause local variations in pressure, such as those that occur when the diaphragm displaces the liver during a large forceful diaphragmatic contraction (2). Pleural pressure may not be uniform in patients with disordered lung architecture, particularly emphysema. The schematic drawing in Figure 1 shows relationships between pressures and intervening respiratory structures and equipment.
3. Pressure differences across structures are usually the relevant “pressures” for characterizing those structures. Table 1 lists pressures measured at a point and pressure differences across structures, which are usually taken in a direction such that positive pressure differences inflate the structure or lung.
4. A pressure difference between two points is always the pressure difference across two or more structures or groups of structures. For example, the pressure difference between the pleural space and the body surface in a breathing person is both the trans-chest wall (transthoracic) and the transpulmonary pressure.

The relationship between pressure and force is complex. For example, thoracic geometry plays a major role in the efficiency of the conversion of force into pressure. The latter also depends on the mechanical characteristics of the rib cage and abdominal wall with which respiratory muscles interact: a stiffer rib cage better resists distortion and therefore allows more pressure to be produced by the diaphragm for a given level of force (3). It follows that pressures should be viewed as indices of global respiratory muscle “output” rather than as direct measures of their “contractile properties.” Phonomyography could in future provide information related to force (4, 5) (*see also* sections on fatigue).

To test respiratory muscle properties, pressures can be measured either during voluntary maneuvers (*see* subsequent section) or during involuntary contractions, notably in response to phrenic nerve stimulation (*see* subsequent section). In the former, the synergistic action of several inspiratory or

expiratory muscle groups is tested. In the latter, the pressure developed is specific to the contracting muscle(s).

The purpose of this article is to describe the methodology used to measure the various pressures for the assessment of respiratory muscle strength.

DEVICES FOR MEASURING PRESSURES

A comprehensive review of the techniques for measurement of pressures in respiratory physiology and of the associated problems was presented by Milic-Emili (6) in 1984.

Pressure Transducers

As for most pressure measurements of respiratory events, a frequency response flat up to 10–15 Hz is adequate to measure both dynamic and static pressures related to contractions of respiratory muscles. The frequency response of a transducer can be much altered by the characteristics of the systems attached to it, including balloons, tubing, and interconnecting fittings (7) (*see* subsequent section). Thus, testing the response characteristics of any transducer with the specific connectors and fittings that are to be used to make the measurements of pressure is highly recommended (7).

When differential pressure transducers are used, care must be taken that their two sides have identical frequency responses. Calibration is best made with water manometers. Electrical calibration is acceptable, but should be checked regularly with a water manometer.

The required range and sensitivity of the transducers depends on the test in question. Phrenic nerve stimulation in disease may develop pressures as low as a few centimeters of water, whereas maximal static maneuvers in healthy subjects can be associated with positive and negative pressures exceeding 200 cm H₂O. It may be possible to use a single type of transducer for all respiratory muscles tests, provided that it is sufficiently sensitive, with a resolution of approximately 0.5 cm H₂O and a range $\pm 200 \text{ cm H}_2\text{O}$. Pressure differences between two points can be measured directly with two catheters connected to a single differential pressure transducer.

Excellent pressure transducers, with such characteristics, are commercially available, including devices based on a metal “membrane.” More recently, other types of transducer that provide good results (e.g., piezoelectric transducers) have been made available at lower cost.

Probes for “Internal” Pressures

Balloon catheter systems. The balloon catheter system is the most widely used method for recording esophageal pressure (Pes, Poes; *see* APPENDIX for a list of abbreviations) as a reflection of pleural pressure (Ppl), and gastric pressure (Pga) as a reflection of abdominal pressure (Pab) (8). Air-containing latex balloons are sealed over catheters, which in turn transmit pressures to the transducers. Single- and double-balloon catheter systems are commercially available, but can be made in-house at low cost. Double-balloon catheters associated with an electromyograph (EMG) electrode have been used (9–11). When choosing or preparing a balloon catheter system, careful attention must be given to its physical characteristics. Indeed, the volume of the balloon, its volume–pressure characteristics, and the dimensions of the catheter can influence the measurement of pressure and introduce major errors. Standardization has been proposed (12).

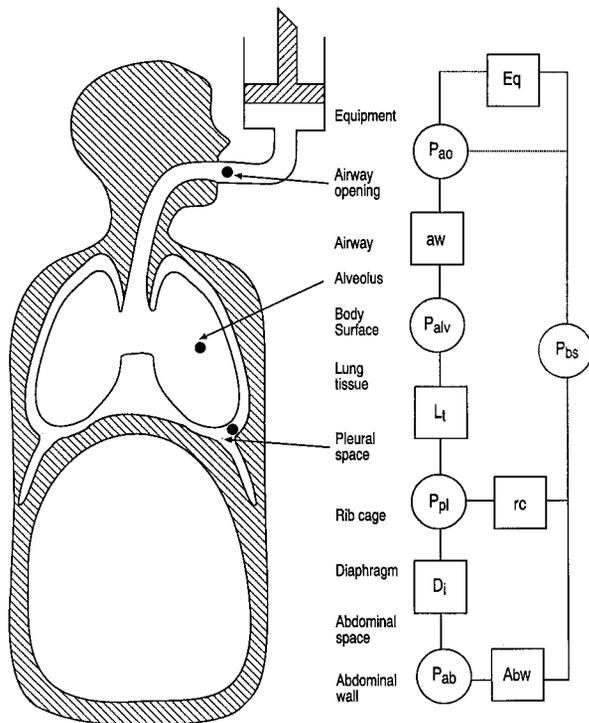


Figure 1. Locations at which pressures can be measured, and pressure differences derived from them (see also Table 1). AbW = abdominal wall; aw = airway; Di = diaphragm; Eq = equipment; Lt = lung tissue; Pab = abdominal pressure; Palv = alveolar pressure; Pao = pressure at airway opening; Pbs = body surface pressure; Ppl = pleural pressure; rc = rib cage.

For the measurement of P_{es} , good results have been provided by latex balloons 5–10 cm long, 3.5–5 cm in perimeter, and with a thin wall (8, 13, 14). For accurate transmission of pressure, air should be introduced into the balloon until it is fully distended to smooth out folds, and then most of the air removed so that a volume is retained at which the rubber is unstretched without distending the esophagus significantly. A volume of 0.5 ml is adequate for balloons with these characteristics. The volume displacement coefficient of the balloon catheter–transducer system should be measured, particularly if the balloon will measure positive pressures, to ensure that the pressure level to be measured does not completely empty the balloon into the catheter and transducer. Thus, if high positive pressures are to be measured (e.g., for P_{es} during maximal expiratory maneuvers) a volume of 0.5 ml may be inadequate (6). Balloon volumes should be checked repeatedly during measurements.

For the measurement of P_{ga} , balloon volume is less crucial and measurements can be made with a balloon volume of 1–2 ml, given that this remains within the range of volume over which the rubber is unstretched. If studies of relatively long duration are planned, the walls of the gastric balloon should be thicker than those of esophageal balloons to increase resilience to gastric secretions.

Respiratory muscle studies can involve dynamic maneuvers with high rates of change in pressure (e.g., sniffs and twitches) resulting in a significant risk of a damped signal if the frequency response of the measuring system is inadequate, as may occur if the internal diameter of the catheter is too small or the gas volume too large. Polyethylene catheters with an internal diameter 1.4–1.7 mm and 70–100 cm in length provide, when associated with adequate transducers, an appropriate frequency response (6).

TABLE 1. PRESSURES FOR BASIC RESPIRATORY MECHANICS

Pressures at a location

P_{ao} = airway opening pressure
 P_{alv} = alveolar pressure
 P_{pl} = pleural pressure
 P_{ab} = abdominal pressure
 P_{bs} = body surface pressure

Pressure differences across structures

$P_{el(L)}$ = elastic recoil pressure of the Lung (pressure across lung tissue)
 P_L = transpulmonary pressure (also P_{tp})
 P_{rc} = pressure across the rib cage
 P_{aw} = flow-resistive pressure in airways
 P_{cw} = pressure across the chest wall
 P_{di} = transdiaphragmatic pressure
 P_{rs} = transrespiratory system pressure
 P_{abw} = transabdominal wall pressure
 P_{eq} = pressure across the equipment

Relationships among pressures

$$\left. \begin{aligned} P_{aw} &= P_{ao} - P_{alv} \\ P_{el(L)} &= P_{alv} - P_{pl} \\ P_{rc} &= P_{pl} - P_{bs} \\ P_{di} &= P_{pl} - P_{ab} \\ P_{abw} &= P_{ab} - P_{bs} \end{aligned} \right\} = \left. \begin{aligned} P_L &= P_{ao} - P_{pl} \\ P_{cw} &= P_{pl} - P_{bs} \end{aligned} \right\} P_{rs} = P_{ao} - P_{bs} = -P_{eq}$$

The catheter should be reasonably stiff, with a series of holes arranged in a spiral pattern over the entire portion of the catheter covered by the balloon, because the gas in the balloon tends to shift to the point where the pressure surrounding it is most negative, i.e., the top of the balloon in upright subjects.

Liquid-filled catheters. Fluid-filled catheter systems have been employed, mainly in neonates and small animals for study of respiratory mechanics. Their advantage is that the transmission of pressure involving a noncompressible fluid (usually water) gives a high-frequency response. The catheters can, thus, be thinner than for balloons, theoretically reducing discomfort. An important practical difficulty is the need for regular flushing of the catheter, to avoid plugging of distal holes and to keep the catheter–manometer system free of air bubbles, which may dampen the measured pressure. Another drawback is that while the gas bubble in the balloon migrates to the point where the pressure is least (which is thought to minimize artifacts in the esophagus and to locate pressure at the surface of the gastric air bubble in the stomach) in a liquid-filled catheter, pressure is always measured at the end of the catheter, which may not be the optimal site. Respiratory muscle studies in adult humans with this technique are limited or not described, and its place in this context is probably limited.

Catheter-mounted microtransducers. Catheter-mounted microtransducers, often referred to as Millar catheters (15, 16), have a level of performance comparable to that of balloon catheters (17, 18). Their management during long studies is probably easier, with a lower risk of technical problems (e.g., leaking balloons), and they may be easier to tolerate for the subject. Their frequency response is high, which may eliminate the phase lag sometimes seen with balloon catheters during extremely rapid pressure changes. However, catheter-mounted microtransducers record pressure at a single focused point so that the measured P_{es} may not be as representative of P_{pl} as balloon catheters, which sample pressure at the point where it is most negative. They are also much more expensive than balloon catheter systems, and may be difficult to sterilize and reuse with confidence.

Other systems. Other systems exist to measure pressures in humans, including fiberoptic sensors. Fiberoptic sensors have long been used for measurement of intracerebral pressures in

neurosurgery (19) (for review, *see* Yellowlees [20] and Shapiro and coworkers [21]). They are probably adequate to measure respiratory pressures (22), and may offer advantages over other devices, including decreased chance of false measurements due to occlusion with water or mucus, less chance of kinking, and, possibly, more rapid response to pressure changes. This remains to be precisely established, and, apparently, no study of fiberoptic systems in respiratory muscle tests is available.

Devices for Measurement of Airway Opening Pressure

Air-filled catheter systems are commonly used to measure pressures in airways and at the mouth. Airway opening pressure (Pao) is usually sampled from a side tap (lateral pressure) in a mouthpiece (Pmo), tracheal tube (Ptr), face mask (Pmask), or from a nostril plug (Pnas) (23). For nasal pressure to reflect airway pressure there must be free communication between the nostrils and mouth, with nasal flows. If Pao is measured from a side tap of a mouthpiece or a tracheal tube during a maneuver that involves gas flow, the cross-section of the device through which the subject breathes must be large enough to avoid measurement errors due to the Bernoulli effect (24). In some cases, Pao serves to estimate alveolar pressure (P_A , Palv) during dynamic respiratory efforts made against an obstructed airway (e.g., mouth pressure response to phrenic nerve stimulation). For Pao to reflect P_A accurately the transmission of pressure from the alveoli to the airway has to be very fast. The time constant of transmission is the product of the flow resistance offered by the airways (R_{aw}) and the compliance of the extrathoracic airways (C_{uaw}) including the mouth, cheeks, and equipment. In practice the internal volume of the measuring equipment (mouthpiece, face mask, tracheal tube) contributes negligibly to the time constant (6), but should be minimized in patients with an already increased time constant, such as patients with chronic obstructive pulmonary disease (COPD). The compliance of the cheeks can be minimized by holding them rigid with the hands.

TECHNIQUES FOR PRESSURE MEASUREMENT

Esophageal, Gastric, and Transdiaphragmatic Pressures

Scientific basis. Transdiaphragmatic pressure (Pdi) is defined as the difference between Ppl and Pab (13) and, in practice, is generally equated to the difference between Pes and Pga, so that $Pdi = Pga - Pes$ (where Pes is usually, but not always, negative). This is contrary to most pressures across a structure, which are taken at a direction such that positive pressures inflate (e.g., positive transpulmonary pressures inflate the lung). For this reason Pdi is also sometimes defined as $Pdi = Pes - Pga$. As the diaphragm is the only muscle in which contraction simultaneously lowers Pes and increases Pga, an increase in Pdi is, in principle, the result of diaphragmatic contraction unless there is passive stretching. An inspiratory effort produced with a completely passive unstretched diaphragm is associated with a negative change in Pes and Pga but no change in Pdi. This assumes that changes in Pes or Pga induced by mechanisms other than diaphragm contraction are uniformly transmitted across the diaphragm from one compartment to the other. This is probably true when the diaphragm is relaxed (6, 13) at functional residual capacity (FRC), but may be modified when the diaphragm is stretched, as at low lung volumes.

Methodology. Pes and Pga are most often measured by passing a pair of probes, generally balloon catheters (*see* previous passages), through the nose, following local anesthesia of the nasal mucosa and pharynx. Their position is usually assessed by asking the subject to perform sharp sniff maneuvers while monitoring the signal on an oscilloscope or computer

screen. A simple technique is to advance both probes well into the stomach, as judged by a positive deflection during a sniff and then to withdraw one of them until the sniff-related pressure deflection first becomes negative, indicating that the balloon has entered the esophagus. It is then withdrawn a further 10 cm. The validity of the Pes measurement can be checked by matching Pes to Pao during static Mueller (inspiratory) maneuvers (the dynamic occlusion test) (6, 12, 14). Displacement of balloons is minimized by taping the catheters to the nose. The distance between the nostril and the tip of the balloons varies with the size of the subject, but is usually 35–40 cm for Pes and 50–60 cm for Pga in adults.

Placing the probes becomes more difficult when the subject cannot perform voluntary inspiration (e.g., with anesthetized patients, diaphragmatic paralysis, cognitive impairment, or muscle incoordination). The pressure signals during a swallow can then be useful: A balloon is positioned in the esophagus if swallowing is associated with a slow, powerful rise in pressure, whereas if this does not occur the balloon is likely to be in the stomach. Measurement of balloon distance from the nostril can be a useful indication of its position.

It is advisable to measure Pes and Pga separately by using two pressure transducers, with Pdi derived from a third differential pressure transducer or reconstructed electronically offline. This allows the investigator to monitor balloon position and detect confounding events such as esophageal spasms, as well as recording the three pressures independently. Resting Pga is usually positive with respect to atmosphere due to hydrostatic pressure in the abdomen. For respiratory muscle measurements Pga is conventionally taken as zero at resting end expiration.

Advantages. Pdi is specific for diaphragm contraction (*see* previous passages). Separate measurements of Pes and Pga provide information on the components of this contraction and Pes on the inspiratory driving pressure (Pes/Pdi ratio).

Disadvantages. The procedures require the subject's cooperation and occasionally untrained healthy volunteers can fail to increase Pdi because of lack of coordination, in the absence of any diaphragmatic abnormality (25). This is, however, unusual during the inspiratory phase of quiet breathing at rest. The measurements are mildly uncomfortable, both initially (when swallowing the catheters) and during studies. However, the discomfort of swallowing a thin catheter is small compared with other established medical procedures and scarcely "invasive." Good-quality equipment and adequate practice minimize the discomfort, but some skill is necessary and passing the probes can be time-consuming. Particular care must be taken in patients with impaired swallowing, as well as esophageal diseases, or disorders at the level of the gastroesophageal sphincter.

Mouth Pressure and Nostril Pressure

Scientific basis. Pmo is easy to measure and changes may give a reasonable approximation of change in alveolar pressure and thus Pes, providing there is relatively little pressure loss down the airways, or across the lungs. This may be realistic with normal lungs, particularly when changes in lung volume are small, but is unlikely to be fulfilled in patients with severe lung or airway disease. When used in combination with voluntary static and dynamic maneuvers at FRC, Pmo provides a global index of the action of synergistic respiratory muscles. When the diaphragm contracts in isolation against a closed airway, as with phrenic nerve stimulation, Pmo may be a useful reflection of Pdi.

Pnas is also easy to measure (*see* VOLITIONAL TESTS OF RESPIRATORY MUSCLE STRENGTH) but has the same caveats as Pmo.

Methodology. Pmo is measured at the side port of a mouthpiece. It should be possible to occlude the mouthpiece at the distal end and a small leak should be incorporated to prevent glottic closure during inspiratory or expiratory maneuvers (26). The type of mouthpiece used can significantly influence the results (27). The issue of the lung volume at which Pmo should be measured during static efforts is addressed in the section on volitional tests (see subsequent section), and the various maneuvers that can be used to obtain useful Pmo data during phrenic nerve stimulation are described in the section on phrenic nerve stimulation (see subsequent section).

Pnas is measured with a polyethylene catheter held in one nostril by a soft, hand-fashioned occluding plug; respiratory maneuvers are performed through the contralateral nostril (23).

A standard mouthpiece for Pmo, or a nasal plug (custom made or commercially available) for Pnas, and one pressure transducer are required. Portable Pmo devices (28) are useful for screening and bedside studies.

Advantages of mouth pressure and nasal sniff pressure. The main advantage of Pmo and Pnas are their simplicity and ease of use, both for the operator and for the subject.

Disadvantages of mouth pressure and nasal sniff pressure. The measurement of Pmo does not allow the investigator to discriminate between weakness of the different respiratory muscles. When Pmo or Pnas is used as a substitute for Pes during dynamic maneuvers (sniff test, phrenic nerve stimulation), glottic closure or airway characteristics may prevent adequate equilibration.

VOLITIONAL TESTS OF RESPIRATORY MUSCLE STRENGTH

The principal advantage of volitional tests is that they give an estimate of inspiratory or expiratory muscle strength, are simple to perform, and are well tolerated by patients. Passage of balloon catheter systems into the esophagus and/or stomach is not usually required. However, it can be difficult to ensure that the subject is making a truly maximal effort. Although normal subjects can potentially activate peripheral and respiratory muscles fully during voluntary efforts (29), even experienced physiologists cannot always do this reliably for respiratory efforts (30) and naive subjects have even greater difficulty (31). Thus, it is hard to be certain whether low mouth pressure measurements truly represent reduced strength, or merely reduced neural activation. Indeed, there may be some activation of agonist muscles simultaneously (32). However, in practice a normal result can be of value in precluding clinical weakness.

Maximal Static Inspiratory and Expiratory Pressure

Scientific basis. Measurement of the maximum static inspiratory pressure that a subject can generate at the mouth (P_{imax}) or the maximum static expiratory pressure (P_{emax}) is a simple way to gauge inspiratory and expiratory muscle strength. The pressure measured during these maneuvers reflects the pressure developed by the respiratory muscles (P_{mus}), plus the passive elastic recoil pressure of the respiratory system including the lung and chest wall (Prs) (Figure 2 [33]). At FRC, Prs is zero so that Pmo represents P_{mus}. However, at residual volume (RV), where P_{imax} is usually measured, Prs may be as much as -30 cm H₂O, and thus makes a significant contribution to P_{imax} of up to 30% (or more if P_{mus} is decreased). Similarly, P_{emax} is measured at total lung capacity (TLC), where Prs can be up to +40 cm H₂O. Clinical measures and normal values of P_{imax} and P_{emax} do not conventionally subtract the respiratory system recoil.

The mouth pressures recorded during these maneuvers are assumed to reflect respiratory muscle strength (P_{mus}) if Prs is subtracted. However, maximum muscle strength in skeletal muscles is the force developed under isometric conditions with a muscle at its optimal length. In generating pressures during respiratory maneuvers, muscle shortening (or lengthening) may occur, with changes in force-velocity and force-length relationships (34-36). The relationship between the tension (force) generated by a respiratory muscle (strength) and the pressure produced in the thorax or mouth is complex. The diaphragm is both a curved structure and acts as a piston so that the pressure or force per unit area output is only indirectly related to muscle tension. In addition, the mechanical linkage of each individual respiratory muscle within the chest wall and with other inspiratory or expiratory muscles influences the net pressure produced. Thus, even though activation may be maximal, the pressure produced is derived from a complex set of interactions within and between muscles and the chest wall and its contents. Nevertheless, it is the pressure developed by the inspiratory muscles that drives ventilation and, in spite of the many assumptions, these measures can usefully reflect global respiratory muscle strength for clinical evaluation as well as physiological studies. Thus, when respiratory muscle weakness occurs, the P_{imax} can be more sensitive than the VC because the relationship between VC and P_{imax} is curvilinear (37), so that decreases in respiratory muscle strength occur before decreases in lung volume can be identified. On the other hand, between- and within-individual variation in muscle strength is considerably greater than that for vital capacity. Between-individual variability may reflect the large variations in strength in normal individuals.

Because of the force-length relationship and the varying contribution of Prs, P_{imax} and P_{emax} vary markedly with lung volume (38). Subjects find it easier to maximize their inspiratory efforts at low lung volumes and expiratory efforts at high volumes; therefore, by convention and to standardize measurement, P_{imax} is measured at or close to RV and P_{emax} at or close to TLC. In some laboratories P_{imax} and P_{emax} are measured at FRC, and this may be more accurate for certain research studies, but in this case the lung volume should be specifically stated (39). In patients with abnormally high lung volumes (e.g., patients with COPD), a low P_{imax} may partly reflect the shortened inspiratory muscle fiber length associated with increased lung volume at RV rather than reduced inspiratory muscle strength (Figure 3). Furthermore, hyperinflation is often associated with intrinsic positive end-expiratory pressure (PEEP_i), so inspiratory efforts start from a negative airway pressure. Thus, if P_{imax} is measured as the maximal negative airway pressure, it will underestimate the actual pressure generated by the inspiratory muscles. Optimally, under such circumstances, P_{imax} should be measured as the total negative deflection of the occluded airway pressure during the inspiratory effort, including the effort required to draw down PEEP_i.

Methodology. A number of authors have reported normal values for P_{imax} and P_{emax} (see Table 2 [26, 40-44]). The variation between these results presumably indicates differences between the groups studied and the way in which the tests were performed and measured. Here, we propose a standardized approach to test performance and measurement.

Flanged mouthpieces are readily available in pulmonary function laboratories and although they give values somewhat lower than those obtained with a rubber tube mouthpiece, the differences are not usually material in a clinical setting (27). These mouthpieces are also easier for patients to use, especially those with neuromuscular weakness. The flanged mouthpiece

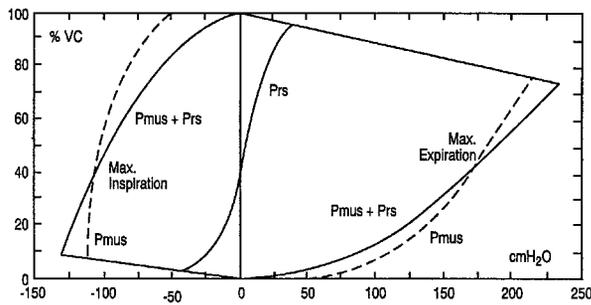


Figure 2. Relationship of muscle and respiratory pressures at different lung volumes. Vertical axis: lung volume as a percentage of vital capacity (%VC). Horizontal axis: alveolar pressure in cm H₂O. The broken lines indicate the pressure contributed by the muscles. P_{mus} = pressure developed by the respiratory muscles; P_{rs} = pressure of the respiratory system. Reprinted by permission from Reference 33.

can be attached to a short, rigid tube with a three-way tap or valve system to allow normal breathing followed by either a maximum inspiratory or expiratory maneuver (Figure 4). For research studies it may be preferable to use a rubber tube as mouthpiece (26). However, this has to be held tightly around the lips, to prevent leaks. This can be difficult for patients and naive subjects particularly at high pressures, leading to significant pressure losses. The system requires a small leak (approximately 2-mm internal diameter [id] and 20–30 mm in length) to prevent glottic closure during the P_{imax} maneuver and to reduce the use of buccal muscles during the P_{Emax} maneuver. The inspiratory and expiratory pressure must be maintained, ideally for at least 1.5 seconds, so that the maximum pressure sustained for 1 second can be recorded. The peak pressure may be higher than the 1 second of sustained pressure but is believed to be less reproducible.

Historically, the aneroid manometer was used to measure the pressure but this is not recommended as the analog signal on the dial can be difficult to read accurately and pressure transients are difficult to eliminate. Mercury should be avoided for safety reasons. A recording system should be used to collect the pressure data and display it in analog form (strip chart recorder), or it can be digitized and displayed for measurement (28) or the 1-second average computed (Figure 5). The pressure transducers should be calibrated regularly against a fluid manometer with baseline pressure equal to atmospheric pressure.

The test should be performed by an experienced operator, who should strongly urge subjects to make maximum inspiratory (Mueller maneuver) and expiratory (Valsalva maneuver) efforts at or near RV and TLC, respectively. Subjects are normally seated and noseclips are not required. Because this is an unfamiliar maneuver, careful instruction and encouraged motivation are essential. Subjects often need coaching to prevent air leaks around the mouthpiece and to support the cheeks during the expiratory efforts, and this may be helped by having them pinch their lips around the mouthpiece. Once the operator is satisfied, the maximum value of three maneuvers that vary by less than 20% is recorded. Less variability may be necessary in a research setting, but even low variability may not guarantee that maximal efforts have been made (45).

Advantages. The pressures measured at the mouth during maximum inspiratory or expiratory maneuvers are widely used specific tests of respiratory muscle strength. Normal values are available for adults, children, and the elderly. The tests are not complicated to perform and are well tolerated by patients. The recent development of hand-held pressure meters means the technique may be easily used at the bedside (28).

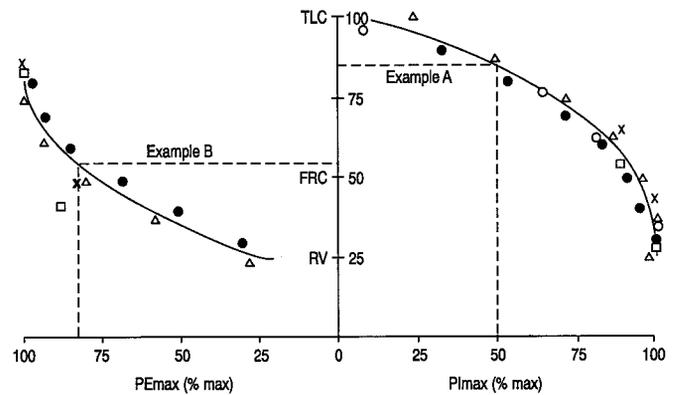


Figure 3. Relationship between maximal static respiratory pressure (P_{imax}, P_{Emax}) and lung volume. Pressures are expressed as a percentage of TLC and the lung volume is expressed as a percentage of TLC. Symbols are data from different studies (39). *Example A* represents a patient with emphysema whose RV is 85% TLC, at which lung volume his predicted P_{imax} is only 50% of that at normal RV. Conversely, *Example B* represents a patient with lung fibrosis with TLC of 55% predicted, at which volume her P_{Emax} is 82% maximum. Reprinted by permission from Reference 39.

Disadvantages. These tests are volitional and require full cooperation. Accordingly, a low result may be due to lack of motivation and does not necessarily indicate reduced inspiratory or expiratory muscle strength.

Normal values and applications. The recorded values of P_{imax} and P_{Emax} may be compared with published normal values (Table 2). The values that most closely reflect the protocol described here with a flanged mouthpiece, are those obtained by Wilson and coworkers (43). Normal values for the elderly (46–48) and children (43, 49–51) have been reported. The normal ranges are wide (Table 2), so that values in the lower quarter of the normal range are compatible both with normal strength and with mild or moderate weakness. However, a P_{imax} of –80 cm H₂O usually excludes clinically important inspiratory muscle weakness. Values less negative than this are difficult to interpret and in such circumstances it would be appropriate to undertake more detailed studies. A normal P_{Emax} with a low P_{imax} suggests isolated diaphragmatic weakness.

Regional measurements. Static respiratory muscle pressures generated against a closed airway can be recorded from bal-

TABLE 2. REFERENCE NORMAL RANGES FOR P_{Emax} AND P_{imax}*

No.	P _{Emax}	P _{imax}	Source (Ref.)	Mouthpiece Design
Male				
106	23.4 ± 4.5	12.7 ± 3.1	40	Tube
60	22.8 ± 4.1	12.1 ± 2.1	26	Tube
80	21.2 ± 4.4	12.4 ± 2.7	41	Tube
325	15.1 ± 8.0	11.1 ± 3.5	42	Flanged
80	14.4 ± 3.3	10.4 ± 3.0	43	Flanged
46	13.7 ± 3.7	10.3 ± 2.5	44	Flanged
Female				
94	16.1 ± 2.9	9.6 ± 2.4	40	Tube
60	14.9 ± 2.6	8.5 ± 1.5	26	Tube
121	13.5 ± 6.7	8.9 ± 2.4	41	Tube
480	9.2 ± 3.2	7.0 ± 2.6	42	Flanged
87	9.1 ± 1.6	7.2 ± 2.1	43	Flanged
60	8.7 ± 2.3	6.9 ± 2.3	44	Flanged

Definition of abbreviations: P_{Emax} = maximum static expiratory pressure; P_{imax} = maximum static inspiratory pressure.

* Values represent kilopascals (1 kPa = 10.19 cm H₂O), mean ± SD.

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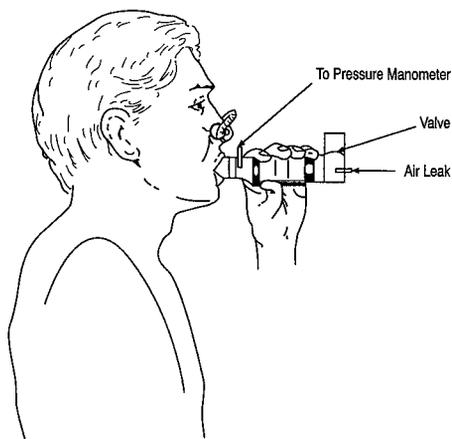


Figure 4. Measurement of maximal static respiratory pressures. A flanged mouthpiece with a nose clip is the preferred technique. A small leak is introduced into the system, and a valve system allows a normal breath to be followed by a maximum maneuver.

loon catheter systems passed into the esophagus (*see* TECHNIQUES FOR PRESSURE MEASUREMENTS) to measure P_{es} as a reflection of P_{pl} or into the stomach where P_{ga} can be used to reflect P_{ab} . Esophageal pressure does not include lung elastic recoil pressure but does include chest wall recoil pressure. The main indication for balloon catheter measurements of maximum respiratory muscle pressures is to estimate the strength of the separate muscle groups, notably the diaphragm (from P_{di}), or to measure strength when the patient is unable to maintain a proper seal around the mouthpiece.

With the balloon catheters in place, various maneuvers can be used to assess global inspiratory muscle or diaphragm strength. These tests are usually performed at FRC. In the Mueller (maximal inspiratory) maneuver the diaphragm and inspiratory muscles are contracted with the aim of creating the biggest negative thoracic pressure without regard to abdominal pressure. However, this usually does not generate maximum P_{di} (25, 52). As an alternative, the subject may perform an expulsive maneuver, wherein the individual is requested to “bear down as for defecation” and simultaneously superimposes a Mueller maneuver. When given visual feedback, this complex maneuver can be mastered by trained subjects to give the largest values of P_{di} (up to 240 cm H₂O or more) (53). It may reflect nearly maximal neural activation of the diaphragm, perhaps with fiber lengthening (52, 54). However, the technique is difficult for naive subjects and in the clinical setting (55). Twitch occlusion studies have confirmed that such maneuvers can produce maximal neural activation of the diaphragm (56).

Advantages and disadvantages for regional measurements. The measurement of maximum static transdiaphragmatic pressure, $P_{i,di,max}$, produced during the described maneuvers, can provide specific information about maximal diaphragm strength. However, these tests require passage of balloon catheters and the necessary coordination is difficult for naive subjects and patients. There are limited normal data. It is difficult to control for muscle (fiber) length, and for velocity of shortening. This test is recommended only as a research tool or in respiratory muscle function laboratories with specialized expertise.

Sniff Tests

Scientific basis. A sniff is a short, sharp voluntary inspiratory maneuver performed through one or both unoccluded nostrils. It involves contraction of the diaphragm and other inspiratory muscles. To be useful as a test of respiratory muscle strength, sniffs need to be maximal, which is relatively easy for most willing subjects, but may require some practice.

The sniff was described in 1927 as a radiological test of diaphragm paralysis because, in normal subjects, it was associated with crisp diaphragm descent during inspiration (57, 58). Esau and coworkers (59) suggested that a short, sharp sniff would approximate the diaphragm contraction elicited by a brief stimulation of the phrenic nerves (59, 60). Miller and coworkers (61) showed that normal subjects generated greater P_{di} during maximal sniffs than during maximal static inspiratory efforts, perhaps because the maneuver achieves rapid, fully coordinated recruitment of the inspiratory muscles (62). The detailed respiratory mechanics of this dynamic maneuver have been little studied, but numerous studies using the sniff in normal subjects and patients have found it to be a robust measure. The nose appears to act as a Starling resistor, so that nasal flow is low and largely independent of driving pressure, P_{es} (63). P_{di} measured during a sniff ($P_{di,sn,max}$) reflects diaphragm strength and P_{es} reflects the integrated pressure of the inspiratory muscles on the lungs (Figure 6).

More recently it has been suggested that pressures measured in the mouth, nasopharynx, or one nostril give a clinically useful approximation to esophageal pressure during sniffs (64, 65). Because these measurements do not require the passage of esophageal or gastric balloons, they are easier for operator and subject. However, pressure transmission may be impaired, particularly when there is significant disease of the lungs (66).

Methodology. For measurement of maximal sniff pressures, patients are encouraged to make maximum efforts. Sniffs can be achieved only when one or both nostrils are unoccluded, to allow the passage of air. An occluded sniff may be called a “gasp,” and is more difficult for subjects to perform reproducibly. Subjects should be instructed to sit or stand comfortably, and to make sniffs using maximal effort starting

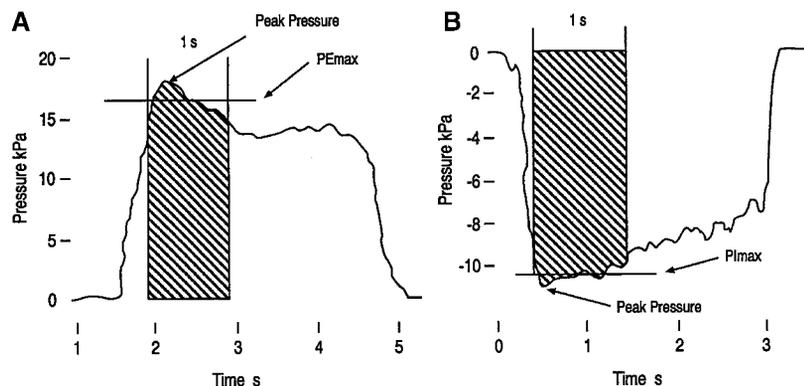


Figure 5. (A) A typical pressure tracing from a subject performing a maximum expiratory maneuver (P_{Emax}). A peak pressure is seen and the 1-second average is determined by calculating the shaded area. (B) A pressure tracing from a subject performing a maximum inspiratory maneuver ($P_{I,max}$).

from relaxed end expiration. Detailed instruction on how to perform the maneuver is not necessary, and may be counterproductive. However, subjects should be exhorted to make maximal efforts, with a rest between sniffs. Most subjects achieve a plateau of pressure values within 5–10 attempts.

Transdiaphragmatic pressure during sniff. Esophageal and gastric balloons are passed by the usual technique. Transdiaphragmatic pressure during sniff ($P_{di,sn}$) is reasonably reproducible within normal subjects, although there is wide variability between subjects (61) (Table 3). The values tend to be as large, or larger, than P_{di} during maximum static inspiratory efforts (61).

Esophageal pressure during sniff. The methodology is as for $P_{di,sn}$ but with the passage of an esophageal balloon alone.

Nasal sniff pressure. Pressure is measured by wedging a catheter in one nostril. Various techniques for wedging are available including foam, rubber bungs, and dental impression molding. The subject sniffs through the contralateral unobstructed nostril. The pressure in the obstructed nostril reflects the pressure in the nasopharynx, which is a reasonable indication of alveolar pressure. This in turn approximates esophageal pressure, particularly if the lungs are normal with a mean P_{nas}/P_{es} ratio of 0.92 (64, 66). In COPD, nasal sniff pressure ($P_{nas,sn}$) tends to underestimate esophageal pressure during sniff ($P_{es,sn}$) but can complement P_{max} in excluding weakness clinically (67).

Mouth and nasopharyngeal pressures can also be measured, and also reflect alveolar pressure, but are less easy for the subject than nasal pressure and have no significant advantages (65) (Figure 7).

The sniff is a dynamic maneuver and so a pressure measurement system is required with a frequency response of > 10 Hz. This can be achieved by a standard balloon catheter system with a suitable pressure transducer. Use of catheter-mounted transducers has also been described (18).

Advantages. The sniff is easily performed by most subjects and patients and requires little practice. It is relatively reproducible and has a smaller range of normal values than mouth pressures (61, 62). It is a useful voluntary test for evaluating diaphragm strength in the clinical setting (55), giving equal or greater pressures than maximal static efforts (61, 68).

It is possible to achieve greater transdiaphragmatic pressures by certain maneuvers, such as the modified Mueller maneuver (see previous passages), in highly trained and well-motivated subjects. This may be important in physiological studies but is not usually clinically relevant.

Sniff nasal pressure is technically simple.

Disadvantages. The pressures measured during a sniff may be less than maximal static values because of shortening of the inspiratory muscles (pressure-velocity relationship) (69). The average volume change during a sniff is approximately 500 ml with some gas rarefaction, which may be somewhat more than the volume by which gas expands during a static maneuver against a closed airway (63).

Sniffs are difficult or impossible if there is upper airway distortion, and particularly if the nose is completely obstructed. It may be difficult to pass the balloons if there is severe bulbar weakness, but this would not preclude measurement of P_{nas} .

Sniffs are voluntary maneuvers and, therefore, poorly motivated subjects may perform submaximal efforts. These can often, but not always, be detected as variability tends to be greater than for maximal maneuvers.

The sniff generates rapid pressure changes, so measurement requires a catheter system and transducer with a higher frequency response (see previous passages) than for static maneuvers.

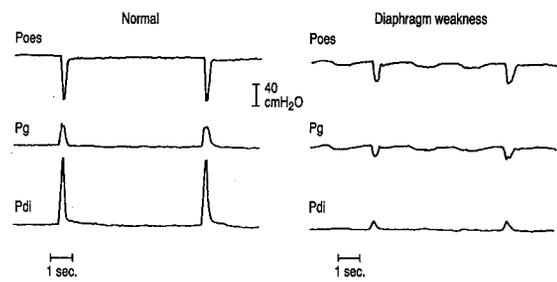


Figure 6. Esophageal (P_{oes}), gastric (P_g), and transdiaphragmatic (P_{di}) pressures measured during maximum voluntary sniffs in a normal subject and in a patient with severe diaphragm weakness. The normal subject reproducibly generates a P_{di} of 120 cm H_2O (11.8 kPa), whereas the weak patient can generate only 15 cm H_2O (1.5 kPa).

Applications. Maximal sniffs have been widely used and validated as reproducible and reliable tests of diaphragm or global inspiratory muscle function. This test can, therefore, be used in research studies, although care must be taken with reproducibility, as in any voluntary maneuver.

The sniff maneuver is a useful part of the clinical evaluation of respiratory muscle strength and correlates well with response to therapy (Figure 6) (68). The normal values are shown in Table 3 (61). There is a wide normal range, reflecting the wide range of normal muscle strength in different individuals. In clinical practice $P_{di,sn,max}$ values greater than 100 cm H_2O in males and 80 cm H_2O in females are unlikely to be associated with clinically significant diaphragm weakness (55). Values of maximal sniff P_{es} or P_{nas} numerically greater than -70 cm H_2O (males) or -60 cm H_2O (females) are also unlikely to be associated with significant inspiratory muscle weakness. However, these reflect the integrated pressure of all the inspiratory muscles and it is possible that there could be a degree of weakness of one or more of these muscles that would not be detected at this level.

Cough Tests

Scientific basis. Measurement of pressure during cough is of interest because the main expiratory muscles, the abdominal muscles, are also those used in cough. Reduced cough pressure is of clinical importance because it may predispose to chest infections. Also, in some patients technical difficulties preclude measurement of mouth pressure during a static maximal expiratory maneuver (P_{Emax}); in these patients measurement of maximal cough pressures is an alternative measurement technique.

A normal cough consists of four phases: inspiratory, compressive, expulsive, and relaxation (70). For cough to be a measurement of expiratory muscle strength, two aspects re-

TABLE 3. TRANSDIAPHRAGMATIC PRESSURES DURING MAXIMAL STATIC RESPIRATORY EFFORTS AND MAXIMAL SNIFFS

	n	$P_{i,di,max}$ (cm H_2O)			$P_{di,sn}$ (cm H_2O)		
		Mean	SD	Range	Mean	SD	Range
Men	37	108	30	52–164	148	24	112–204
Women	27	65	31	16–40	121	25	82–182
All	64	90	37	16–164	137	28	82–204

Definition of abbreviations: $P_{i,di,max}$ = maximum static transdiaphragmatic pressure; $P_{di,sn}$ = transdiaphragmatic pressure during sniff.

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quire consideration: how standard is the maneuver and what should be measured.

Expiratory muscle strength is influenced by lung volume (71). It is normal to take a deep breath before a maximal cough. Thus, although no instructions are given concerning the magnitude of inspiration, the actual lung volume is probably relatively constant for a given individual during serial measurements. Compression requires a functional glottis; in some disorders, for example bulbar type amyotrophic lateral sclerosis, this may not be present (72). A glottis that does not open immediately causes an uncomfortable choking sensation and makes measurement of mouth pressure (during either a P_{EMax} maneuver or a cough) difficult, but would not exclude obtaining useful measurements from a gastric or esophageal balloon (73).

Theoretically, the peak cough pressure could be measured at the mouth, esophagus, or stomach, but measurements at the mouth have not been reported. P_{di} is generated during cough (74) and forced expiration (75) so that $P_{es,co}$ is always less than $P_{ga,co}$ (76). This P_{di} can be substantial in a few subjects (76); it may be due to active contraction of the diaphragm, or passive stretching. In general, gastric pressure can be viewed as a reasonable measure of abdominal muscle strength. The surface EMG from abdominal muscle also varies with cough intensity (77), but difficulties in standardizing it between measurements make this relatively impractical as a measurement of strength.

Methodology. After passage and positioning of appropriate balloon catheters the subject is asked to cough as forcefully as possible. Visual feedback seems to be helpful, as with the diaphragm (53). Peak pressures are measured between the baseline at relaxed end-expiratory lung volume, and peak pressure (Figure 8).

Voluntary coughs are usually initiated from above FRC. Lung volume may need to be controlled or measured, although this may not be necessary for clinical measurements.

It would, theoretically, be possible to measure the pressure generation during an induced (e.g., with citric acid) cough in patients unable to cough voluntarily, for example, those in intensive care units.

Cough pressures can be large, so it is necessary to have an adequate volume of air in the balloon, to avoid compression of the gas bubble in the balloon and its displacement into the catheter-transducer system.

Normal ranges. No normal data exist from large studies. Black and Hyatt (78) found P_{max} and cough esophageal pressures comparable in a subgroup of their subjects. Other authors have found lower values in patients with COPD (79). The mean maximal $P_{ga,co}$ in a small group of normal subjects 20–75 years of age was 230 cm H_2O for men and 166 cm H_2O for women, with lower limits of 160 cm H_2O for men and 120 cm H_2O for women (76).

PRESSURES OBTAINED VIA PHRENIC NERVE STIMULATION

Scientific Basis

The diaphragm is innervated exclusively by the phrenic nerve and thus phrenic nerve stimulation (PNS) provides a specific means to investigate the diaphragm independent of other inspiratory muscles. Indices that may not be specific for diaphragm contraction when measured during voluntary maneuvers do relate to the diaphragm when they are derived from PNS. Examples include surface recordings of the electromyogram of the costal diaphragm (EMG_{di}), P_{mo} or P_{es} , and phonomyogram (PMG_{di}). The other major feature of PNS is that it eliminates the influence of the central nervous system.

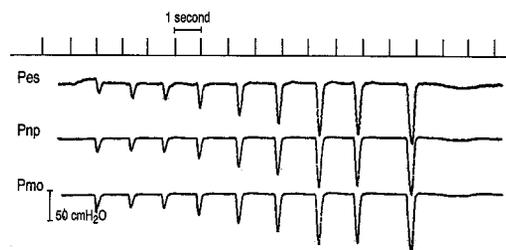


Figure 7. Simultaneous pressure measurements from esophageal (P_{es}), nasopharyngeal (P_{np}), and mouth (P_{mo}) balloons in a normal subject performing sniffs of increasing strength, to illustrate close correlation of the waveforms. Reprinted by permission from Reference 65.

PNS can give important information about the mechanical function of the diaphragm, namely, about how the force of contraction is transformed into pressure, and can be used to confirm whether a contraction is maximal. PNS superimposed on naturally occurring or voluntary contractions (twitch occlusion principle; see subsequent section) can provide an objective estimate of the maximal voluntary pressure that the diaphragm can produce.

Methodology

Since 1980, PNS has been investigated as a technique for elucidating mechanical aspects of diaphragm function. The 1989 National Heart, Lung, and Blood Institute (NHLBI) workshop on respiratory muscle fatigue identified it as one of the most promising techniques in this field (80).

The stimulus to the nerve, which can be an externally applied electric field or secondary currents surrounding a magnetic field (see MAGNETIC STIMULATION), elicits synchronized activation of motor units and subsequent muscle contraction. The effects of phrenic nerve stimulation can be studied both electrophysiologically (see STIMULATION TESTS in Section 3 of this Statement) and mechanically (this Section).

Four main PNS techniques have been used, mostly in healthy volunteers, less often in patients. Two of them, needle stimulation (81, 82) and implanted wire stimulation (83), are invasive, with the risk of hematoma and phrenic nerve damage. Needle stimulation is not now recommended, and is not further discussed. Implanted wire stimulation is probably safer, and may be a convenient means to obtain repeated twitches over long periods of time. The two others techniques, transcutaneous electrical PNS (ES) and magnetic stimulation (MS), have been more extensively studied and have minimal side effects.

Subjects in Phrenic Nerve Stimulation

For laboratory and clinical studies subjects should be sitting in a comfortable chair. Headrests may be helpful for ES.

Lung volume. A major condition for evaluating the pressure response to PNS is adequate relaxation of the respiratory muscles at FRC, or within approximately 500 ml (84).

Posture. Most studies have been performed with seated subjects, but twitch transdiaphragmatic pressure ($P_{di,tw}$) seems to be little altered by posture in contrast to sniff transdiaphragmatic pressure ($P_{di,sn}$) and static P_{di} (56, 65, 84, 85). This feature could be useful in an intensive care unit (ICU) setting.

Abdominal binding. Abdominal binding has little effect on voluntary P_{di} values (86), but markedly increases $P_{di,tw}$ (56, 65, 84, 87). The rationale for binding the abdomen during PNS is to make the contraction closer to isometric than with a com-

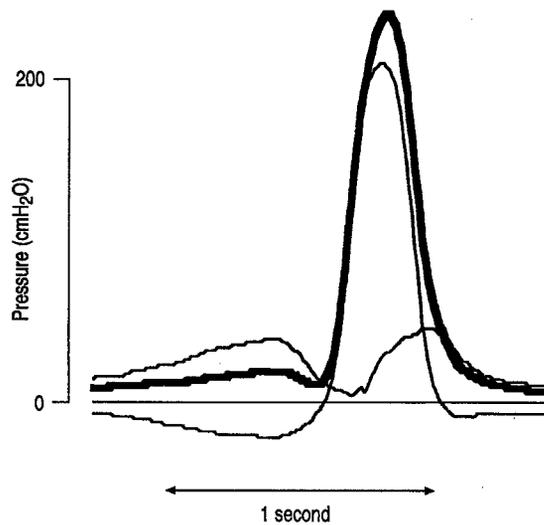


Figure 8. Pressures during a maximal voluntary cough in a normal subject showing high positive gastric pressures generated in abdomen (Pga; thick line) and esophagus (Pes) with low Pdi during the maneuver.

pliant abdominal wall; this may be appropriate for physiological studies (56, 88, 89). In a clinical setting it is difficult to standardize a binding technique and so the abdomen is usually unbound.

Transcutaneous Electrical Phrenic Nerve Stimulation

Scientific basis. An externally applied electrical field induces depolarization of phrenic nerve fibers, at mid-distance between the electrode and the cathode. If the stimulus is intense enough, all fibers are activated synchronously, giving predictable and reproducible results (see STIMULATION TECHNIQUES in Section 3 of this Statement).

Methodology. For bilateral ES, the operator should stand behind the seated subject. The skin in the stimulated region is degreased and mildly abraded to decrease its electrical impedance, allowing lower current intensities. Monopolar or bipolar electrodes can be chosen (Figure 9). For monopolar electrodes, the anode is usually taped on the skin below the clavicle medially, and the cathode is held in the hand. Monopolar electrodes probably make it easier to find the nerve because a greater number of spots can be tested. However, because the electrical field is less focused than with bipolar electrodes, it may be more difficult to avoid costimulation of the adjacent sternocleidomastoid muscle or the brachial plexus. Bipolar electrodes are more specific but are also slightly more difficult to use. Various models of bipolar electrode are commercially available. They generally include felt tips 5 mm in diameter with an interelectrode distance of approximately 2 cm. When performing stimulation, the tips of the electrode should be soaked in saline and the cathode should be proximal.

The phrenic nerve is usually located beneath the posterior border of the sternocleidomastoid muscle, at the level of the cricoid cartilage (Figure 9). It is easier to locate and to isolate from the brachial plexus in subjects with long and slender necks. A simple technique to locate the nerve is to set the stimulator on repetitive stimulation mode, e.g., at a frequency of 1 Hz, with a relatively low intensity, and to try various sites. Identification of the correct site may be aided by careful observation of the abdomen; it will therefore be desirable to remove the shirt. Once the nerve is identified, the operator marks the spot and the orientation of the electrode. Current intensity is then increased, while monitoring the EMG to ob-

tain supramaximal stimulation (see subsequent paragraphs), which is generally achieved with 30- to 50-mA shocks. This procedure is performed on each side separately, before applying ES bilaterally. It is then advisable to reconfirm that stimulation is supramaximal. It is also possible to judge supramaximality from the plateau of pressure response, but changes can be more difficult to interpret unless the plateau procedure is repeated to check that there is no loss of supramaximality.

Equipment. A constant-current stimulator capable of delivering square wave shocks of 0.1-millisecond duration and of modifiable intensity is used, which should include two synchronized outputs to allow bilateral stimulation. Two triggered EMG amplifiers and a display should be available, so that the muscle action potential (M wave) can be checked online by the operator. Several manufacturers provide complete machines that offer a wide panel of sophisticated stimulation and EMG acquisition options. Stimulators and amplifiers can also be bought separately.

Advantages. If skillfully performed, ES generates a "pure" diaphragmatic contraction. The corresponding output is thus representative of diaphragm properties alone. ES can be reproducible in skilled hands.

Disadvantages. The stimulus intensities required to achieve supramaximal stimulation can be uncomfortable. From the technical point of view, there are several difficulties. First, maintaining optimal contact between the stimulating electrode and the nerve can be difficult. It may be necessary to impose a significant degree of pressure on the soft tissues of the neck, which can be painful for the subject and awkward for the operator, particularly in obese or old subjects, or those with hypertrophy of neck muscles. Skin-taped stimulating electrodes have been used in healthy volunteers (90), but they probably do not guarantee reproducible results in all settings. Neck- and electrode-stabilizing devices have been proposed (10, 85) that can be effective, but are cumbersome. Second, it is sometimes impossible to dissociate PNS from brachial plexus stimulation, particularly at high current intensities. This can be a source of discomfort for the subject, and can theoretically modify the characteristics of the rib cage, with which the contraction of the diaphragm interacts. Third, it can be impossible to locate the nerve, or to do so easily enough to obtain reliable supramaximal stimulation. Because of these difficulties, maintaining a constant symmetric maximal stimulus may need repetitive ES, which in itself can increase twitch pressure by potentiation or the staircase phenomenon (91, 92) (see also TWITCH POTENTIATION).

The technical expertise required for effective ES may, thus, be a source of variability in research studies and limit its use in the clinical field, particularly in demanding settings such as the ICU or exercise.

Magnetic Stimulation

Scientific basis. The ability of magnetic fields to stimulate nervous structures has long been known (93). Magnetic stimulation creates intense and brief magnetic fields, which, unlike electric currents, are only mildly attenuated by natural barriers such as skin and bone. They can therefore reach deep nervous structures, where stimulation is produced *in situ* by the electrical fields induced by the rapidly changing magnetic fields (Figure 10). The mechanisms of neural response to magnetic stimulation are different from those of the response to electrical stimulation (94–97), and therefore the results obtained with the two techniques may have different interpretations. Nevertheless, magnetic stimulation has the advantage of being relatively painless and is thus easily applicable in the clinical setting. Several review articles were discussed by Chokroverty (98).

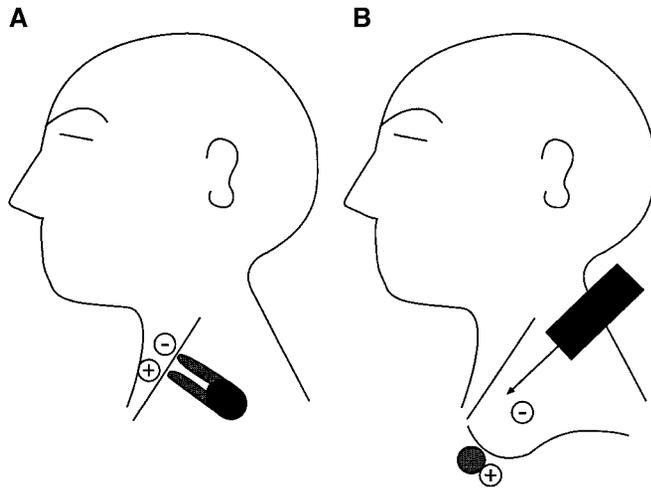


Figure 9. Technique for transcutaneous electric stimulation of the phrenic nerve. (A) Use of a bipolar electrode to locate and stimulate the phrenic nerve; (B) the monopolar technique. The phrenic nerve is usually found underneath the posterior border of the sternocleidomastoid muscle, at the level of the cricoid cartilage. The operator stands or sits beside (possible for unilateral stimulation) or behind (for bilateral stimulation) the patient and uses the electrode to push the muscle forward. Firm pressure on the soft tissues of the neck avoids changes in the relationship between the electrode and the nerve.

During the last 10 years, magnetic stimulation has been extensively used to stimulate the central nervous system in conscious humans (99). From the respiratory point of view, magnetic stimulation applied to the cervical spine (CMS) elicits a bilateral diaphragm contraction (100). The coil is centered over the spinous process of the seventh vertebral body (C7), but this does not mean that the seventh roots are stimulated. Depolarization of a nervous structure by magnetic stimulation requires that the stimulating current and the nerve share a common pathway: centering a circular 90-mm coil around C7 would, thus, generally stimulate the third to fifth cervical roots (101–103), depolarized in their intraforaminal segment (104, 105). Although it is generally believed that CMS provokes diaphragm contraction through the stimulation of cervical roots, it has been suggested that the C7 CMS magnetic field may reach the phrenic nerves anteriorly, through the neck, and thus stimulate the phrenic nerve trunk at a point more distal than with ES (106) (Figure 11).

Cervical magnetic stimulation also stimulates other elements of the cervical roots and nearby nerves, thus causing some contraction of neck and upper rib cage muscles, as well as diaphragm (100, 107–109) (*see COMPARISON BETWEEN TRANSCUTANEOUS ELECTRICAL PHRENIC NERVE STIMULATION AND CERVICAL MAGNETIC STIMULATION*).

Methodology. The subject, comfortably seated in a chair, is asked to bend the neck forward slightly. The coil is applied to the back of the neck, its midline coinciding with the axis of the vertebral column (Figure 11). Optimal results are generally obtained with the coil centered around the spinous process of the seventh cervical vertebra (C7), but slightly higher and lower positions should be tried with monitoring of pressure or EMG, although care may be required to obtain satisfactory surface EMG signals. The optimal coil position may vary with the size and neck morphology of the subject. Stimulation intensity is generally set to the maximal output of the stimulator (*see SUPRAMAXIMAL STIMULATION*).

Several manufacturers provide magnetic stimulators suitable for CMS. High-powered machines, capable of producing mag-

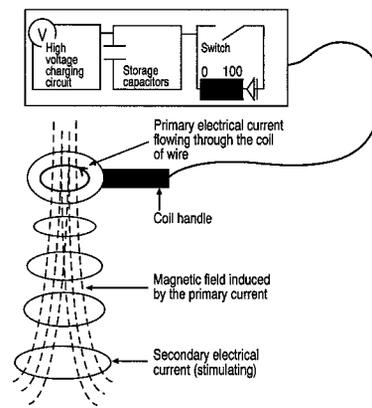


Figure 10. Schematic representation of the principle of magnetic stimulation. The electric current produced by the charging circuit is stored in capacitors. Switching on the trigger circuit results in a sudden pulse of electric current in the coil of wire held in contact with the patient. The intensity of this pulse of current can be modulated (from 0 to 100% of maximal intensity). A pulsed magnetic field orthogonal to the current flowing through the coil is produced. This magnetic field is able to penetrate

body tissues such as skin or bone with little attenuation. It in turn induces secondary electric currents of low intensity in deep structures. If such a structure, for example, the cerebral cortex or the trunk of a peripheral nerve, lies at a tangent to the secondary electric currents, it is depolarized at a point that depends on the local geometry and on the intensity of the current. The intensity of the magnetic field induced within the tissues decreases with distance. The maximum magnetic field intensity produced by modern stimulators is around 2.5 Tesla.

netic fields of 2–2.5 T with a medium-size circular coil, should be used. Doughnut-shaped coils 90 mm in diameter are particularly suitable for generating bilateral diaphragmatic contractions for the measurement of twitch pressure (100, 107–110).

Advantages. Cervical magnetic stimulation provides easy bilateral PNS. It is not painful: The subject simply perceives a contraction of neck muscles that provoke an extension movement, and a hiccup-like sensation. Any operator reasonably familiar with medical or physiological tests can obtain reliable results after a brief period of training. The number of stimulations applied during a given CMS session is often lower than with ES, which reduces the risk of potentiation and the staircase phenomenon (*see previous passages, and TWITCH POTENTIATION, subsequent section*). Location of the nerves is technically easier with CMS. The risk of falsely low results due to difficulty in locating the nerves and other technical problems is lower with CMS than with ES. In addition, because of its sites of action (cervical roots of the phrenic nerve [101, 103] or intramediastinal segment of the phrenic nerve [106]), CMS can activate diaphragm fibers innervated by an accessory or ectopic phrenic nerve (111) that would not be accessed by ES (112).

Disadvantages. Cervical magnetic stimulation lacks the specificity of ES for the diaphragm, because of coactivation of muscles innervated by cervical roots or the brachial plexus. Interpretation of Pdi,tw by CMS is, therefore, not exactly the same as that of Pdi,tw by ES (*see subsequent section*). Confirming supramaximal stimulation can sometimes be difficult (*see subsequent section*). Obtaining a reliable EMGdi signal is difficult with CMS, but technical solutions are available (use of shielded EMG cables, transient muting of the EMG amplifiers, etc.) (113) and modern EMG recorders are now designed to support magnetic stimulation. A reasonable distance should be maintained between the stimulating coil and credit cards, computer disks, and the like.

Other Magnetic Stimulation Techniques

Focal magnetic phrenic nerve stimulation. Small figure of eight-shaped magnetic coils can be used for focal stimulation (focal MS) of the phrenic nerve in the neck unilaterally or bilaterally, at the same point as stimulation by ES (114, 115). Bilateral focal MS is easily applied by an operator standing in front of the sub-

ject and gives values for $P_{di,tw}$ and the $P_{ga,tw}/P_{es,tw}$ ratio that are close to ES (115), thus avoiding any problems associated with stimulating upper trunk muscles (see subsequent section). This technique could make bilateral PNS easier in supine patients, as in the ICU, because for ES the operator has to stand behind the patient and for CMS the subject's neck has to lie over the coil, which may be uncomfortable and impede optimal positioning. Unilateral focal MS may allow assessment of the mechanical properties of one hemidiaphragm alone (87, 114, 116).

Anterior magnetic stimulation. The possibility of evoking a bilateral diaphragm EMG response through anterior magnetic stimulation (antMS) with a 90-mm circular coil similar to that used for CMS, placed flat over the upper part of the sternum, has been described (106). Anterior magnetic stimulation is potentially a simple technique also applicable to supine subjects in difficult settings, but pressure responses remain to be evaluated.

Diaphragmatic Response to Phrenic Nerve Stimulation

Diaphragmatic response to PNS would ideally be measured as work or power. However, length changes and velocity of shortening are invariably ignored and the focus has been on assessing diaphragm force development, either by measurement of pressure, or sound (phonomyography).

Pressure responses to PNS (twitches) are widely used to study diaphragm contraction. They depend not only on dia-

phragm properties, but also on the load the diaphragm acts against, as for any muscle. This load depends on the mechanical characteristics of the rib cage and abdominal wall (see TECHNIQUES FOR PRESSURE MEASUREMENTS).

Measurement of the sounds created by muscle contraction can now be quantified by phonomyography. At present this is a research tool, but it has considerable promise as it is technically easy and noninvasive (117).

Transdiaphragmatic pressure. In response to PNS, P_{di} rapidly rises to a peak, and then decreases exponentially to its baseline value (Figure 12) to give a characteristic $P_{di,tw}$. The

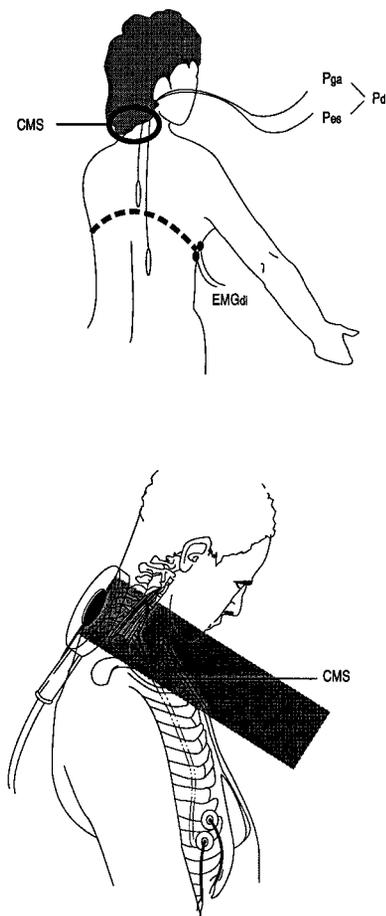


Figure 11. Technique for cervical magnetic stimulation (CMS). *Top:* The usual technique for CMS. The subject being seated, a circular coil of approximately 90 mm in diameter attached to a magnetic stimulator is centered on the spinous process of the seventh cervical vertebra (C7). The subject is usually asked to bend the neck forward to facilitate contact between the coil and the posterior surface of the neck. In this example, esophageal and gastric pressures (P_{es} and P_{ga} , respectively) are measured via conventional balloon-catheter systems (see TECHNIQUES FOR PRESSURE MEASUREMENTS). Subtracting P_{es} from P_{ga} gives transdiaphragmatic pressure (P_{di}). Surface electrodes are shown for the assessment of the electromyographic response of the diaphragm to stimulation (EMGdi). *Bottom:* Sites of nervous stimulation possibly responsible for the diaphragmatic contraction induced by CMS using a conventional 90-mm doughnut-shaped coil. The gray area is a schematic representation of the magnetic field. This can, theoretically,

depolarize cervical roots, and also the phrenic nerve itself anteriorly, behind or below the clavicle. Phrenic nerve stimulation is theoretically possible with a circular coil placed anteriorly (lying flat on the upper part of the sternum: anterior magnetic stimulation) or posteriorly but lower (coil held vertical on the upper dorsal vertebral column).

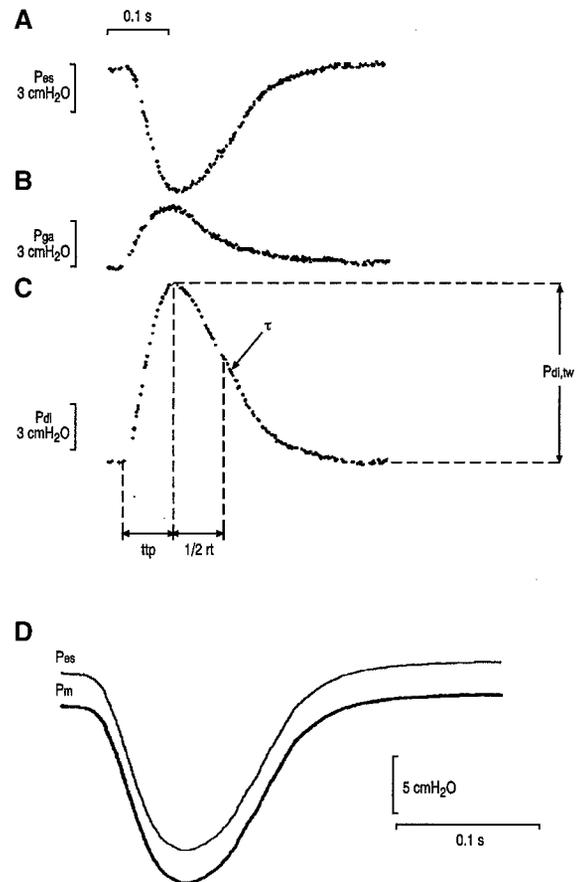


Figure 12. Typical pressure tracings in response to phrenic nerve stimulation. Traces A to C show, respectively, the esophageal pressure (P_{es}), gastric pressure (P_{ga}), and transdiaphragmatic pressure (P_{di}) responses to bilateral, supramaximal, electrical stimulation of the phrenic nerve in the neck, in a patient with COPD (hence the relatively low amplitudes). On the P_{di} trace (C) are indicated some indexes often used to describe quantitatively the twitch response: (1) $P_{di,tw}$ is the amplitude of the response from baseline to peak; it is the result of the interaction of diaphragm contraction with the rib cage and the abdomen; although not a direct measure of diaphragm intrinsic contractile properties, it is related to diaphragm strength and can be used to characterize it if all other intervening factors are otherwise kept identical (e.g., lung volume, thoracic geometry, rib cage and abdomen compliance, diaphragm state of activation, etc.); (2) t_{tp} and $1/2rt$ are the time-to-peak and half-relaxation time, respectively; these indexes are used to characterize the dynamics of diaphragm contraction, and are influenced, for example, by muscle shortening or fatigue; and (3) τ is the time constant of an exponential function fitted to the after-peak decline in P_{di} (often referred to as the relaxation time constant); it is influenced by diaphragm intrinsic properties and, for example, is prolonged by fatigue. The trace in D illustrates the similarity in shape, time dynamics, and amplitude in the P_{es} twitch (*thin line*) and the mouth pressure (P_{mo}) twitch (*thick line*) to phrenic nerve stimulation, in a normal healthy volunteer.

time-to-peak and its first time derivative (rate of rise, dp/dt) depend on several factors, including previous muscle shortening (e.g., increase in lung volume). The amplitude of the twitch reflects the transformation of diaphragm force into pressure and depends on diaphragm strength and contractile properties as well as rib cage and abdominal wall compliance. The dynamics of relaxation of the twitch can be described by the time necessary to reach a P_{di} value of 50% of the peak (half-relaxation time) or by the time constant (τ) of an exponential fitted to the pressure–time relationship (87, 118) (see RELAXATION RATE in Section 5 of this Statement).

Mouth pressure. Provided that the diaphragm contracts in isolation and that the corresponding change in alveolar pressure is adequately transmitted to the airways opening, P_{mo} can in theory reflect diaphragm contraction. In response to PNS, a twitch-shaped negative P_{mo} swing is seen ($P_{mo,tw}$) (Figure 12). In healthy subjects, $P_{mo,tw}$ closely matches $P_{es,tw}$ at different lung volumes and correlates with $P_{di,tw}$ (119). Conversely, in patients with COPD, $P_{mo,tw}$ at relaxed FRC is damped and time lagged with respect to $P_{es,tw}$, due to an increased airway time constant (120). Both in normal subjects (110) and in patients with diaphragm weakness (121) there is adequate matching of $P_{mo,tw}$ and $P_{es,tw}$ with CMS, when precautions are taken to prevent glottic closure. In normal subjects, $P_{mo,tw}$ measured during CMS is generally more negative than 11 cm H₂O (110), depending on lung gas volume (V_L).

Although there are not yet enough data to propose a precise technique to measure $P_{mo,tw}$, the following recommendations seem reasonable. Stimulation should be attempted at relaxed FRC when respiratory system recoil pressure is ordinarily zero. When PEEPi is present, the twitch amplitude should be measured starting at the PEEPi level. If a supramaximal stimulation is obtained, the data can be retained, if time to peak tension is normal. If it is prolonged with low amplitude and prolonged relaxation, then abnormal pressure transmission (probably due to glottic closure) should be first suspected, and stimulation should be repeated during a mild expiratory effort against an occluded mouthpiece.

Advantages. The principal advantage of $P_{mo,tw}$ is its simplicity and ease of use. Thus, portable P_{mo} or P_{sn} devices (28) could probably be adapted for combination with CMS as a simple screening test.

Disadvantages. The main disadvantage of $P_{mo,tw}$ is in ensuring the adequacy of pressure transmission from the alveoli to the mouth, particularly in airway obstruction. It seems that glottic closure, which may prevent change in P_{mo} , is particularly frequent with CMS, although it can occur with ES as well. A technique such as a mild inspiratory effort at FRC (120) or an expiratory effort (110) not only makes the procedure more complicated, but it also changes the meaning of the observed results. Indeed, central nervous system activation and lung volume influence the pressure response to PNS (see CONFOUNDING FACTORS). With CMS, $P_{mo,tw}$ can be the product of diaphragm contraction but also of neck muscle contraction. The importance of this confounding factor remains to be studied in detail (see CONFOUNDING FACTORS).

Esophageal Pressure

The measurement of esophageal pressure alone in response to PNS provides an intermediate approach between the measurement of P_{di} and P_{mo} . Measuring $P_{es,tw}$ is less simple than measuring $P_{mo,tw}$, but the problem of incomplete pressure equilibration due to glottic closure or airways time constant does not exist. Normal values for $P_{es,tw}$ are by definition similar to values for $P_{mo,tw}$.

Comparison between Transcutaneous Electrical Phrenic Nerve Stimulation and Cervical Magnetic Stimulation

Practical aspects. The practical aspects of ES and CMS are described in previous sections. In summary:

1. ES is the original method for generating an isolated contraction of the diaphragm, but for the operator is difficult to master.
2. CMS is easier and faster to apply, with a lower risk of false results due to technical problems. It is better tolerated by the subject. There is some cocontraction of the upper rib cage and neck muscles, stiffening the rib cage, so that P_{di} may be greater than with ES.

Physiological aspects. The two techniques are comparable with respect to reproducibility (similar within-occasion and between-occasion coefficients of variation) (100, 107) and the time characteristics of the P_{di} twitches are very close. When supramaximal bilateral ES and CMS are compared in the same subjects (107–109) $P_{di,tw}$ values measured during CMS appear consistently higher by approximately 20–25% than $P_{di,tw}$ measured during ES, the difference being accounted for by more negative P_{es} values.

Conclusion and perspectives. Cervical magnetic stimulation and ES do not provide the same physiological information, so that normal values for PNS-related pressures (see APPLICATIONS AND PERSPECTIVES) depend on the technique used. This also means that the results of CMS and ES may be affected differently in diseases affecting both diaphragm and rib cage muscles. The possibility of focused phrenic nerve magnetic stimulation in the neck with small figure-of-eight coils bilaterally (114, 115) will probably reconcile the physiological need for pure diaphragm contraction and the clinical need for simplicity. CMS and other techniques of magnetic stimulation of the phrenic nerve, being easier to use than ES, should then overcome the limitations of ES for large series, exercise, ICU, or intraoperative studies.

Confounding Factors

Supramaximal stimulation. To provide valid information about the maximal strength of the whole diaphragm, PNS should be bilateral and supramaximal.

Although PNS should be supramaximal if P_{tw} is to accurately reflect maximal diaphragm mechanical output, this is not necessary when PNS is used to study phrenic conduction time (see Section 3 of this Statement). Failure to achieve supramaximality leads to underestimation of diaphragm mechanical output, overestimation of central drive when using twitch occlusion (see PARTICULAR TECHNIQUES), and variability. The “gold standard” to achieve a reasonable degree of certainty about the supramaximality of PNS is to establish a recruitment curve using the EMG_{di}, and stimulation is maximal when there is no further increase in EMG_{di} in response to an increase in intensity. Increasing stimulus intensity by a further 10–20% provides a reasonable safety margin that compensates for slight changes in the quality of the stimulus. With CMS, it can be difficult to reach a clear plateau in amplitude of the action potential with intensity, but the peak-to-peak amplitudes of the action potentials produced by CMS at the maximal intensity of stimulation with a 2.5-T magnet are not different from the peak-to-peak amplitudes produced by supramaximal bilateral ES (109). The increasing power of stimulators may help reduce this problem in the future.

Lung volume. Lung volume has a major influence on the ability of the diaphragm to produce pressure, during voluntary static or dynamic maneuvers (13, 36, 122–128) and in response

to PNS (83, 84, 117, 119, 129–134). This is a result of the inverse relationships of length with force in skeletal muscles, and of lung volume with diaphragm length (36, 69, 125). Pdi,tw decreases as lung volume increases, with a prominent reduction in Pes,tw that is close to zero at TLC (83, 129–131, 134–136) (Figure 13). Isovolume changes in rib cage and abdominal configuration also influence Pdi,tw (83, 84, 125).

A long-standing increase in lung volume tends to be compensated for by adaptive mechanisms at the level of the sarcomere, known as “length adaptation” in animals (137–141) and probably in humans (131, 142). Thus, the observations made during acute changes in lung volume may not be as relevant to chronic hyperinflation.

How sensitive to changes in lung volume is the pressure response to PNS? Between FRC and TLC, Pdi,tw and Pmo,tw decrease by approximately 3%/100 ml (83, 84, 119, 130, 132), and between RV and FRC by approximately 5%/100 ml (83, 128). These changes appear to be reduced if care is taken to avoid potentiation (129) and may be less in the elderly (131, 134).

Lung volume, and if possible rib cage/abdominal configuration, should be carefully controlled when assessing PNS pressures in research settings. When PNS is repeated in patients with labile lung volumes, FRC should be measured on the day of the study. Assessing lung volume may be less crucial for clinical assessment, recognizing that a change in Pdi,tw or Pmo,tw can reflect changes in diaphragm properties, or lung volume, or both.

Twitch potentiation. A transient increase in the contractility of a skeletal muscle follows its contraction. This phenomenon is called potentiation (143, 144).

The possibility of twitch potentiation should be taken into account when interpreting studies involving PNS. A period of quiet breathing, e.g., 15 min, should be allowed before recording diaphragm twitches, particularly if maximal maneuvers or sniffs are performed beforehand (145–147).

Hypertrophy of neck muscles. When there is a bilateral paralysis, Pes,tw and Pdi,tw during ES are zero. With CMS, coactivated neck muscles can, theoretically, produce some degree of Pes,tw during CMS. This effect may be small in most subjects (148), but could be larger in patients with hypertrophied inspiratory neck muscles (149).

Particular Techniques

Twitch occlusion. Scientific basis. The degree of activation of a skeletal muscle during voluntary efforts can be assessed by use of the twitch occlusion technique. Twitches produced by electrical stimulation of a parent nerve are superimposed on a voluntary isometric contraction of the muscle (150). The amplitude of the twitch decreases linearly as the strength of the underlying contraction increases. When the activation is maxi-

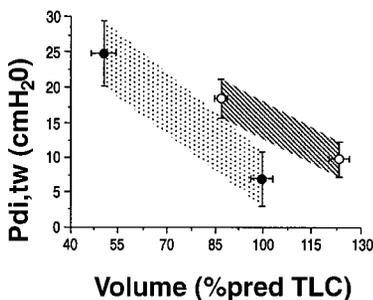


Figure 13. The effects of lung volume on twitch pressure. Shown is the marked decrease in the amplitude of transdiaphragmatic pressure (Pdi,tw) during an acute inflation from functional residual capacity to total lung capacity, both in normal volunteers (solid circles) and in patients with preexisting hyperinflation impairing baseline diaphragm efficacy (open circles). This reduction in Pdi with volume is mainly due to a reduction in the esophageal pressure (Pes) component of the twitch, which becomes very close to zero at TLC in normal subjects.

mal it completely suppresses the twitch (150–153) (Figure 14). It is usual to compare the amplitude of the interpolated twitch with that of the fully potentiated twitch performed on the relaxed muscle.

Normal subjects can voluntarily produce maximal diaphragmatic contraction during inspiratory and expiratory efforts as judged by twitch occlusion (56, 154, 155), as can patients with COPD (131). However, interpolation can be complicated by the effects of series compliance on twitch height (156).

Main results and applications. Superimposed Pdi,tw decreases linearly with the degree of underlying voluntary Pdi (Pdi,vol) (Figure 14) according to:

$$Pdi,tw = a - b \times Pdi,vol \quad (1)$$

The y intercept (a) of Equation 1 closely matches the value of Pdi,tw obtained at relaxed FRC, and its x intercept closely matches Pdi,max. The a/b ratio corresponds to the diaphragm twitch-to-tetanus ratio, which is 0.20–0.25 in most studies, close to the twitch-to-tetanus ratio of skeletal muscles in mammals (157), giving credibility to the technique.

From the twitch occlusion technique, it has been possible to:

1. Assess the degree of central activation associated with voluntary diaphragm contraction (88, 158).
2. Discriminate between the central and peripheral components of diaphragm fatigue or weakness (88, 159, 160) (see TYPES OF FATIGUE in Section 5 of this Statement).

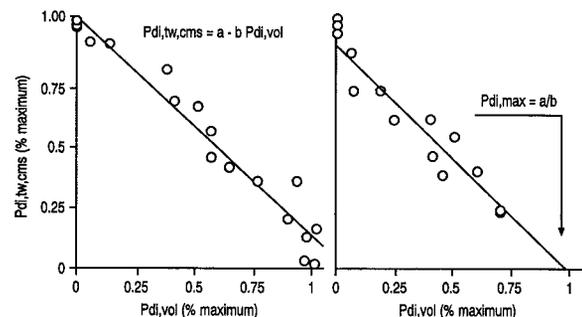
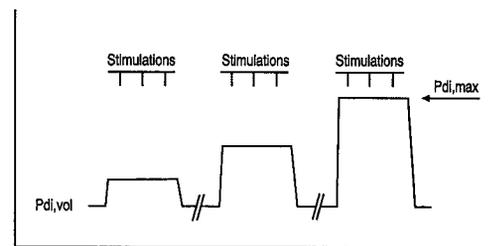


Figure 14. Twitch occlusion technique. *Top:* Procedure that can be used to study the effects of a voluntary diaphragmatic contraction (Pdi,vol) on the response to phrenic nerve stimulation (Pdi,tw). Pdi is displayed on an oscilloscope visible to the subject and the operator. The subject is asked to perform stepwise graded contractions, guided by the Pdi trace, and to sustain several levels of Pdi for a few seconds. The operator superimposes one or more stimulations during each sustained contraction. *Bottom:* two examples of twitch occlusion procedures. In both cases, Pdi,tw decreases linearly with Pdi,vol, according to $Pdi,tw = a - b Pdi,vol$. The *left panel* illustrates a subject capable of maximally activating the diaphragm: the subject can produce a voluntary contraction that is associated with complete absence of Pdi,tw. The *right panel* illustrates a subject not capable of maximal contraction: Pdi,max can be estimated by extrapolating the Pdi,tw–Pdi,vol relationship to the x axis, and is equal to the ratio of the intercept of this relationship to its slope ($Pdi,max = a/b$, arrow).

3. Detect central inhibition of the drive to breathe (131, 161, 162).
4. Estimate Pdi,max from submaximal efforts (56).

Methodology. The technique by which bilateral supramaximal PNS is to be performed should be that established for ES (56, 88, 120, 131, 154, 155, 160, 161, 163–167) or CMS (108). A visual feedback of Pdi is provided to the subject and the operator on an oscilloscope or computer screen. A standard procedure is as follows. First, Pdi,max is determined. Then, the subject is asked to produce, in a stepwise manner, fractions of Pdi,max previously marked on the screen of the oscilloscope. While a given step is briefly sustained, one or a few stimuli are delivered so that data for Equation 1 can be built up. To assess the degree of central activation a single stimulus over any inspiratory effort followed by a stimulus in relaxed condition may be sufficient (88).

Advantages. Twitch occlusion allows an investigator to separate central from peripheral weakness or fatigue of the diaphragm (80).

Disadvantages. The twitch occlusion technique is restricted by the difficulties inherent in ES and Pdi measurement. The consistency of the stimulus delivered to the nerves becomes increasingly difficult to maintain as neck muscles are recruited during intense inspiratory maneuvers, although CMS (109) or Pmo (120) could help. When graded voluntary Pdi maneuvers are performed, neck muscles often stay relaxed during low-intensity diaphragm contractions, but are coactivated during high-intensity contractions (70% of Pdi,max and above) (56), which may decrease rib cage distortability. During twitch occlusion from relaxed conditions to maximal effort, diaphragm contraction will interact with a distortable rib cage at low Pdi,vol values, and with a much stiffer rib cage at high Pdi,vol values, complicating the results. This problem may disappear with CMS, because it tends to stabilize the upper rib cage at all levels of Pdi,vol (109). The impact of twitch potentiation on the twitch occlusion procedure is not known. Theoretically, potentiation of Pdi,tw would lead to an underestimate of the central component.

Force–frequency curves. When stimulation frequency increases, the mechanical output of the stimulated muscle increases up to a plateau (tetanic contraction). Force–frequency curves contain much information about skeletal muscle contractility, and reflect the type and severity of muscle fatigue.

Human diaphragm force–frequency (or, rather, pressure–frequency) characteristics *in vivo* have been described with unilateral PNS (81, 168, 169) and bilateral PNS (116, 170–172), in a limited number of highly motivated subjects. Despite their interest, data remain scarce, because the studies are difficult. First, sequences of supramaximal stimuli are painful and can barely be tolerated, even unilaterally. Second, maintaining adequate sustained supramaximal PNS is demanding, especially as uncomfortable spread of the stimulus to the brachial plexus becomes almost unavoidable with repeated stimuli. Therefore, the use of pressure–frequency curves appears limited and cannot reasonably be proposed for clinical purposes or even for patient-based research. An alternative is to generate a surrogate force–frequency curve using paired phrenic nerve stimuli (173). This approach is acceptable to naive elderly subjects (174) and patients (175).

Normal Values

Values for Pdi,tw or Pmo,tw in normal subjects can be found in more than 40 published studies, irrespective of the technique used (10, 56, 65, 83–85, 88–90, 100, 107, 110, 115, 116, 118–120, 129, 131, 132, 134, 145, 146, 155, 160, 161, 165–167,

170–173, 175–190) (Table 4). Normal young (20–35 years) male individuals provide the vast majority of the data.

Bearing in mind that the technique used and various methodological factors can exert a major influence on the results, it seems possible to propose the following, for bilateral PNS.

Amplitude of bilateral twitch transdiaphragmatic pressure. Assuming a correct technique, at FRC, Pdi,tw with ES should be above 15 cm H₂O and Pdi,tw with CMS should be above 20 cm H₂O.

A Pdi,tw below 15 cm H₂O, whatever the PNS technique, should raise high suspicion of diaphragm dysfunction (110, 114, 131, 179, 187, 190–196).

Influence of age, sex, and other characteristics. As with voluntary pressures (26, 128, 197), normal Pdi,tw tends to be lower in women than in men and tends to decrease with age (120, 131, 182, 190). The influence of other factors such as height, race, fitness, etc., is unknown, although data suggest that baseline Pdi,tw in highly fit subjects is not different from normal subjects (185), but with a better resistance to maximal exercise-induced fatigue.

Other characteristics of the twitch transdiaphragmatic pressure response to phrenic nerve stimulation. The ratio of Pes,tw to Pdi,tw in normal individuals is usually between 0.35 and 0.55.

Amplitude of twitch transdiaphragmatic pressure. Available data are still scarce, but a value of Pmo,tw during CMS less negative than –11 cm H₂O should probably prompt more detailed investigation (110). Pmo,tw during ES tends to be lower, and a value more negative than –8 cm H₂O with this technique is probably normal (119).

Applications and Perspectives

The use of PNS-derived pressures to study the mechanical action of the diaphragm assumes that stimulation is bilateral and supramaximal, and that care is taken to control for lung volume and twitch potentiation.

Research applications. Bilateral ES is an important tool in human diaphragm research, used to study the properties of the diaphragm and the mechanisms of its fatigue independently of volitional influences. The twitch occlusion technique, as the only means to separate the peripheral and central components of diaphragm dysfunction, is also an important, if complex, research tool. The use of paired stimuli could facilitate research on the frequency characteristics of diaphragm fatigue (174).

Cervical magnetic stimulation provides slightly different information from ES, mainly because of rib cage muscle coactivation. However, its simplicity for the subject and the operator makes it a valuable tool for clinical research, especially in difficult settings, such as the ICU, or when repeated studies are needed, such as the evaluation of therapeutic interventions.

Clinical applications. Contraindications. There are virtually no contraindications to ES and MS, but their use requires some precautions. MS should not be performed in patients with a cardiac pacemaker. Patients with orthopedic implants, even metallic ones, can be studied with MS (e.g., candidates for phrenic pacing after high cervical cord injury) (198) after sufficient time for consolidation.

Clinical use. Pressure responses to PNS play an important part in the clinical evaluation of inspiratory muscle function. Diaphragmatic weakness can be established and quantified with PNS, particularly when voluntary maneuvers are equivocal. The use of MS with Pmo may be an even simpler nonvolitional measure.

The preoperative assessment of patients for possible phrenic pacing after high cervical cord lesions constitutes a particular application. PNS provides information on phrenic nerve con-

TABLE 4. TWITCH TRANSDIAPHRAGMATIC PRESSURES MEASURED IN A VARIETY OF STUDIES

First Author (Ref.)	Pdi,tw (cm H ₂ O, mean)	Note
Bilateral Supramaximal ES: Healthy Young Volunteers		
Bellemare (56)	34.6	
Aubier (118)	34.4	Needle stimulation
Hubmayr (83)	31.4	Implanted wire stimulation
Mier (179)	8–33	15 control subjects referred for suspected diaphragm weakness; significant overlap between groups; Pdi,tw was discriminant only for diagnosis of severe diaphragm weakness
Mier (84)	24.4	Supine position
Gandevia (155)	28.0	
Mier (82)	19.4–29.3	3 subjects; comparison between transcutaneous electrical stimulation and needle stimulation
Mador (90)	28.9	
Wragg (107)	29.7	Comparison CMS–ES
Eastwood (85)	21–28	3 subjects; validation of a cervical apparatus aiming at standardizing PNS for repeated studies: data reproducible among 25 repeated studies
Laghi (108)	32.3	Comparison CMS–ES
Similowski (109)	23.3	Comparison CMS–ES
Bilateral Supramaximal ES: Older Healthy Volunteers		
Similowski (131)	19.8–31.7	6 subjects aged 50–72 yr, serving as control subjects in a study of diaphragm properties in hyperinflated patients with COPD
Mancini (182)	18.8	6 subjects aged 50 ± 8 yr, serving as control subjects in a study of diaphragm function in chronic heart failure
Cervical Magnetic Stimulation: Healthy Young Volunteers		
Similowski (100)	33.4	First-generation stimulator; supramaximality of PNS not always certain
Wragg (107)	36.5	Comparison CM–ES
Wragg (146)	36.5	Study of diaphragm twitch potentiation; values in the table are the unpotentiated ones
Laghi (184)	38.9	12 subjects
Hamnegard (129, 187)	17–34	
Similowski (109)	27.5	Comparison CM–ES
Laghi (108)	37.7	Comparison CM–ES
Cervical Magnetic Stimulation: Older Healthy Volunteers		
Polkey (190)	25.4	
Patients with COPD		
Similowski (131)	10–26	Bilateral ES
Wanke (183)	15.2	Bilateral ES
Polkey (134, 190)	18.2	CMS

Definition of abbreviations: CMS = cervical magnetic stimulation; COPD = chronic obstructive pulmonary disease; ES = electrical stimulation; Pdi,tw = twitch transdiaphragmatic pressure; PNS = phrenic nerve stimulation. Values represent means or ranges.

duction time, which is important in making the decision to undertake pacing (198). It also provides an estimate of the degree of diaphragm disuse atrophy, which is an important determinant of the reconditioning strategy (199).

Given that methodological precautions are rigorously respected, PNS is one of the more reproducible respiratory muscle tests, and this makes it suitable for follow-up studies (*see PHRENIC NERVE STIMULATION* in Section 3 of this Statement).

ABDOMINAL MUSCLE STIMULATION

The abdominal muscles are major contributors to respiration, both through their expiratory action on the rib cage and their mechanical linkage with the diaphragm. Their function can be explored by voluntary maneuvers (*see VOLITIONAL TESTS OF RESPIRATORY MUSCLE STRENGTH*), with the usual limitations of subjects understanding and cooperation. A nonvolitional test giving information on abdominal muscle mechanical output would, therefore, be of interest.

Contraction of the abdominal muscles can be provoked by their direct electrical stimulation. This technique has been

used in humans to study the action of various abdominal muscles on the rib cage (200), and in a study of diaphragm maximal voluntary activation (155). From a therapeutic point of view, its use has been considered to enhance cough in patients with cervical cord injury (201). However, direct electrical stimulation is painful and supramaximality is difficult to achieve. It is also difficult to activate all muscles groups at once.

Contraction of the abdominal muscles can also be provoked by stimulation of their parent nerves and roots (202). Theoretically, this allows supramaximal stimulation (and therefore reproducibility) and, if the stimulus is widespread enough, simultaneous activation of all abdominal muscles. Magnetic stimulation over the vertebral column at the level of the eighth to tenth thoracic vertebra could provide an easy-to-use nonvolitional assessment of abdominal muscle strength and fatigue (202, 203).

CONCLUSION

The purpose of this Section is to describe the tests used to assess respiratory muscle strength. To test strength, pressures

can be measured either during voluntary maneuvers or during involuntary contractions, particularly in response to phrenic nerve stimulation.

A. Volitional Tests of Respiratory Muscle Strength: Volitional tests are often simple for patients to perform, but it can be difficult to be certain that a maximum effort has been made. This can lead to difficulty in the interpretation of low results.

1. Maximum Static Inspiratory and Expiratory Pressure

i. P_{imax} and P_{Emax} are commonly used, clinically useful measurements. Some individuals have difficulty with the technique and the interpretation of low results can be problematic.

ii. Maximum static transdiaphragmatic pressure ($P_{\text{I,di,max}}$) provides specific information on diaphragm strength, but can be a difficult maneuver in naive subjects and patients. $P_{\text{I,di,max}}$ has a wide normal range and has limited usefulness in clinical practice.

2. Maximum Sniff Pressures: Maximum sniff efforts can be achieved by patients with little practice; sniff pressures are reproducible and have a narrower normal range than static mouth pressures or $P_{\text{I,di,max}}$. Sniff esophageal pressure assesses global inspiratory muscle strength and sniff P_{di} is a clinically useful measure of diaphragm strength. Sniff nasal pressure provides a useful noninvasive measure of inspiratory muscle strength and has been validated in patients with neuromuscular disease.

3. Maximum Cough Pressure: Cough gastric pressure is measured as an index of abdominal muscle strength. $P_{\text{ga,co}}$ is a useful test to supplement P_{Emax} , particularly in patients unable to perform the P_{Emax} maneuver reliably. To date, few data are available for normal values of $P_{\text{ga,co}}$.

B. Nonvolitional Tests of Respiratory Muscle Strength

1. Phrenic Nerve Stimulation: Phrenic nerve stimulation is specific for the diaphragm and is not influenced by the central nervous system.

i. Electrical phrenic nerve stimulation (ES) can achieve selective supramaximal stimulation of the diaphragm, but requires considerable skill, is sometimes uncomfortable for patients, and is difficult to achieve in some clinical settings (e.g., the ICU).

ii. Magnetic phrenic nerve stimulation (MS) is technically easier for the operator and less uncomfortable for the patients. Cervical magnetic stimulation (CMS) elicits a bilateral diaphragm contraction. CMS is less specific than ES, and coactivates muscles innervated by the brachial plexus. Achieving and confirming supramaximal nerve stimulation can be difficult, and recording the diaphragm EMG can pose problems. Unilateral anterior-lateral MS is more specific than CMS, and results are similar to ES. Unilateral MS allows the investigation of hemidiaphragm function, and bilateral anterior-lateral MS reliably achieves supramaximal stimulation.

iii. Twitch transdiaphragmatic pressure ($P_{\text{di,tw}}$) provides an index of diaphragm, or hemidiaphragm, strength. Normal values are available and $P_{\text{di,tw}}$ is a useful clinical measurement. Twitch mouth pressure ($P_{\text{mo,tw}}$) can provide a noninvasive measure of diaphragm strength, but inadequate transmission of alveolar pressure to the mouth, in patients with airway obstruction or when there is glottic closure, is a substantial practical problem limiting clinical application.

iv. $P_{\text{di,tw}}$ is a research technique useful to assess the degree of activation of the diaphragm during voluntary

efforts (the technique of twitch occlusion) and $P_{\text{di,max}}$ can be estimated from submaximal efforts.

2. Abdominal Muscle Stimulation: Magnetic stimulation over the eighth to tenth thoracic vertebrae posteriorly, and the recording of twitch gastric pressure, provide a clinically applicable nonvolitional test of abdominal muscle strength. Data on normal values for twitch gastric pressure are limited.

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APPENDIX: ABBREVIATIONS

Measures

P	Pressure (usually mouth pressure if site not specified, as P _{imax})
L	Length
V	Volume
EMG	Electromyogram
PMG	Phonomyogram

Sites and Modifiers

A, alv	Alveolar
ab	Abdomen
abw	Abdominal wall
ao	Airway opening
aw	Airway
bs	Body surface
di	Diaphragm, transdiaphragmatic
es, oes	Esophageal
g, ga	Gastric

ia	Intercostal/accessory muscles
mo	Mouth
mus	Muscle
nas	Nostril, nasal
np	Nasopharynx
ph	Phrenic
pl	Pleural
rc	Rib cage
rs	Respiratory system (lung and chest wall)
w, cw	Chest wall
ant	Anterior
post	Posterior
E	Expiratory
I	Inspiratory

Maneuvers

co	Cough
max	Maximal
sn	Sniff
tw	Twitch
vol	Voluntary

Stimulation Descriptors

ELS	Electrical stimulation
MS	Magnetic stimulation
Ant MS	Anterior magnetic stimulation
CMS	Cervical magnetic stimulation
fMS	Focal magnetic stimulation
PNS	Phrenic nerve stimulation
EMG	Electromyogram
PMG	Phonomyogram
M-wave	EMG response to PNS

Lung Volumes

FRC	Functional residual capacity
RV	Residual volume
TLC	Total lung capacity
VC	Vital capacity

General

CNS	Central nervous system
HFF	High-frequency fatigue
LFF	Low-frequency fatigue
MVC	Maximal voluntary contractions
SMVC	Submaximal voluntary contractions

Principles

Give measure, then site, then maneuver, then descriptor. Thus: P_{es,tw,CMS} = twitch esophageal pressure following cervical magnetic stimulation
 P_{E,mo,max} = maximal expiratory mouth pressure (usually abbreviated to P_{E,max})
 P_{g,co} = gastric pressure during a cough

3. Electrophysiologic Techniques for the Assessment of Respiratory Muscle Function

Respiratory muscle contraction depends on electrical activation of the muscles. Influenced both by involuntary and voluntary inputs, the electrical impulses originate in the respiratory neurons of the brainstem, are carried via motor nerves, transmit through neuromuscular junctions, and propagate throughout muscle membranes. Failure at any of these sites can result in dyscoordination and reversible or irreversible muscle weakness. The task of electrophysiologic tests is to assess the integrity of the respiratory neuromotor apparatus.

There are two main types of electrophysiologic tests of respiratory muscle function: electromyography and stimulation tests. These tests are interrelated, and they are related also to tests of mechanical action of the respiratory muscles, described elsewhere in this Statement.

ELECTROMYOGRAPHY

Rationale

Electromyography (EMG) is the art of describing myoelectric signals (1), the electrical manifestations of the excitation process elicited by action potentials propagating along muscle fiber membranes. The EMG signal is detected with electrodes, and then amplified, filtered, and displayed on a screen or digitized to facilitate further analysis. Electromyography of respiratory muscles can be used to assess the level and pattern of their activation, so as to detect and diagnose neuromuscular pathology, and, when coupled with tests of mechanical function, to assess the efficacy of the muscles' contractile function (see ELECTROMECHANICAL EFFECTIVENESS in Section 6 of this Statement).

Scientific Basis

Single fiber action potential. Depolarization of a muscle fiber membrane, caused by the flow of ions across the sarcolemma, generates an electric field outside the muscle fiber, which can be detected by extracellular recording electrodes as voltage changes over time; this voltage transient is known as the action potential. Although the transmembrane potential changes generated by depolarization of a given fiber are always identical in shape and amplitude (the "all or nothing" phenomenon), the shape and amplitude of a recorded action potential depend on factors such as the orientation of the recording electrodes with respect to the active muscle fibers, the distance between the muscle fibers and the electrodes, the filtering properties of the electrodes, and the muscle fiber action potential conduction velocity (2).

In humans, muscle fiber conduction velocity ranges from 2 to 6 m/second (3), depending on passive and active components of the muscle fiber membrane. The passive components (cable properties) include capacitance per unit length (proportional to fiber circumference) and internal resistance (inversely proportional to the square of the fiber diameter). The active components (membrane excitability) depend on ion gradients across the membrane and properties of the ion gating channels, which in turn are influenced by electric field strength, temperature, and chemical milieu (especially pH and Ca^{2+} concentrations). Muscle fiber conduction velocity has been shown to vary with fiber diameter (4), temperature (3), electrolyte gradients across the cell membrane (5), pH (5), and fatigue (1, 6).

Single motor unit action potential. Each motor unit is composed of a number of individual muscle fibers innervated by a single anterior horn cell. All individual fibers within a motor unit are activated almost simultaneously. The amplitude and shape of the resulting motor unit action potential (MUAP) are influenced not only by all the factors that can affect single fiber action potentials, but also by such factors as the number of fibers within the motor unit, the spatial dispersion of motor unit fibers, differences in length of the motor neuron terminal axons, and possibly fiber-to-fiber differences in action potential conduction velocity (2, 7).

Summation of motor unit signals. Compound muscle action potentials (CMAPs) represent the summated electrical activity generated by all motor units synchronously activated by nerve stimulation (see subsequent passages). The observed CMAP is influenced by the number of activated motor units, their synchronization, the shape of individual MUAPs, and cancellation of opposite phase potentials.

The interference pattern EMG results from the temporal and spatial summation of asynchronously firing MUAP trains during spontaneous muscle contractions, when individual MUAPs can no longer be distinguished (8). The observed interference pattern EMG is thus a function of the number of active motor units, their firing rates and synchronization, the shapes of their individual MUAPs (in turn dependent on all the factors listed here previously), and cancellation of opposite phase potentials (2, 8).

EMG Equipment

Recording electrodes. Electromyography signals can be detected as the difference between the signal from an electrode placed on or in the muscle under investigation (active electrode) and the signal from another electrode placed in an electrically silent region ("indifferent" or reference electrode). This electrode arrangement is usually referred to as a monopolar electrode. When the two electrodes connected to a differential amplifier are positioned on or in the same muscle under investigation, the electrode arrangement is usually referred to as bipolar. Optimal EMG signals depend on the use of electrodes with appropriate configuration and fixed geometry, on maintenance of electrode position relative to the muscle, on alignment of the electrodes with respect to fiber direction, on selection of sites with relatively low density of motor end plates, and on avoidance of signal disturbances.

Electrodes can be placed on the skin overlying the neck, the chest wall muscles, or the area of apposition of the diaphragm to the chest wall; they can be swallowed into the esophagus to measure crural diaphragm EMG; or they can be inserted into the respiratory muscle of interest, using needle, wire, or hook electrodes. Selection of an appropriate electrode system requires consideration of advantages and disadvantages specific to the technique and the context of the study (Table 1).

Surface electrodes. Surface electrodes have been used to measure activity of diaphragm, intercostal, scalene, abdominal, and accessory muscles. After the skin is shaved, cleaned, and dried, electrodes are placed over or as close as possible to the muscle to be investigated and are secured with optimal skin contact. The placement is determined by palpation and by the investigator's knowledge of respiratory muscle anatomy,

TABLE 1. TYPES OF RECORDING ELECTRODES FOR RESPIRATORY MUSCLE ELECTROMYOGRAMS

Type of Electrode	Advantages	Disadvantages
Surface electrodes		
Chest wall	Noninvasive Large volume sampling	Cross-talk Variable filtering
Esophageal	Less influenced by body habitus Less cross-talk	Discomfort Unreliable in diaphragm hernia
Intramuscular electrodes	Less influenced by cross-talk Single motor unit recordings possible	Discomfort Difficult to place Small pneumothorax risk Possible sampling error

but no standards exist for electrode design or positioning. Furthermore, there is no consensus on methods either to maintain electrode orientation with respect to muscle fibers and innervation zones or to control for influences of variable muscle-to-electrode distance (as, e.g., with variations in the amount of subcutaneous fat), or for cross-talk from adjacent muscles.

Advantages of surface electrodes are their noninvasive nature and their ability to sample a large number of motor units. For many individual nondiaphragm respiratory muscles, however, their proximity to one another and to nonrespiratory trunk muscles makes surface electrode recordings unreliable. Examples include cross-talk from scalenes and platysma in recordings of sternocleidomastoids (9), from external oblique and pectoralis in recordings of intercostal muscles, and among various abdominal muscles (10, 11). Furthermore, variations in interindividual body habitus, for example, subcutaneous fat tissue or deformity of the chest wall, produce variable muscle-to-electrode filtering effects.

Esophageal electrodes. Esophageal electrodes are metal electrodes mounted on a catheter, which is inserted via the nose or

mouth and positioned with the electrode rings at the level of the crural diaphragm. In adults, the motor innervation zone of the crural diaphragm lies 1–3 cm cephalad to the gastroesophageal junction, with the left side approximately 1 cm cephalad to the right (12).

Esophageal electrode catheters are often equipped with gastric balloons and weights on the proximal end, which anchor them in position when outward traction pulls the gastric balloon snugly against the gastroesophageal junction. This feature may limit motion of the electrodes with respect to the esophagus, but it does not prevent either diaphragm movement relative to the electrodes, or the resulting artifacts (13–16). Motion artifacts are minimized in semistatic contractions.

A more reliable method to reduce electrode positioning artifacts during dynamic maneuvers is continuous optimization of diaphragm-electrode positioning. An electrode array of eight rings mounted 1 cm apart on a catheter is introduced and adjusted to provide optimal EMG activity from the central pair of electrodes (17, 18) (Figure 1A). A computer program samples all electrodes continuously, and selects the pair closest

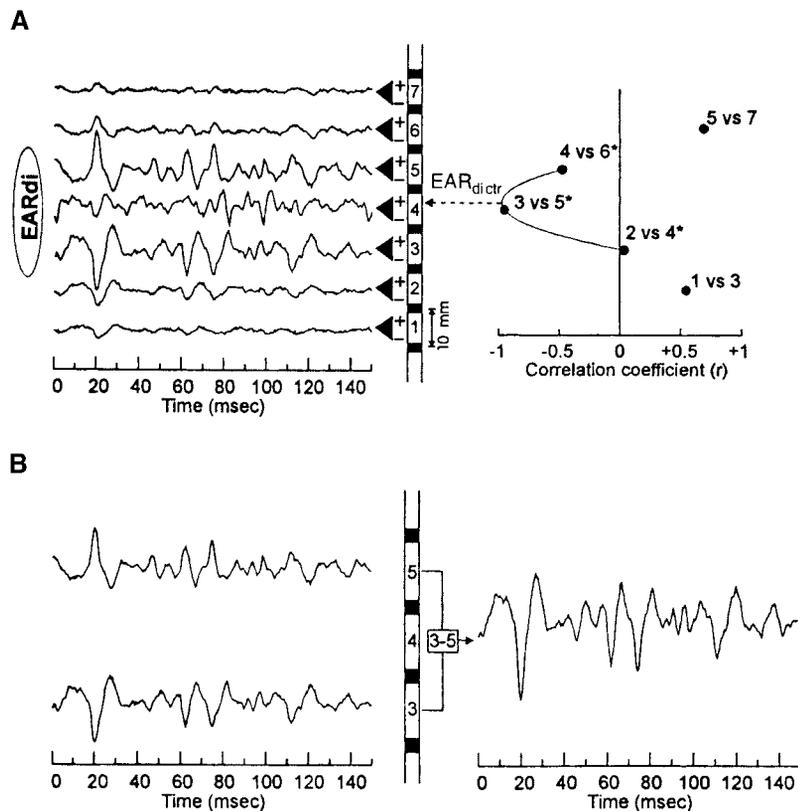


Figure 1. (A) Schematic description of the methods used to locate the center of the electrically active region of the diaphragm (EAR_{di,ctr}). *Left:* Raw signals from each of seven electrode pairs on an esophageal probe. *Center:* The probe with its eight electrodes. *Right:* Correlation coefficients for cross-correlation of signals from various pairs of electrodes. The dashed curve is the best fit curve, from which the ERA-di ctr position is calculated. (B) An example of the double subtraction technique. Diaphragm EMG signals from electrode pairs located 10 mm caudal and cephalad to the EAR-di ctr are shown. In this case, the signal from Pair 5 was subtracted from that of Pair 3, resulting in increased signal amplitude. Reprinted by permission from Reference 19.

est to the crural diaphragm at any point in the respiratory cycle. Application of a double subtraction technique using the difference between signals obtained from each electrode pair caudal and cranial to the crural diaphragm (19) further enhances the signal-to-noise ratio.

Advantages of esophageal recordings are that they are not influenced by obesity and that, when used with or combined into the same catheter as esophageal and gastric pressure monitors (12), they enable simultaneous recordings of diaphragm EMG and transdiaphragmatic pressure. Disadvantages include the discomfort and the remote risks of regurgitation, aspiration, and vagally mediated bradycardia associated with their placement. Diaphragmatic hernia may be a source of error in esophageal recordings. In theory, the EMG from esophageal electrodes may not be representative of the diaphragm as a whole, because it samples only the crural portions of the diaphragm. However, although crural-costal dissociation during breathing has been demonstrated in animals (20, 21), it appears not to be a problem in humans (22–24).

Intramuscular electrodes: advantages. Intramuscular electrodes provide relatively selective recordings from nondiaphragm respiratory muscles (9–11, 25–30) with sufficient discrimination of individual motor unit activity to allow evidence of denervation or myopathy to be detected. Whitelaw and Feroah (30) have provided a detailed description of a safe method to record single motor unit activity in intercostal muscles with wire electrodes. A number of investigators have demonstrated techniques for placement of monopolar or bipolar needle electrodes in the human diaphragm, either by a medial subcostal approach (31, 32) or by a lower intercostal approach (33, 34) (Figure 2), sometimes assisted by real-time ultrasound. Fine wire electrodes for single motor unit recordings have also been implanted in the right hemidiaphragms of humans (13, 35). Although the flexible nature of wire electrodes makes them relatively stable during volume changes of up to 1.5 L around the FRC, artifactual changes in recording conditions occur with larger volume changes (13). Wire im-

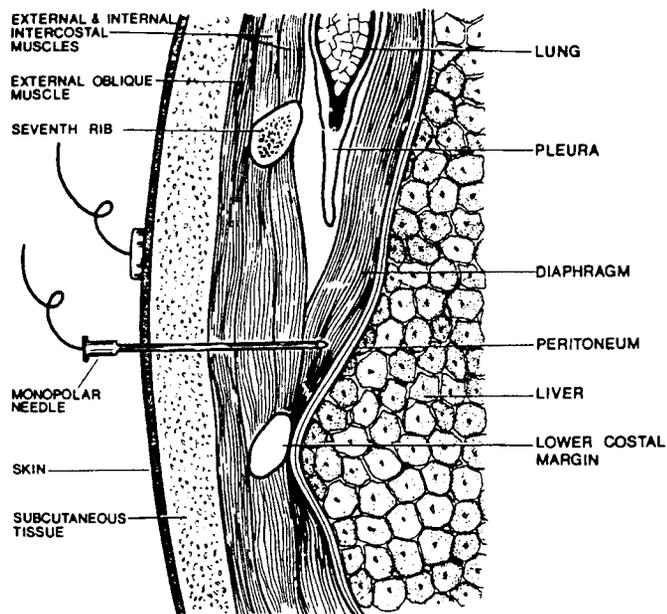


Figure 2. Intercostal approach to placement of an electromyography needle in the diaphragm. The needle is inserted one interspace above the lower costal margin between the anterior axillary and medial clavicular lines. During quiet respiration, the needle passes well away from the visceral pleura. Reprinted by permission from Reference 34.

plants are often used in upper airway muscle studies (*see ELECTROMYOGRAPHY* in Section 8 of this Statement).

As far as advantages and disadvantages are concerned, intramuscular electrodes are optimal for analysis of action potentials in the assessment of myopathic changes and for comparing single motor unit firing frequencies among different respiratory muscles and clinical conditions (13) (Figures 3 and 4). Cross-talk is less of a problem with implanted than surface electrodes, although it is not completely eliminated. Implanted electrodes are difficult to place, however, and are potentially less useful than surface or esophageal recordings for quantifying global respiratory muscle activity. For intercostal recordings and especially for triangularis sterni and diaphragm recordings (26), there is a small risk of pneumothorax. As with any skin-penetrating technique, there are risks of bleeding and bruising. With the use of sterile disposable needles or wires, there is no practical risk of transmission of infectious disease.

EMG signal processing. The preferred amplifier design for detection of weak myoelectric signals is a differential amplifier, which amplifies the difference between two paired inputs and thereby eliminates signals, such as 50 or 60 Hz from power lines, that have common influences on both outputs (common mode rejection). Input impedance is high to minimize loss of voltage across the two active electrodes. Bandpass filtering is usually employed, with a high-pass filter to remove the signal's direct current component and a low-pass filter set below the data acquisition frequency to avoid distortion (by aliasing) of the signal caused by undersampling. Filter settings will vary, depending on the type of electrode and the application; for surface or esophageal recordings, a band width of 10 to 1,000 Hz is often used.

For simple measurements of motor latencies or CMAP amplitudes, the data display can be as simple as a storage oscillo-

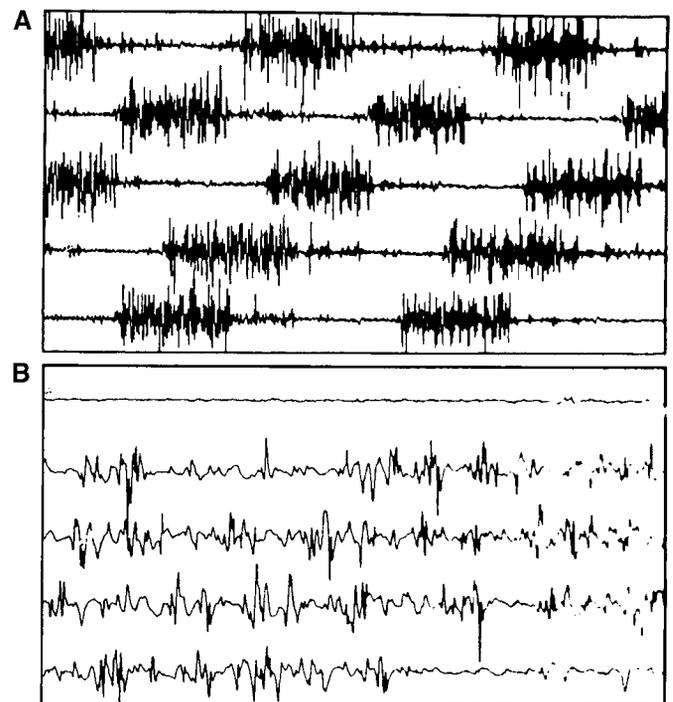


Figure 3. (A) A needle EMG record from a normal diaphragm at 200 milliseconds/division and 200 mV/division (B) The same subject recorded at 10 milliseconds/division and 200 mV/division. Reprinted by permission from Reference 34.

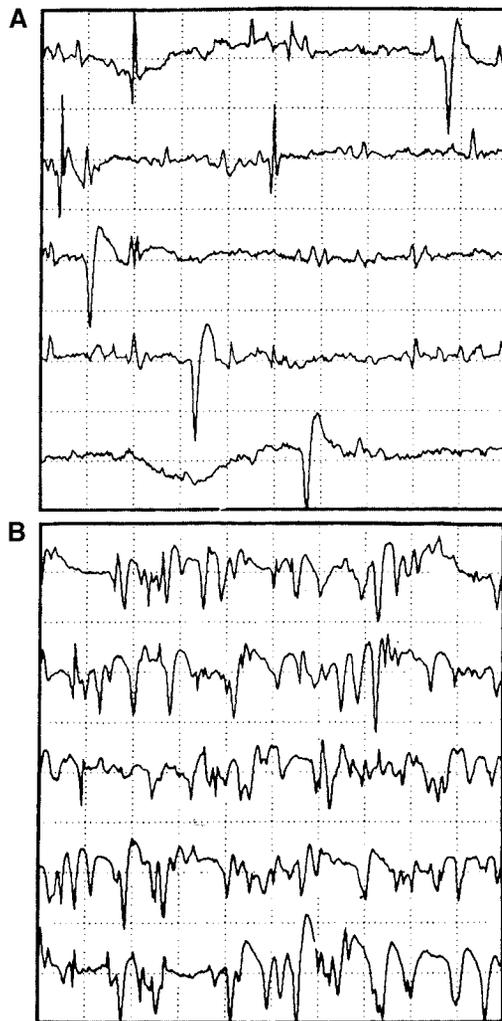


Figure 4. (A) Needle EMG of the diaphragm of a patient with porphyric neuropathy, showing a few fibrillation potentials and positive wave potentials, along with QRS complexes (calibration, 10 milliseconds/division and 100 mV/division). (B) Needle EMG of the same patient 4 weeks later, showing increased numbers of positive sharp waves and fibrillation. Reprinted by permission from Reference 34.

scope equipped with a camera. A more versatile system, essential for frequency domain measurements, is a computer with an analog-to-digital converter. Because in digitally sampled signals only spectral components of frequencies lower than half the sampling frequency can be observed (the Nyquist theorem), the sampling frequency should be chosen accordingly.

To provide an analog signal proportional to “average” EMG activity at any point in time, many investigators subject the raw EMG signal to rectification and “leaky” integration. Unless sophisticated analog gating and/or filtering techniques are employed, however, the effects of multiple artifacts detailed in the following sections limit this technique to providing only a crude estimation of the level of muscle activation.

Data Analysis

Time domain EMG analysis. Time domain EMG analysis represents the electrical activity of the muscles as a function of time. At low levels of contraction, isolated MUAPs can be distinguished and analyzed by such time domain indices as signal amplitude and different types of integrated EMG, including full wave rectified and averaged signal (FRA) and root mean square of the signal

(RMS) (36), all of which increase as a function of the number of motor fibers in the unit. Frequency-related indices, such as rise time and duration, can also be measured (36, 37); these are influenced more by action potential conduction velocity and the width of the innervation zone than by the size of the motor unit.

With increasing levels of contraction, more motor units are recruited, and the firing rate increases. The resulting interference pattern EMG can be analyzed by indices such as amplitude, RMS, and FRA, and by frequency-related indices such as zero crossing distance and turn-point distance (36).

Frequency domain analysis. Frequency domain analysis is a technique to express EMG power as a function of frequency. EMG power is intimately related to its frequency characteristics (8), and frequency characteristics in turn are related to muscle membrane conduction velocity, to filtering properties of the electrodes, to muscle–electrode distances, and to noise (36). Frequency domain analysis greatly simplifies the evaluation of all of these factors, which are difficult to evaluate in the time domain.

The relative contributions of high and low frequencies to EMG signals can be estimated crudely by splitting the signal, filtering the signal with different bandpass filters, integrating the output of each bandpass filter, and comparing the two integrals, to yield a ratio of high-frequency power (e.g., 130–250 Hz) to low-frequency power (e.g., 30–50 Hz), the H/L ratio (38). More useful information can be obtained by power spectral analysis, for which a “window” of time domain EMG data is digitized and subjected to a computerized fast Fourier transform. The fast Fourier transform components are squared and their products are calculated, giving the power spectrum, which graphs the power of the signal as a function of frequency (Figure 5). To avoid artifactual overestimation of high-frequency content, it is necessary to condition the window of data by tapering its amplitude at the beginning and end of the window or by replacing all data before the first and after the last zero crossing with zeros. These “shaping” processes lead to a slight underestimation of high-frequency content of the EMG (39).

Numerical quantification of the power spectrum is possible by calculating the spectral moments (36). Spectral moments (M) of order n are defined as:

$$M_n = \sum_{i=0}^{i_{\max}} P_i \cdot f_i^n$$

where P is power density, f is frequency, i is the index over which the power density product is summed, $i = 0$ is the direct current component, and i_{\max} is the index associated with the highest frequency in the spectrum.

The spectral moment of zero order (M_0) and the root mean square ($\text{RMS} = M_0^{1/2}/p$, where p is the number of points in the sample) are indices of total EMG power. Theoretically, RMS reflects the force output of the muscle (8). However, both M_0 and RMS are influenced by a number of other parameters, especially conduction velocity (8). In applications in which the power spectrum is expected to shift, as in fatigue, the first-order spectral moment (M_1) may be a more useful index of muscle activation, because it is not affected by changes in action potential conduction velocity (36). Quantification of the distribution of power in the spectrum can be obtained by calculating the center frequency ($f_c = M_1/M_0$), also known as the mean or centroid frequency. Figure 5 shows how EMG signal power spectra are influenced by interelectrode distance.

Artifacts

Filter effects. Muscle-to-electrode distance. Increasing muscle-to-electrode distance results in reduced signal amplitude with relatively larger attenuation of high- than low-frequency power,

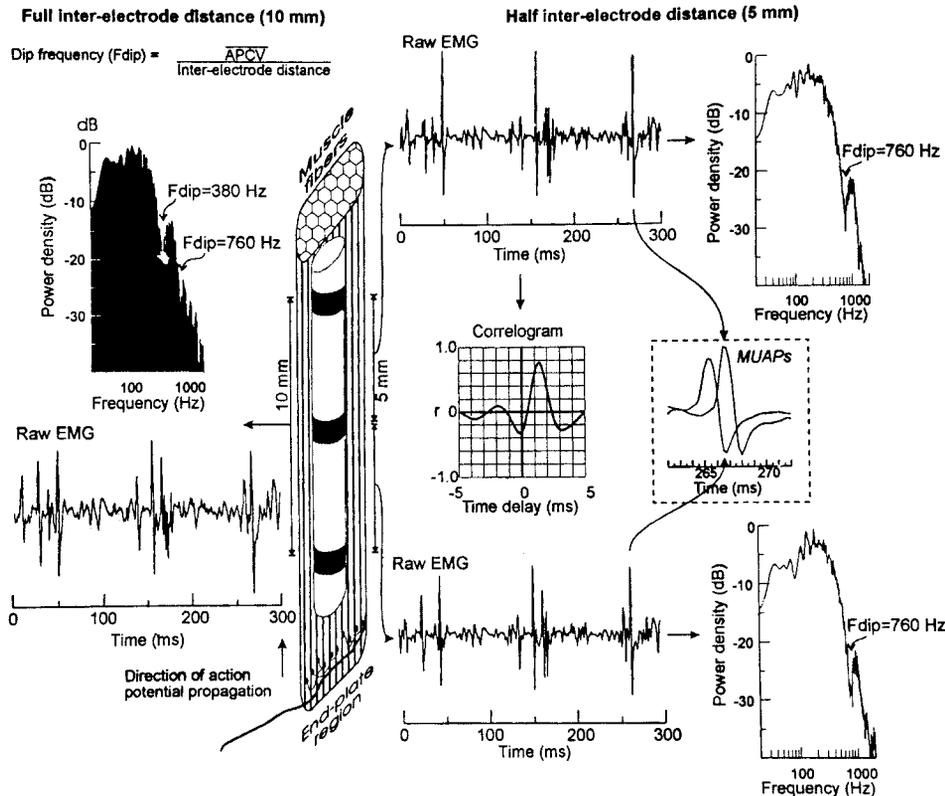


Figure 5. Time and frequency domain characteristics of diaphragm EMG signals obtained with bipolar esophageal electrodes positioned near a region with low density of motor end-plates and aligned in the direction of diaphragm fibers. Left: Raw EMG and computed power spectrum from a pair of electrodes with a 10-mm interelectrode distance. Right (top and bottom): Signals derived at the same time from the same region using electrodes with a 5-mm interelectrode distance. Right (middle): On the left is shown a cross-correlogram obtained from the successive cross-correlations at various time delays between EMG signals obtained with a 5-mm interelectrode distance; on the right is shown two motor unit action potentials (MUAPs) obtained from the two electrodes pairs with a 5-mm interelectrode distance. Reprinted by permission from Reference 46.

so that the relative distribution of power in the spectrum is altered and f_c is reduced (1, 14–17, 40) (Figure 6).

Interelectrode distance and alignment with respect to fiber direction (bipolar arrangement). Both interelectrode distance and the orientation of the electrodes with respect to fiber direction can affect power spectra (1, 18, 41). As shown in Figure 5, reductions in interelectrode distance reduce signal

power, with relatively higher attenuation of low-frequency components. With bipolar recordings of EMG, electrode orientation with respect to fiber direction and interelectrode distance should be standardized, and investigators should recognize that these relationships are likely to change with muscle contraction.

Signal disturbances. Electrode motion-induced artifacts. Movement of the electrode or a change in the pressure on the electrode results in a redistribution of the charges in the resistive-capacitive interface between the electrode and the tissues, causing relatively large amplitude artifacts with low frequency (mostly below 20–25 Hz) (39, 42). Most of the motion artifact can be filtered out with high-pass filters. However, some EMG power occurs at frequencies below 25 Hz, and even the most efficient filter attenuates some of the power above its cutoff frequency. Thus, high-pass filtration inevitably leads to loss of low-frequency power from the EMG signal. When power spectrum analysis is applied, the power related to electrode movement can be reduced (42) or replaced by an extrapolation of the diaphragm EMG power to those frequencies (39).

Noise. Background noise, signals of unidentifiable origin, can be assumed to have constant power density over the frequency region of interest in EMG recordings. On the basis of this assumption, the noise component of the signal-to-noise ratio is usually estimated from power density values obtained in the uppermost frequency range of the EMG power spectrum (39, 43, 44). Noise originating from modern electrophysiologic instruments is not usually a problem, but ancillary equipment, such as pressure or motion sensors, pumps, or respirators, may introduce noise in various frequency ranges.

Disturbances from power lines. Sinusoidal alternating currents (ACs) originating from power lines can usually be reduced to a negligible level by proper shielding of electrode cables and connections, by using amplifiers with high common

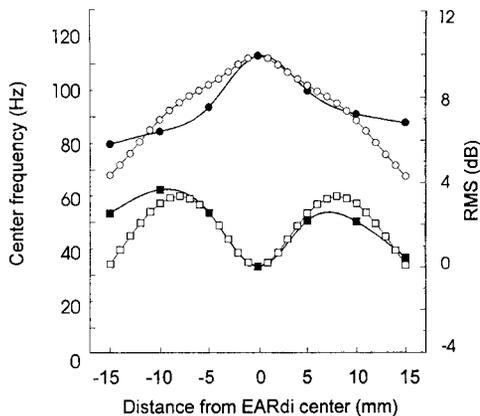


Figure 6. The influence of esophageal electrode positioning on diaphragm EMG center frequency (f_c) (left axis; circles) and root mean square (RMS) (right axis; squares). Solid symbols indicate experimental data, whereas open symbols indicate computer-simulated power spectra. The "0" on the x axis indicates the center of the electrically active region (source). RMS was lowest at the electrode pair positioned directly over the source (due to the cancellation effect of a bipolar electrode). Caudal and cephalad to the source, RMS increased progressively to maxima at approximately 10 mm from the source in either direction. f_c was maximal at the electrode pair directly over the source, hence less high frequency is filtered by the electrode being closer to the muscle. Reprinted by permission from Reference 46.

mode rejection ratio, and by connecting all instruments to the same ground point. Residual power line disturbances can be filtered out with “notch filters,” or, alternatively, the power of the affected frequency and its harmonics can be excluded in power spectral analysis.

Potential artifactual influences of physiologic origin. Cross-talk signals. These are signals originating from muscles other than the muscle being investigated. The best-described source of cross-talk is electrical activity from the heart (EKG). Esophageal recordings of diaphragm EMG are particularly susceptible to cardiac cross-talk, which provides a signal with some 10 times the power of the diaphragm EMG but with a much lower f_c (39, 42). For measurements of stimulation-elicited CMAPs, EKG artifacts are relatively easy to avoid by triggering the stimulus from the QRS complex with an appropriate delay. Alternatively, any record visibly superimposed on the QRS complex can simply be discarded.

For time domain analyses over long periods of time or for power spectral analyses, EKG artifacts pose a significant problem. Heart rates often change, as, for example, with inspiration and with exercise. The frequency content of the EKG is lower than that of EMG activity, but there is considerable overlap (39, 43). Thus, if the high-pass filter is set high enough to eliminate most of the EKG activity, it will also eliminate much of the EMG activity. When EMG frequency content might be shifting toward lower frequencies, as during increasing muscle effort, excessive high-pass filtration will result in spurious reductions in measured RMS. Methods to eliminate the cardiac activity from esophageal recordings of diaphragm EMG by template subtraction (45) have been proposed. However, because the amplitude and shape of the electrocardiogram change with changes in lung volume, the safest method to avoid cardiac influences on diaphragm EMG signals still appears to be selection of signal segments that are free of cardiac activity (39).

Another source of cross-talk in esophageal recordings of diaphragm EMG is esophageal peristalsis (39). The esophageal peristalsis signals show a relatively large amplitude and relatively low-frequency content. In general, signal segments contaminated by esophageal peristalsis, usually easily identified as strong, slow esophageal pressure waves, should be excluded from analysis.

Other examples of cross-talk sources include contamination of diaphragm EMG data recorded from electrodes on the lower rib cage with abdominal or intercostal muscle activity and contamination of intercostal muscle EMGs by interference from pectorals, abdominals, or diaphragm (46).

Innervation zones. Electrodes positioned close to or over an innervation zone (a region with a high density of motor end

plates) produce complex interference patterns, because the action potentials elicited by firing of an individual motor unit may propagate in opposite directions relative to the electrodes (2, 47, 48). Characteristically, there is reduced total power and increased high-frequency content (49). This effect is maximal when bipolar electrodes are oriented parallel to fiber direction; esophageal electrodes, which are arranged approximately perpendicular to fibers, are less susceptible (18).

Influence of changes in muscle length or chest wall configuration. Changes in chest wall configuration systematically affect the amplitude and frequency content of evoked CMAPs measured with chest surface or esophageal electrodes (13, 50). With spontaneous EMG activity, artifact-free signals recorded from esophageal electrodes are not systematically affected by changes in chest wall configuration (17, 18, 25, 50, 51). Because conduction velocity is not significantly affected by muscle length (52), most of the chest wall configuration effects on EMG are probably due to muscle-to-electrode distance or orientation changes.

Influence of changes in muscle temperature. Muscle temperature increases during exercise, because of the increase in blood flow to the muscle (53, 54), and metabolic heat production (55). Because the propagation velocity of the muscle fiber action potential is correlated with temperature (56, 57), EMG frequency content must also be temperature dependent. No method for control of or correction for temperature in recordings of respiratory muscles has yet been described.

Applications

See Table 2.

Single fiber and motor unit analysis. Single fiber and motor unit signal analyses are useful for diagnosis of nerve or muscle pathology. For the diagnosis of neuromuscular disease, limb muscles are more commonly studied than respiratory muscles, because they are more readily accessible. A number of investigators have demonstrated the usefulness of needle electromyography of the diaphragm for the diagnosis of neuromuscular disease, particularly neuropathic processes such as Guillain-Barré syndrome, lower motor neuron involvement with spinal cord injury, and polyneuropathy of critical illness (31, 32, 34).

Bolton (34) has pointed out that the relatively high-frequency, low-amplitude potentials of the normal diaphragm are often difficult to differentiate from myopathic potentials. Nevertheless, several neuromuscular diseases present primarily with respiratory muscle weakness; as experience is gained with single fiber and motor unit analysis of respiratory muscles, these techniques applied to respiratory muscles may provide the earliest evidence of the neuro- or myopathic process.

TABLE 2. APPLICATIONS FOR RESPIRATORY MUSCLE ELECTROMYOGRAMS

Type of Test	Condition	Finding
Needle EMG	Denervation	↓MUAPs, fibrillation potentials, and positive sharp waves
	Demyelination	↓MUAPs, without potentials
	Chronic denervation	↓No., ↑size of MUAPs
	Myotonia	Myotonic discharges
	Myopathy	Short, polyphasic potentials
Interference pattern EMG signal	Paralysis or dyscoordination	Respiratory muscle activation pattern
	Quantification of neural drive	Changes in FRA or RMS
	Efficiency of contraction	$\Delta P_{di}/\Delta E_{di}$
	Fatigue	Spectral analysis

Definition of abbreviations: $\Delta P_{di}/\Delta E_{di}$ = ratio of tidal respiratory change in transdiaphragmatic pressure to tidal respiratory change in integrated diaphragm EMG; EMG = electromyography; FRA = full wave rectified and averaged signal; MUAP = motor unit action potential; RMS = root mean square of the signal.

Interference pattern signal. The interference pattern EMG (raw EMG from surface electrodes) of respiratory muscles is useful for the determination of the timing and level of muscle activation during respiratory activities. Thus, EMGs can help to determine which of the many respiratory muscles are active in various phases of respiration, in various body positions, in various states of consciousness, and in various clinical conditions (see ELECTROMYOGRAPHY in Section 8 of this Statement). Specifically, the absence of voluntary or involuntary EMG activity can be used as evidence of paralysis of specific respiratory muscles. EMGs can also help to quantify the respiratory muscle activation responses to loaded breathing and to CO₂-stimulated breathing or to monitor and control mechanical ventilation (58, 59). Furthermore, when related to pressure or force developed by respiratory muscles, EMGs can help to assess the electromechanical “efficiency” of respiratory muscle function (see ELECTROMECHANICAL EFFECTIVENESS in Section 6 of this Statement).

Interindividual comparisons of absolute FRA or RMS values do not meaningfully reflect respiratory drive, because of varying filtering influences of electrode placement relative to the contracting muscles and/or anatomic differences between subjects, for example, the amount and type of interlaying tissue. However, changes in these indices in response to interventions such as changes in inspired CO₂ concentration, loaded breathing, exercise, states of consciousness, drugs, or other influences, reflect changing motor output of the central nervous system (CNS) to respiratory muscles. Because some respiratory muscles are silent during quiet breathing, it is not practical to normalize respiratory muscle EMG activity to that observed during resting tidal breathing. It is often more practical to normalize EMG activity to that observed during sniff inhalations or maximal inspiratory efforts (22).

The interference pattern EMG of respiratory muscles may also be useful for the assessment of respiratory muscle fatigue (see ELECTROMYOGRAPHY in Section 5 of this Statement). Localized muscle fatigue is accompanied by a reduction in muscle fiber action potential conduction velocity (1), which is reflected in the diaphragm EMG power spectrum as a shift toward lower frequencies (41, 52). This “spectral shift” is most commonly quantified as a reduction in f_c . Spectral shifts have been detected in healthy subjects during inspiratory resistive breathing (38, 60), in patients with weak inspiratory muscles constrained to breathe with prolonged inspiratory duty cycles (61) or with exertion-induced inspiratory muscle overload (62), and in patients with chronic obstructive pulmonary disease during exertion (43), and they are associated with changes in respiratory effort sensation (63). The EMG frequency spectrum is often influenced by other factors, such as the signal-to-noise ratio, electrode position, and recruitment of muscles that potentially

contribute to cross-talk. Technical factors affecting the EMG power spectrum must always be taken into account before any physiologic interpretations of a spectral shift can be made (1, 15–19, 41–48).

STIMULATION TESTS

Rationale

Peripheral nerve, spinal, or cortical stimulation, either by implanted electrodes (for peripheral nerves) or by externally applied electric or magnetic fields, elicit relatively synchronized activation of motor units at reproducible and predictable levels. The resulting compound action potentials and subsequent muscle contraction allow for measurement of the efficiency of neural and neuromuscular transmission. The muscle responses to stimulation are discussed in PHRENIC NERVE STIMULATION in Section 2 of this Statement.

Scientific Basis

For practical purposes, human respiratory motor nerves are not accessible over a sufficient length to permit phrenic or other respiratory nerve conduction velocities to be measured. However, motor latency can be measured. Included in the latency are the times required for (1) initiation of action potentials in the axons, (2) rapid saltatory conduction through myelinated axons, (3) slow conduction along the thinner terminal twigs, and (4) chemical transmission across the neuromuscular junctions.

Equipment

Nerve stimulation. Stimulation of respiratory nerves can be accomplished with electrical or magnetic stimulators (Table 3). The former are less expensive, less cumbersome, more rugged, and more precisely controllable; the latter are easier to apply and less painful for patients. For electrical stimulation, the phrenic nerve is stimulated transcutaneously by surface electrodes at the posterior border of the sternomastoid, or with implanted needle, wire, or hook electrodes. The phrenic nerve(s) can also be stimulated magnetically, via a dorsal cervical approach, which stimulates the lower cervical nerve roots; via an anterior presternal approach, which stimulates both phrenic nerves; or, using one or two figure-of-eight coils, unilaterally or bilaterally over the anterior neck to stimulate one or both phrenic nerves.

Several other respiratory nerves and muscles can also be stimulated, either transcutaneously or by needle or wire electrodes. Pradhan and Taly (28) have demonstrated a technique for stimulating lower intercostal nerves via probe electrodes for latency measurements. The ventral roots of intercostal nerves have been stimulated either by high-voltage stimulation over the spine (64–66) or by surgically implanted wire elec-

TABLE 3. TYPES OF RESPIRATORY MUSCLE STIMULATION

Type of Stimulation	Advantages	Disadvantages
Electrical		
Implanted	Less uncomfortable during stimulation Precise control of stimuli	Difficult to place
Transcutaneous	Inexpensive Requires little preparation	Painful Difficult to maintain contact during voluntary effort
Magnetic	Does not require contact with skin Painless	Expensive and cumbersome Relatively unselective Difficult to stimulate repetitively Precise location of stimulus uncertain (so latency measurements may be problematic)

trodes (67). The rectus abdominus and oblique muscles can also be stimulated with large surface area electrodes (68), and abdominal muscle stimulation has been shown to be effective enough to facilitate cough in tetraplegic patients with impaired expiratory muscle function (66). The abdominal muscles can be activated by magnetic stimulation of nerve roots at the level of T10.

In most cases, it is important to be sure that the delivered stimulus is strong enough to activate maximally all motor units in the muscle of interest. To that end, elicited CMAP amplitude is measured as a function of stimulus intensity, and, for subsequent measurements, stimulus intensity is set to be supramaximal, 20–50% above that required for maximal response. During long experiments, it should be regularly verified that stimulus intensity is supramaximal.

Cortical stimulation. It is now possible to stimulate cortical and subcortical neural pathways in human subjects, using high-voltage (up to 1,500 V) electrical stimulators (69) and magnetic stimulators (up to 3.0 T) (70). Electrical stimulation of the cortex requires saline-soaked gauze pads (or silver–silver chloride electrodes) on the scalp with the anode positioned over the relevant region of the motor cortex. For the diaphragm and intercostal muscles, the optimal site is close to the midline at or just anterior to the vertex (71). The cathode can either be a single electrode 6–8 cm anterior to the anode, a ring of electrodes placed around the scalp, or an electrode several centimeters lateral to the anode at the vertex. Commercially available magnetic stimulation coils consist of several circular coils in a single housing (usually > 10 cm in diameter) positioned (usually tangentially) with their edges close to the scalp region of interest. Positioning of large circular coils slightly anterior or posterior to the vertex will routinely activate corticofugal output from the medial parts of both hemispheres, including major inspiratory and expiratory muscles in normal subjects, and structures as lateral as the hand area are also activated. More focal stimulation can be achieved with double or “butterfly” coils. There are several nonstandard coils, but their properties must be carefully determined before their clinical utility can be assessed.

To obtain minimal latencies for response to transcranial stimulation, and thereby to avoid coming to the erroneous conclusion that there is a deficit in corticospinal conduction, it is best to record them during voluntary (or reflex) contractions producing at least 10% of maximal force. Responses can be obtained without a background contraction, but the latencies are more variable.

The presence of cardiac or other implanted electrical devices, including pacing wires and pulmonary artery catheters equipped with thermistors, is an *absolute* contraindication for magnetic stimulation and for high-voltage electrical stimulation of cranial or spinal structures. Epilepsy and known intracortical pathology are relative contraindications for cranial stimulation, as is the presence of intracranial clips.

Although transcranial stimulation has now been used for well over a decade with few reports of side effects, two issues deserve mention. First, there is a risk of induction of a seizure, particularly in those with pre-existing cortical pathology (such as a recent cerebrovascular accident). Although seizures have not been observed with repeated single stimuli, greater precautions are necessary for the newer rapid-rate stimulators (72, 73). Second, the use of some but not all transcranial magnetic stimulators has caused sustained elevations in auditory threshold, presumably due to the brief, but high-intensity “click” produced by the stimulus passing into the coil.

Data Analysis

Nerve stimulation is essential for measurements of nerve conduction velocity or latency. Furthermore, the electromyographic

signal elicited by supramaximal nerve stimulation (CMAP) provides a different perspective than spontaneous EMG, with two distinct advantages: assurance of maximal activation, and a generally higher signal-to-noise ratio. CMAPs are detected, usually with surface electrodes applied over the costal margin, and the time between triggering of the stimulus and detection of the elicited CMAP is recorded. In most cases, CMAP amplitude and/or area are also recorded.

Latencies can also be measured after cortical stimulation (Figure 7). The “central” conduction time (CCT) is an indirect estimate of the time taken for the descending volley to travel from the motor cortex to the relevant motoneurons. The CCT can be measured by subtraction of the peripheral conduction time (estimated by stimulation over the relevant spinal segment or root) from the total conduction time, from stimulus to onset of the motor-evoked potential (MEP). The measured CCT, however, is not a true measurement of central conduction velocities, because the exact site and timing of the relevant descending corticofugal volleys show some variability and because stimulation over the spinal cord activates the motor axons at a variable distance from the motoneurons. The MEP observed in EMG recordings of most human trunk and neck muscles, including diaphragm, intercostals, scalene, and abdominal muscles (64), has an onset latency consistent with a rapidly conducting oligosynaptic pathway. There is no evidence that this MEP involves a contribution from bulbopontine respiratory neurons.

The MEP can also be assessed in terms of amplitude (and dispersion). Transcranial electrical stimulation via an anode over the appropriate scalp site evokes a direct corticospinal volley (D-wave) followed by a series of indirect trans-synaptically evoked corticospinal volleys (I-waves; interval between volleys, 0.8–1.0 milliseconds). With increased intensity of electrical stimulation, the site of activation along the corticospinal path is located deeper within the brain, reaching the level of the pyramidal decussation in the medulla with strong stimuli (74). The size of the D-wave increases with increased stimulus intensity, as does the size of I-waves. With transcranial magnetic stimulation, the precise corticospinal response depends on the location of the evoked currents. Hence, there are differences in the magnetic activation of the corticospinal output from the hand areas (lateral region of the primary motor cortical strip) compared with the leg areas (within the medial edge of the motor cortex) with different directions of stimulus current. With high-power nonfocal coils (which have the greatest diagnostic utility) transcranial magnetic stimuli evoke not only

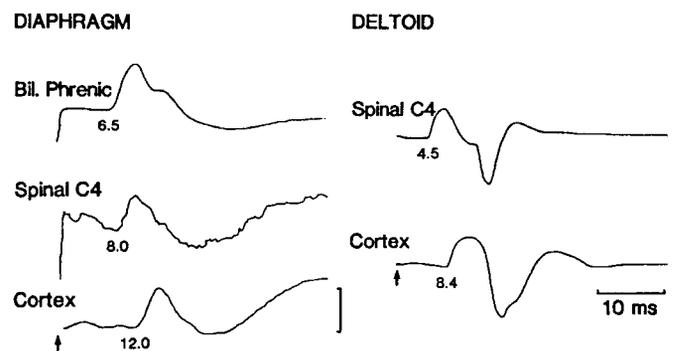


Figure 7. Comparison of motor latencies and compound diaphragm or deltoid action potentials elicited by magnetic stimulation at the phrenic nerve, spinal level, and cortical level. The latencies are indicated in milliseconds. Bil. = bilateral; C4 = level of the 4th cervical root. Reprinted by permission from Reference 64.

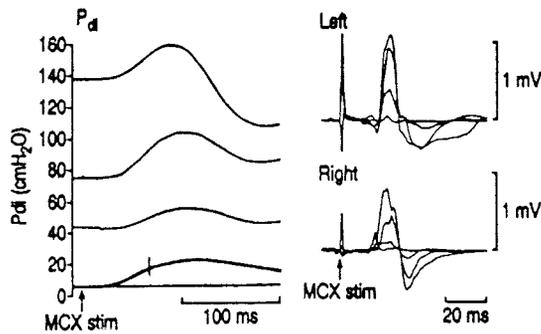


Figure 8. Effects of cortical stimulation at rest and during voluntary inspiratory efforts of varying strength. *Left:* Transdiaphragmatic pressure (Pdi) twitches obtained by bilateral supramaximal phrenic nerve stimulation during relaxation (thick trace). The thin traces show twitches resulting from transcranial magnetic stimulation (stimulator set at 85% maximal) at rest (lowest trace, no twitch) and during three graded static inspiratory efforts. Note the facilitation of Pdi twitches at intermediate voluntary efforts and the partial occlusion at high effort. *Right:* Compound muscle action potentials (CMAPs) recorded from surface electrodes on right and left chest wall (over the diaphragm) during magnetic stimulation at the four levels of voluntary effort shown at left. Note the progressive facilitation in CMAP amplitude. Reprinted by permission from Reference 76.

I-waves but also small D-waves (75). There is probably more trial-to-trial variability in the components of the descending volley to magnetic stimulation than to electrical stimulation.

During voluntary contraction, the minimal latency of responses is reduced, and the MEPs are increased in size compared with relaxation (Figure 8), reflecting increased excitability not only at the spinal level (76) but also at the motor cortex (77). For the diaphragm, this effect has been documented during both volitional efforts (35) and CO₂-driven hyperpnea (78).

Interpretation of the results of motor cortical stimulation must be made with caution for several reasons. First, stimulation over the motor cortex activates both excitatory and inhibitory structures within the cortex. Second, a single stimulus as brief as 50 milliseconds evokes multiple descending corticospinal volleys. Third, the evoked motor response is elicited preferentially in α motoneurons that are close to firing threshold as a net result of voluntary, involuntary, and reflex inputs. Finally, change in MEP can be said to reflect a change in cortical physiology only if the excitability of the spinal cord has been proven to remain constant.

When cortical stimulation is delivered during voluntary effort, the MEP is followed by a period of near silence in the EMG recorded from the relevant muscle. The latter part of the silent period is due to inhibition of motor cortical output (79–81). The duration of the silent period grows with increasing intensity of cortical stimulation but does not vary greatly with the relative strength of voluntary contraction.

Applications

Normal phrenic nerve/diaphragm latencies, elicited by electrical stimulation at the neck, have been reported to average 6–8 milliseconds in adults (12, 16, 82, 83), with lower values in children (*see* Table 4). Because the right phrenic nerve is shorter than the left, latency is slightly shorter on the right side. CMAP amplitudes, recorded from chest wall surface electrodes, average 500–800 mV. Normal values for magnetic stimulation-induced phrenic nerve/diaphragm latency or for intercostal nerve/muscle latency have not been fully established (84, 85).

Phrenic nerve/diaphragm latencies are abnormally slow in demyelinating polyneuropathies, notably Guillain-Barré syndrome. They are usually nearly normal, but are associated with markedly depressed CMAP amplitude, in traumatic neuropathies, such as postcardiac surgery phrenic nerve palsy or the polyneuropathy of critical illness. In myasthenia gravis, a reversible decrement in diaphragm CMAP can be elicited by repetitive phrenic nerve stimulation.

CCTs from cortex to phrenic motoneurons are approximately 4 milliseconds in normal adults (35). Normal values for D- and I-wave amplitudes and the effects of disease are not yet established, but it is apparent that I-wave amplitude is reduced by general anesthetic agents.

Transcranial stimulation to determine CCT has been used in the assessment of a range of upper motor neuron disorders and particularly in the assessment of patients with possible CNS demyelination, including multiple sclerosis. It can be applied specifically to the respiratory muscles, or, more commonly, to muscles in both upper and lower limbs.

Compound muscle action potentials (CMAP) in response to electrical or magnetic nerve or cortical stimulation can also provide useful information. Lack of a CMAP after nerve stimulation is an indication of paralysis, with the lesion located proximal to or at the neuromuscular junction. Lack of a CMAP in response to cortical stimulation when a CMAP is elicited by phrenic nerve stimulation has been used to identify good candidates for phrenic nerve pacing.

Changes in CMAP amplitude, especially as compared with changes in elicited muscle twitch strength (such as phrenic stimulation-induced diaphragm CMAP as compared with transdiaphragmatic twitch pressure [Pdi,tw]) can be used as evidence for or against the development of neural or neuromuscular transmission defects (when both Pdi,tw and CMAP decrease) or contractile defects (when Pdi,tw decreases but CMAP does not) (86).

CONCLUSION

In a manner analogous to the use of the electrocardiogram to assess cardiac function, electrophysiological tests of respiratory muscles—respiratory muscle motor latencies and elec-

TABLE 4. APPLICATIONS OF RESPIRATORY MUSCLE STIMULATION TESTS

Stimulation Test	Normal Values (in Adults)	Abnormal in:
Phrenic nerve/diaphragm latency	6–8 ms	Demyelinating polyneuropathies, e.g., Guillain-Barré syndrome
Elicited CMAP	Depends on recording electrode	Phrenic nerve palsy, neuromuscular transmission defect, polyneuropathy of sepsis, myopathies
Central conduction time, total conduction time minus phrenic nerve latency	~ 4 ms	Multiple sclerosis

Definition of abbreviation: CMAP = compound muscle action potential.

tromyography—can be used to assess (1) respiratory drive, respiratory muscle coordination, and the level of activation of individual muscles; (2) the presence of neural and neuromuscular pathology; and (3) the apparent efficacy of the contractile function of the muscles, when used in conjunction with measurements of contractile force. The special challenges presented by data analysis complexity and by a host of potential artifacts lead to the need for great care in the application of EMG techniques to respiratory muscles. Nevertheless, neurophysiological tests are emerging as indispensable components of the respiratory muscle physiologist's arsenal.

SUMMARY

This Section of the Statement has described available electrophysiologic tests, the functions of which are to assess the integrity of the respiratory neuromotor apparatus. These electrophysiologic tests are technically complex and require considerable expertise.

There are two main types of test: electromyography (EMG) and stimulation tests.

Type 1: EMG. For the respiratory muscles the EMG can be used to assess the level and pattern of activation, to detect and diagnose neuromuscular pathology, and when combined with tests of mechanical function to assess the efficacy of contraction.

The EMG can be recorded with surface electrodes (for diaphragm, intercostal, scalene, abdominal, and accessory muscles) or an esophageal electrode (for the crural diaphragm). Surface electrodes are noninvasive and sample a large number of motor units, but contamination (cross-talk) from other muscles is a substantial problem, as is the effect of body size and shape on signal amplitude. Esophageal electrodes provide more specific information, but the technique is invasive and complex.

Surface and esophageal electrodes can record the interference pattern EMG (raw EMG) of the respiratory muscles and are useful to determine the timing and level of respiratory muscle activation during breathing, at rest, and under load. Frequency domain analysis of the EMG is used, as a research tool, to investigate respiratory muscle fatigue (discussed in Section 5 of this Statement).

Intramuscular electrodes can be used to record, relatively selectively, from the diaphragm and intercostal muscles. Motor neuron firing frequency can be measured and neuromuscular disorders diagnosed. However, the techniques are invasive and technically difficult.

Type 2: Stimulation Tests. Stimulation tests measure the efficiency of neural and neuromuscular transmission.

Nerve stimulation can be achieved with electrical or magnetic stimulators. Electrical stimulation is inexpensive and relatively selective, but is uncomfortable and can be technically difficult. Magnetic stimulation is easier to achieve and less uncomfortable, but can be less selective and is expensive.

Most commonly the phrenic nerves are stimulated and the diaphragm EMG elicited, for the measurement of phrenic nerve/diaphragm latencies and CMAP amplitudes. Latencies are prolonged in some neuromuscular disorders (e.g., demyelination) and CMAP is reduced in amplitude (e.g., traumatic damage to the phrenic nerves).

Cortical stimulation is most commonly performed with a magnetic stimulator, and permits the measurement of central conduction times (CCT) for limb muscles and diaphragm. CCT can be prolonged as, for example, in multiple sclerosis. Cortical stimulation is not selective, and the application of the technique to the respiratory system is a highly specialized skill.

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4. Tests of Respiratory Muscle Endurance

Muscle endurance is the ability to sustain a specific muscular task over time. It is a highly integrated and complex quality of a muscle or a group of muscles that is related to its resistance to fatigue. To a large extent, any measurement of endurance is task specific because different tasks result in varying recruitment patterns of motor units and synergistic muscle groups, each with varying endurance qualities. The wide variety of techniques that have been developed to measure endurance of the respiratory muscles differ largely on the type of task that is being performed. For each specific task, an endurance curve can be generated by plotting task intensity versus the time it can be sustained. Task failure is an event defined by the inability to continue performing the required task (Figure 1). At high levels of intensity, a task can be performed for only a few repetitions. As the intensity is decreased, each task can be endured for a longer time until a level can be sustained for an indefinite period (i.e., hours). The latter is referred to as the maximum sustainable task or load. Another estimate of endurance involves performing incremental increases in task intensity for a given time period until a peak intensity is identified, which is the maximum that can be maintained for a finite period of time (Figure 1). This intensity is not sustainable but may also be used to reflect endurance properties.

Although respiratory muscle strength and endurance appear to be closely linked in many conditions (1–3), there are numerous examples in which endurance would not be accurately predicted from estimates of maximum pressures or maximum ventilatory capacity. Furthermore, the characteristics of endurance curves for a given muscle may change with training, disuse, drug treatment, and so on. For example, in heart failure patients (4) or in normal subjects (5) following certain respiratory muscle training protocols, larger relative effects are seen on endurance compared with strength. Some patients with asthma show inherent elevations in endurance properties as a fraction of strength (6), as do patients with cystic fibrosis (7), suggesting these patients naturally train for endurance during periods of airway obstruction. In contrast, patients with chronic obstructive pulmonary disease (COPD) (8) or patients receiving acute steroid treatment (9) show marked reductions in endurance properties relative to strength. Therefore, endurance measurements can be useful in some clinical and investigative settings for evaluating patient populations and responses to treatment and rehabilitation.

MEASURES OF RESPIRATORY MUSCLE ACTIVITY USED IN ENDURANCE TESTING

Rationale

Many different kinds of tasks have been used to quantify the endurance properties of the respiratory muscles. Most often, endurance has been defined in terms of the ability to sustain a level of minute ventilation (ventilatory endurance) or a level of inspiratory and sometimes expiratory pressure. However, these simple measures often present limitations to evaluating the effect of the load on the respiratory muscles. From a muscle energetics viewpoint, the energy requirements of a working muscle (and therefore a rough estimate of its level of activation) are determined largely by the tension developed over time (i.e., tension–time product) and the rate of mechanical work being performed (\dot{W}) (10, 11).

Pressure–Time Product

Methodology. Refer to PRESSURE MEASUREMENTS in Section 2 of this Statement for specific techniques for the measurement

of pressure at the airway opening and esophageal, gastric, and transdiaphragmatic pressures. The pressure–time product (PTP) is the integration of respiratory pressure over time (i.e., $\int P dt$). It is common to express PTP over a 1-minute interval (i.e., units = pressure \times time; e.g., cm H₂O \times minutes). The integration process can be performed by most medical amplifiers or digital computers, much like flow is integrated to obtain minute ventilation. If such techniques are used, assurances must be made that expiratory pressures during the expiratory phase, or inspiratory pressures generated due to chest wall elastic recoil, are excluded from the analysis of inspiratory PTP.

A common expression of the PTP is the mean pressure generated over an entire breath cycle (\bar{P}) in Equation 1, in which

$$\text{Mean pressure } (\bar{P}) = \text{PTP}/(\text{sampling period}) \quad (1)$$

For example, if PTP is measured for a single breath period, then the sampling period would be total breath period (T_{tot}). A signal averaging circuit (available on most medical amplifiers for determining mean vascular pressure) can often be used to measure \bar{P} directly, online. These are usually composed of “leaky integrators” with time constants of approximately 20 seconds. The analysis can also be done by digital computer or mechanical devices (12).

The \bar{P} value calculated in Equation 1 can be measured at the mouth or airway opening if one wishes to estimate the average pressure generated by all the respiratory muscles working against an external load (i.e., \bar{P}_{mo}). Alternatively, it can be measured using: transpulmonary pressure (\bar{P}_{L}) for measurements of activity of the chest wall and its muscles against the lung and airways (2); transdiaphragmatic pressure (\bar{P}_{di}) for the activity of the diaphragm alone (1); or total respiratory muscle pressure (\bar{P}_{mus}) for activity of the synergic respiratory muscles against the lung and rib cage (13).

When \bar{P} is normalized to a fraction of the maximum inspiratory pressure available, it is referred to as the pressure–time index (PTI). For example, for measurements of pressure at the mouth or airway opening, Equation 2 is

$$\text{PTI}_{\text{mo}} = \bar{P}_{\text{mo}}/P_{\text{i,max}} \quad (2)$$

where PTI_{mo} is the pressure–time index measured at the mouth and $P_{\text{i,max}}$ is the maximum inspiratory pressure that can be generated at the mouth or airway opening (usually obtained for a period exceeding 1 second). For the PTI for the diaphragm (PTI_{di}), maximal transdiaphragmatic pressure ($P_{\text{di,max}}$) is substituted for $P_{\text{i,max}}$ and \bar{P}_{di} is substituted for \bar{P}_{mo} . Refer to Section 2 of this Statement for techniques of measuring $P_{\text{i,max}}$ and $P_{\text{di,max}}$. Traditionally, the term tension–time index (TTI) has been applied to this measurement (1). From a physiologic viewpoint, TTI is the “ideal” variable, which is deterministic for a large number of relevant factors in muscle physiology, including muscle energetics and blood flow. However, for most experimental and clinical measurements for the respiratory system, the transduction of muscle tension into respiratory pressures is not straightforward. Therefore, to avoid misinterpretation of the data, it is recommended that PTI be substituted for TTI when pressure comprises the measured variable (see Section 5 of this Statement).

Advantages. Under conditions of relatively constant ventilation, respiratory muscle endurance (1), blood flow (14), and changes in oxygen consumption of the respiratory system

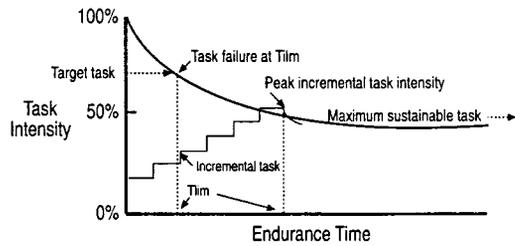


Figure 1. A schematic showing an idealized endurance curve for a given task (e.g., maximal voluntary ventilation) and its relationship to an endurance test (dotted line) as well as to an incremental loading test (thin stepped line). T_{lim} = Time limit a task can be endured before task failure.

($\dot{V}_{O_{2,rs}}$) (15, 16) have been shown to be significantly correlated to changes in PTI (Figure 2). Furthermore, PTI is a parameter that describes the pressure-generating activity of the muscles, independent of a specific breathing rhythm, breathing frequency, or type of load within the experimental limits tested (1). Normalizing to maximum pressure can also be useful as a measure of the amount of pressure “reserve” utilized during contraction. For example, most normal subjects can sustain a PTIdi of up to approximately 0.18 (1) and a PTI for the chest wall muscles and the synergic inspiratory muscles of up to approximately 0.3 (2). These “critical” PTI values may be useful in estimating whether the muscles are undergoing contractions that are “likely” to lead to a loss of force, or fatigue (17, 18). However, critical PTI should be used with considerable caution, as it is highly likely that the critical PTI may vary somewhat across various pathological conditions. This has not been studied extensively. In addition, in clinical situations there is often some uncertainty regarding the accuracy of measurements of $P_{i,max}$ or $P_{di,max}$ used to calculate PTI (see VOLITIONAL TESTS OF RESPIRATORY MUSCLE STRENGTH in Section 2 of this Statement).

Disadvantages. When the level of ventilation increases at a constant PTP, the $\dot{V}_{O_{2,rs}}$ is increased and endurance is reduced (15, 19). For example, in Figure 3A, when a subject is inspiring with a constant PTP (individual isopleths), increasing flow rates result in markedly increased oxygen consumption of the respirator system ($\dot{V}_{O_{2,rs}}$). Furthermore, when PTP is kept constant, increasing mechanical work rates of the respiratory system \dot{W}_{rs} result in reduced inspiratory muscle endurance (Figure 3B). Therefore, when the tasks involve high levels of ventilation, as may occur during exercise, during ventilatory endurance measurements, or in patients with high or changing ventilatory requirements, the various measures of pressure over time (i.e., PTP, \bar{P} , and PTI) become less predictive as global measures of the activity or endurance of the muscles. Under these conditions, the mechanical work rate (\dot{W}_{rs}), discussed below, begins to take on a greater significance (19). As shown in Figure 3C, when ventilation is allowed to vary over a wide range of PTP, \dot{W}_{rs} becomes highly predictive of the $\dot{V}_{O_{2,rs}}$ and therefore the energy utilization of the respiratory muscles.

Another illustration of these points is that the critical PTI for the respiratory muscles working synergically can vary from 0.12 to 0.4, depending on the particular pattern of ventilation, particularly when inspiratory flows and timing are varied over a wide range (13, 20). Nevertheless, under most testing conditions, when ventilation remains relatively low and constant, and duty cycle is kept within a range that is normally seen during spontaneous ventilation (i.e., 0.3–0.5), measures of PTP (alternatively, PTI or \bar{P}) are still the most predictive global measure of respiratory muscle activity available.

Work Rate of the Respiratory System

Methodology. Generally, the ventilatory work rate (power output) of the respiratory system (\dot{W}_{rs}) refers to mechanical work performed by the respiratory muscles against the lungs and chest wall during ventilation. It is calculated as the integration of the appropriate measures of pressure \times volume (see ASSESSMENT OF THE FUNCTION OF THE ACTIVE CHEST WALL: CAMPBELL DIAGRAM in Section 6 of this Statement). In this discussion, we will use \dot{W}_{rs} to also include the work rate performed by the respiratory system against any external loading device. Work rate is expressed in joules per minute (1 J = 1 kPa \cdot 1 L; 1 kPa = 10.2 cm H₂O). The complete measurement of work of breathing against the lung and chest wall, for both inspiration and expiration, is complex, largely because components involving movement and distortion of the chest wall are difficult to quantify without relatively sophisticated analyses. However, in many cases, measuring the work performed against an external load (\dot{W}_{ext}) may provide sufficient information for purposes of respiratory muscle endurance testing.

If a subject is breathing against an external load and ventilation remains near spontaneous levels during loading, the rate of work performed against the lung and chest wall remains relatively unchanged from normal breathing. Therefore, any “changes” in \dot{W}_{rs} can be attributed largely to changes in the work performed against the external load, or \dot{W}_{ext} . For example, if a subject were breathing against an inspiratory resistive load, \dot{W}_{ext} would be directly proportional to changes in \bar{P}_{mo} because (Equation 3)

$$\dot{W}_{ext} = \bar{P}_{mo} \times \dot{V}_I \quad (3)$$

where \dot{V}_I = inspiratory minute ventilation. Equation 3 emphasizes one of the reasons why measures of the pressure–time product are so powerful in predicting endurance and changes in energy consumption during external loading. If \dot{V}_I stays constant, changes in \bar{P}_{mo} become the sole determinant of changes in \dot{W}_{ext} .

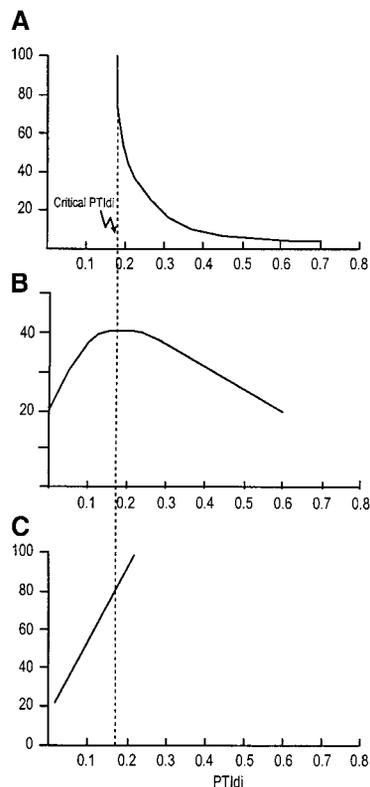


Figure 2. Three important physiologic variables that are directly related by the pressure–time index of the diaphragm (PTIdi). (A) Endurance time (T_{lim}) of the diaphragm in human subjects. The critical PTIdi of approximately 0.18 refers to the maximum PTIdi that is sustainable for a period longer than 2 hours. Values above 0.18 result in fatigue and task failure; redrawn by permission from Reference 1. (B) Diaphragmatic blood flow is affected by the PTIdi such that above a critical level, increases in PTIdi result in reductions in blood flow; redrawn by permission from Reference 14 (data on dogs). (C) Oxygen consumption of the respiratory system ($\dot{V}_{O_{2,rs}}$) increases as a function of PTIdi. Measures above 0.2 are difficult to measure in the steady state because of fatigue. Redrawn by permission from Reference 16.

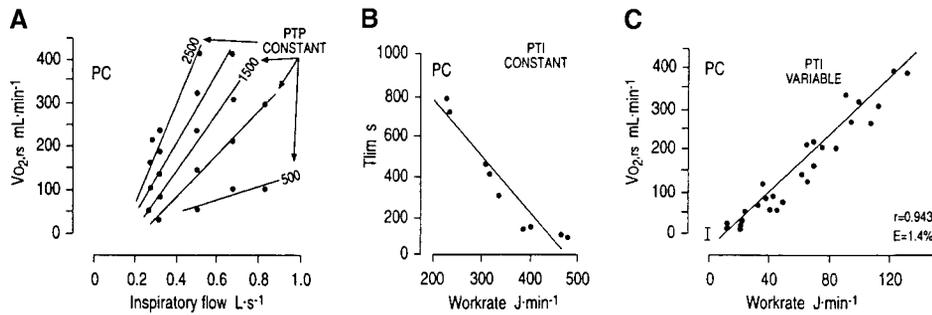


Figure 3. (A) Effects of inspiratory flow rate on the oxygen consumption of the respiratory muscles ($\dot{V}_{O_{2,rs}}$) at constant pressure-time products (isopleths). Reprinted by permission from Reference 15 (data on humans). (B) Effects of changes in respiratory work rate on endurance time (T_{lim}) at constant pressure-time product. Reprinted by permission from Reference 19. (C) Effects of respiratory work rate on $\dot{V}_{O_{2,rs}}$ when pressure-time product is allowed to vary. Reprinted by permission from Reference 15.

The use of Equation 3 eliminates the necessity of performing complex integrations of individual pressure-volume loops for each breath, which are required for more sophisticated estimates of the total \dot{W}_{rs} , discussed below. Therefore, it is possible to measure changes in \dot{W}_{ext} , online, with digital or electronic multiplication of \bar{P}_{mo} and \dot{V}_I .

An additional component of \dot{W}_{ext} occurs from gas compression (expiration) or decompression (inspiration) when large pressures are generated in the airways (15). During inspiratory loading, this gas decompression can account for as much as 0.4 L of displaced tidal volume in normal subjects, elevating the work of breathing by as much as 50%. If thoracic volume is measured in a volume displacement box, this additional volume is measured directly. However, it can also be calculated. Appropriate equations for adjustment of \dot{V}_I for gas decompression depend on the nature of the loading device (15, 19, 21). For example, if a threshold loading device is used, in which inspiratory pressure generation is approximately constant, the inspired minute ventilation can be adjusted appropriately by adding the decompression volume calculated in the following way:

$$\Delta V_{T,I} = (FRC + V_{T,I})[1 - (P_{bs} - P_{mo} - P_{H_2O}) / (P_{bs} - P_{H_2O})] \quad (4)$$

where $\Delta V_{T,I}$ is the additional inspiratory tidal volume in liters (due to gas decompression) that must be added for each breath in the calculation of inspiratory minute ventilation (\dot{V}_I) in Equation 3. $V_{T,I}$ is the inspired tidal volume (before gas decompression); FRC is the functional residual capacity in liters (measured independently); P_{bs} is body surface pressure (usually atmospheric); P_{H_2O} is water vapor pressure at body temperature; and P_{mo} is the threshold loading pressure at the end of an inspiration. Of course, all pressures in Equation 4 must be of the same units (e.g., mm Hg or kPa). For measures of ventilatory endurance, or when there are changing levels of ventilation, a significant portion of the work being performed by the respiratory muscles is done against the resistive and elastic properties of the lung and chest wall. Therefore, accurate estimates of total \dot{W}_{rs} must include these measurements. The work rate against the lung and chest wall is most often obtained by the Campbell method (22), which requires the use of an esophageal balloon for estimating pleural pressure and measurement of a relaxation-pressure-volume curve for the lung and chest wall. The original Campbell method (22) is somewhat tedious to apply practically for routine clinical endurance measurements. Equipment is now available to perform the calculations automatically by computer; but even with computerized techniques, examination of the breath-by-breath pressure-volume loops is required. For relevant discussions of the appropriate use of the Campbell method and the Campbell pressure-volume diagram, refer to reviews (23–25).

Advantages. As discussed previously, when ventilatory flow rate increases, total \dot{W}_{rs} becomes an increasingly important

determinant of both energy consumption of the muscles and endurance time (Figure 3). For ventilatory endurance testing, measurements of \dot{W}_{rs} overcome the problems of variability in lung and chest wall impedance between subjects and in the same subjects over time. Such changes in lung mechanics are inevitable in patients who may have wide diurnal variations and fluctuations over more extended time periods. Therefore, measurement of \dot{W}_{rs} may be necessary to draw appropriate conclusions regarding the endurance properties in various patient groups. To a large extent, these studies have yet to be systematically performed.

Whether \dot{W}_{rs} or \bar{P} should be chosen as the primary global measure of respiratory muscle activity for endurance testing cannot be stated with certainty at this time. It would be ideal if a comprehensive relationship between \dot{W}_{rs} , \bar{P} , $\dot{V}_{O_{2,rs}}$, and endurance for the respiratory muscles could be derived for all loading conditions. From an energetics standpoint, the relationship between them is roughly described for the inspiratory muscles by Equation 5:

$$\dot{V}_{O_{2,rs}} = \dot{W}_{rs} / E_{rs} = (\bar{P}_{mus} \times \dot{V}_I) / E_{rs} \quad (5)$$

where E_{rs} is the efficiency of the inspiratory muscles and \bar{P}_{mus} is the mean respiratory muscle pressure per breath (15). Equation 5 suggests that if one knew E_{rs} in a given subject, as well as \dot{V}_I , the energetics and presumably the endurance of the respiratory muscles could be predicted. Unfortunately, E_{rs} is not particularly constant at different relative velocities of muscle shortening (24) or at differing ventilations, depending on the way breaths are performed (21), making this ideal difficult to obtain.

Disadvantages. The largest disadvantage of monitoring \dot{W}_{rs} during endurance measurements is the complexity of its accurate measurement and analysis. This is not true, however, for the component of \dot{W}_{rs} that comes from \dot{W}_{ext} . Furthermore, after decades of studies regarding the work of breathing, there are portions of chest wall movement and distortion that remain elusive and difficult to quantify under loading conditions. As shown in Figure 4, distortions of the chest wall are commonly seen as an adaptive response to external loading (26). Distortions are also seen during maximum ventilatory maneuvers (27). Finally, the simple measurement of the relaxation pressure-volume curve is not easy to obtain in many patients because of the requisite for complete muscle relaxation (28, 29).

Finally, one component of \bar{P} that may be important in determining endurance characteristics, and that is not directly related to \dot{W}_{rs} , involves the influence of developed pressure on blood flow during contraction. For example, as \bar{P}_{di} increases, blood flow to the diaphragm is limited, presumably by the relationships between tissue pressure and vascular conductance (14, 30) (Figure 2B). Because sustainable task intensities may in part reflect a balance of energy utilization and supply, it is likely that the influence of \bar{P} on muscle perfusion has an independent effect on endurance that cannot be fully accounted for

by its mathematical contribution to \dot{W}_{rs} or its energetic contribution to $\dot{V}_{O_2,rs}$.

VENTILATORY ENDURANCE TESTS

Rationale

The goal of ventilatory endurance testing is to define the maximum sustainable ventilation (MSV), usually expressed as a fraction of maximal voluntary ventilation (MVV). The time duration needed to define "sustainable" is a topic of some controversy and varies with the specific technique described below. As shown in Table 1, normal subjects can sustain ventilations ranging from 60 to 80% of MVV. Therefore, with submaximal exercise, it is probably rare that any normal individuals ever exceed their MSV, because maximum exercise ventilations average approximately $61 \pm 14\%$ of MVV in the normal population (31). In some athletes, ventilation is maintained near the sustainable level of sedentary subjects. For example, elite cross-country skiers can sustain ventilation averages during exercise in excess of 100 L/minute, or approximately 61% of their predicted MVV for periods of 30 to 85 minutes (32), with little or no evidence of fatigue. However, the baseline MVV in these athletes is frequently elevated above normal, and unlike normal subjects, they can sustain 86–90% of MVV for 4 minutes, presumably because of their extreme conditioning. In a clinical setting, the measurement of ventilatory endurance takes on a much greater importance because patients with chronic lung disease or perhaps heart failure (4) may progress to a condition in which exercise is limited by their ability to sustain ventilation. The ventilatory endurance test is a measure of both inspiratory and expiratory muscle endurance.

Methodology

Early techniques for measuring MSV required repeated trials of MVV with gradually decreasing levels of ventilation, until an MSV could be determined (33). These have generally been found to be exhaustive and time-consuming, rendering them largely impractical for most clinical investigations. However, more recent methods have been developed that make the procedure more practical to perform, requiring only 10–25 minutes/test (4, 34, 35).

For all measurements of MSV in obstructed patients, it is recommended that the test be preceded by administration of a nebulized bronchodilator. This may be particularly useful if ventilatory endurance is to be repeated at different times, for example, before and after rehabilitation, to reduce inherent variability in airway resistance.

The test begins with the routine measurement of a 12-second MVV, using the same equipment employed for the MSV test. Protocols for technique and reproducibility of MVV, which meet American Thoracic Society (ATS) criteria, are available (36, 37). Accurate MVV measurements are critically important for interpretation of MSV. There are two primary techniques for acquiring MSV, the maximum effort technique and the maximum incremental technique, as discussed below.

The maximum effort technique requires subjects to target a ventilation of approximately 70–90% of their MVV (7, 34), using visual feedback from a spirometer or an oscilloscope (Figure 5). Sometimes, one or two short practice trials are used to determine the starting target ventilation. During the first 2–5 minutes, the target ventilation is adjusted up or down to a level slightly lower than the subject's maximum effort. The subject is then continually encouraged to meet the target for the next 8 minutes. There are some studies that have described measuring only a 4-minute MVV as an indicator of endurance

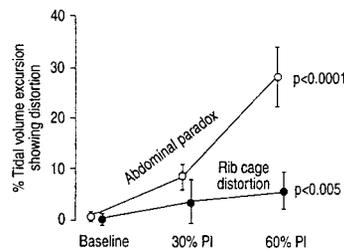


Figure 4. Chest wall distortion during inspiration, shown as rib cage (solid symbols) and abdominal movement (open symbols), with progressive increases in inspiratory mechanical loads. The y axis represents the percentage of tidal volume excursion in which the abdominal compartment is moving "in" during inspiration ("abdominal paradox") and the rib cage compartment is distorted "out" during inspiration, along a path that is greater than its expected path of expansion. Reprinted by permission from Reference 26.

partment is distorted "out" during inspiration, along a path that is greater than its expected path of expansion. Reprinted by permission from Reference 26.

(32). Although a potentially useful and practical approach, insufficient data are available to evaluate whether this provides a sufficient estimate of sustainable ventilation. In all studies, it is necessary to control end-tidal carbon dioxide (P_{ETCO_2}) during the test, usually by adjustment of the carbon dioxide fraction (F_{CO_2}) in the rebreathing dead space. The average ventilation achieved over the last minute is considered to be the MSV. It is not routine to measure the \dot{W}_{rs} or $\dot{V}_{O_2,rs}$, but there are rational advantages in doing so, as discussed below.

There is no standardized equipment available for measuring ventilatory endurance. However, the system used should have the following capabilities: (1) provide for maintaining isocapnia during hyperpneic maneuvers; (2) have a low impedance to air flow, which meets accepted standards for spirometry such as ATS criteria (e.g., < 2.5 cm $H_2O/L/second$ to 14 L/second) (36); (3) provide reasonable humidification of the inspired air; and (4) provide real-time visual feedback of ventilation. Mechanical systems that approach these criteria have been described in the literature (5, 7, 34, 38), one of which is illustrated in Figure 5. Care must be taken if pneumotachographs are used for ventilation measurements, to ensure that they are linear over the range of measured flows, that their electronic drift is compensated for, and that they do not contribute significantly to the resistance of the system. If the pneumotachograph is in the patient line, appropriate compensations should be made for changes in gas viscosity due to supplemental oxygen if it is used.

The maximum incremental technique is a newer procedure for obtaining an estimate of MSV. It uses 10% incremental increases in target ventilation, every 3 minutes, beginning at 20% of MVV until the subject cannot sustain the target ventilation for the last 3-minute period (4, 35) (MSV is calculated from the last 10 breaths of the last minute of the highest target ventilation). This technique, which resembles an incremental exercise test, was demonstrated to result in MSV measure-

TABLE 1. PREDICTED VALUES FOR MAXIMUM SUSTAINABLE VENTILATION/MAXIMUM VOLUNTARY VENTILATION

Author (Ref.)	Subject Age (yr)	No. of Subjects	Subject Sex (No. F/M)	MSV/MVV* (%)
Keens (7)	26 ± 2	16	16/0	60 ± 8
Keens (7)	31 ± 1	14	0/14	62 ± 9
Leith and Bradley (5)	31 ± 3	12	1/11	80 ± 6
Bai (39)	31 ± 3	5	0/5	75 ± 4
Belman and Gaesser (69)	67 ± 4 (estimate)	25	14/9	63 ± 11
Mancini (4)	50 ± 1	8	1/7	55 ± 9

Definition of abbreviations: F = female; M = male; MSV = maximum sustainable ventilation; MVV = maximum voluntary ventilation.

* Results represent means ± SD.

ments nearly identical to those that could be attained by traditional approaches, and was well tolerated by subjects (4).

The importance of sustaining a maximum ventilation for the three or more minutes at the end of the test should be emphasized. Presumably, during this period, fatigue of the respiratory muscles is progressing rapidly because it is a period of maximum effort following a relatively long period of "near-maximum effort." Presumably this results in a decay of ventilation to a near sustainable level.

Normal Values

Normal values for MSV, by any method, have not been systematically obtained over a wide population, and results vary considerably between laboratories (Table 1). The large differences in predicted values may be due in part to variations in technique, particularly with respect to impedances of the mechanical measuring devices. The system impedance can have substantial effects on the total \dot{W}_rs at high ventilations. In addition, there are differences in the populations studied and what was defined as sustainable. It is recommended that when publishing reports of ventilatory endurance, the value for the impedance of the measuring device be stated. Until more complete population standards and uniform equipment and techniques are available, each laboratory is advised to establish its own population standards.

Results for MSV should be reported as a fraction of measured MVV (MSV/MVV%) and either as an absolute value (L/minute) or as a fraction of predicted MVV (MSV/MVV% pred). The latter, which has not been used routinely, provides a normalization of the absolute sustainable value to the patient's age, height, and sex, independent of inherent lung or respiratory muscle function.

Advantages

There are a number of advantages to measuring MSV as an indicator of respiratory muscle endurance, the most important of which is its close resemblance to the task performed during exercise. It therefore provides clinically relevant data that can be related to function. Second, it is probably a measure of both inspiratory and expiratory muscle endurance because in normal subjects there appear to be decrements in both inspiratory and expiratory function after MSV maneuvers (39). Finally, maximum ventilatory maneuvers result in evidence of

diaphragm fatigue (39–41). Interestingly, this does not appear to be true for patients with COPD (42).

Disadvantages

The disadvantages of using MSV as an indicator of endurance are related to the difficulty in estimating the relative contribution of lung and chest wall mechanics to the measurement. MVV measurements are highly susceptible to relatively small changes in flow resistance, the effects of which are amplified exponentially as ventilation increases (24). Therefore, the load on the respiratory muscles is not uniform across patients or even in the same patients over time.

This is of considerable importance in COPD or other obstructive lung diseases in which day-to-day and diurnal variations in airway mechanics are common. Second, the wide variety of strategies utilized in a given patient to perform MVV-like maneuvers leaves many potential sources of variance between subjects. For example, in patients with COPD, effective use of the expiratory muscles is often limited during elevated ventilations (compared with normal subjects) because of early maximum flow limitation. This is accompanied by hyperinflation and shorter inspiratory muscle lengths with a greater proportional burden on the inspiratory muscles than would be seen in normal subjects. In patients with COPD, measurements of MSV/MVV% as an indicator of respiratory muscle endurance have suggested excellent ventilatory muscle endurance relative to strength, as compared with control subjects (34). However, because their mechanical abnormalities have greater relative influence at higher ventilations, the denominator of the MSV/MVV fraction may be artificially low in these patients, giving the impression that endurance properties are normal. When external resistive loading techniques are utilized, which reduce the contribution of lung and chest wall mechanics as a factor in the measurement, it is found that the endurance capacity of the respiratory system is relatively low in the COPD population compared with normal subjects (8).

The problem of the contribution of the inherent impedance of the respiratory system could be overcome by careful measurement of \dot{W}_rs during the test. As shown in Figure 6, redrawn from the experiments of Tenney and Reese (33), a strikingly different view of endurance can be seen when work rate or power output is quantified. Although this subject could sustain approximately 68% of his MVV, he could sustain only approximately 30% of maximum \dot{W}_rs . The investigators also showed that despite experimental alterations in pulmonary

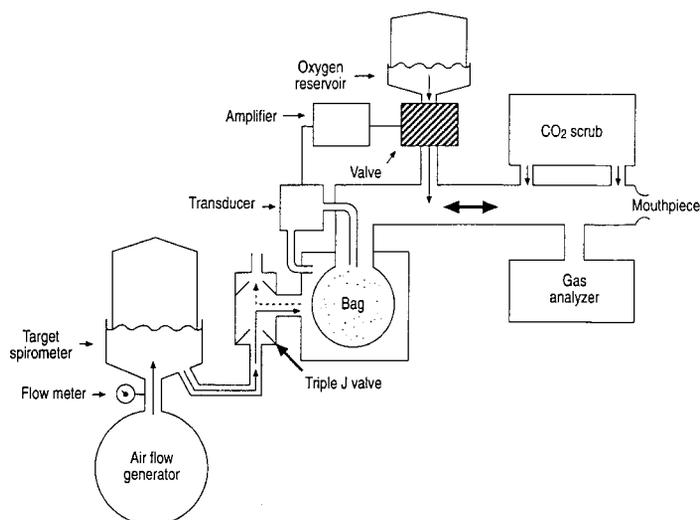


Figure 5. A typical apparatus for measuring ventilatory endurance. Reprinted by permission from Reference 34.

impedance, the \dot{V}_{rs} -versus- T_{lim} relationship did not change appreciably (33).

In summary, ventilatory endurance testing can be useful as a functional measurement, particularly in the setting of rehabilitation or other forms of treatment. Results should be viewed with some understanding of the test's limitations with respect to separation of muscle properties versus intrinsic mechanical properties of the lungs and chest wall. This limitation could potentially be overcome by measuring \dot{V}_{rs} , although this may not be practical in many clinical settings. The most promising approach appears to be the incremental method. However, full support of the technique awaits verification in other laboratories.

ENDURANCE TO EXTERNAL LOADS

Rationale

When an external mechanical load is applied to the airway opening, the respiratory muscles must generate an additional pressure to overcome the impedance of the load. The external load can be one of several types: (1) a flow resistive load, in which the pressure required of the muscles is dependent on the flow rate across the resistance. Flow resistive loads can be linear or nonlinear depending on whether they produce laminar or turbulent flow; (2) elastic loads, in which the pressure required of the muscles is dependent on lung volume. The higher the tidal volume, the higher the pressure required. Such loads are flow independent; (3) threshold loads, in which a finite pressure is required to open a valve that allows flow to occur. Therefore, the pressure required of the muscles at the airway opening is relatively constant, independent of both volume and flow. Threshold loads result in contractions that are similar to isotonic contractions; or (4) isoflow loads, in which the flow rate and therefore, the rate of inflation is held constant and the pressure generated against the flow is a measured output variable. Isoflow loads are similar in concept to "isokinetic" contractions of limb muscles, in which velocity of shortening is held constant.

To conduct a respiratory muscle endurance test with an external load requires setting the task that the subject must perform against the load. For example, the subject may be asked to breathe normally or to breathe with a set breathing pattern or with a specific muscle configuration. Different ways of contracting against the load result in markedly different measures of endurance, reemphasizing the importance of the concept of task specificity.

The advantage of using externally applied loads is that it is much easier to control the relevant variables during the test. It is even possible to design tests that are specific to the diaphragm (1) or the rib cage muscles (2, 43). Generally, these tests require large developed pressures against normal or relatively modest changes in ventilatory requirements. Such conditions are similar to those of weight lifting, with relatively low velocities of shortening. In contrast, measures of ventilatory endurance, described previously, are more like activities of running with large velocities of shortening and participation by a large number of synergic muscle groups. Interestingly, measurements of endurance to high inspiratory resistive loads appear to be more a reflection of rib cage muscle endurance than diaphragm endurance (44). Therefore, the exact extent to which measurements of endurance to high external loads apply to ventilatory endurance or to clinically relevant conditions such as exercise has not been well defined.

A large number of devices and techniques have been developed to measure endurance of external loads. The most common is the use of orifice-type flow resistance applied to the in-

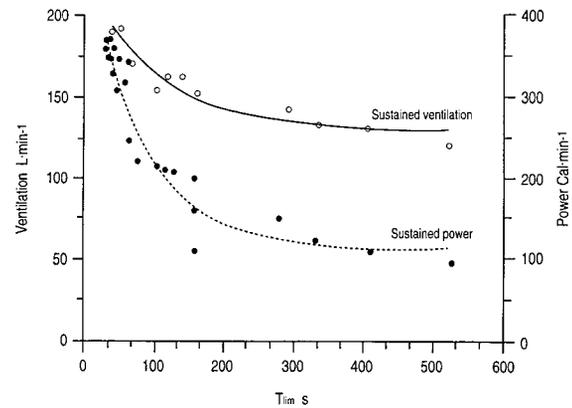


Figure 6. Relationships between power output, ventilation, and endurance time (T_{lim}). *Solid line:* Maximum voluntary ventilation. *Dotted line:* Calculated work rate or power output of the respiratory muscles. Redrawn by permission from Reference 33.

spiratory circuit (20, 45). Excellent studies can be performed with flow resistances, but because the pressure load seen by the respiratory muscles depends on the developed flow, the technique requires visual feedback of some form of ventilation, preferably the flow rate. Therefore, for practical reasons, flow resistances have largely been replaced in most clinical laboratories by threshold loading devices or other techniques discussed below. The techniques below have generally been used to measure inspiratory muscle endurance.

Maximum Sustainable Threshold Loading

Methodology. Nickerson and Keens (46) developed a method in which endurance times are measured in response to gradually decreasing threshold pressures, starting near $P_{i,max}$. They described one of the first threshold loading devices that was relatively flow independent. The test usually begins with a careful measurement of $P_{i,max}$. Sequential T_{lim} measurements are then made, beginning at approximately 90% of $P_{i,max}$ and decreasing in increments of 5%. Subjects are allowed to rest between each measurement for approximately 10 times the length of T_{lim} . No attempt is made to control the breathing pattern. Task failure is determined at each load by the inability to maintain ventilation against the load, resulting in the subject coming off the mouthpiece. Other definitions of task failure define a point at which a subject is unable to generate the threshold pressure or a target flow for three consecutive breaths (47). The first pressure that can be sustained for more than 10 minutes is considered the sustainable inspiratory pressure (SIP). The SIP is determined by averaging the pressures over the last 20 breaths.

The original Nickerson and Keens (46) threshold loading device has never been available commercially, but is made of a simple plunger, with leaded rings added to the inside of the chamber to weight the valve. A more modern version is illustrated in Figure 7. There is a linear relationship between increases in weight and the pressure required to lift the plunger. The original device used a plunger, seated with a 1-in. O ring onto a 45° surface (46). Larger O rings result in more flow independence but less stability. Even small changes in the size of the contact circumference and the precision of the seating can have large effects on the weight/pressure relationship. Therefore, each homemade valve requires independent additional supports for the plunger, which improve its stability (48), and the use of standardized, commercially available valve mechanisms (nondisposable positive end-expiratory pressure valves),

which improve the pressure–flow characteristics (Figure 7) (49). Some commercially available spring-loaded threshold valves do not have the pressure range necessary for testing endurance in most patients.

Normal values. As with most respiratory muscle endurance testing techniques, normal values have not yet been developed. For example, the influence of stature, age, and sex is not described and the numbers of subjects have been low. Nickerson and Keens (46) tested 15 normal individuals ranging from 5 to 75 years of age. The 12 adults could maintain a mean \pm SD SIP of 82 ± 22 cm H₂O, or $71 \pm 10\%$ of P_{I,max}. On a second trial, in 12 subjects, both P_{I,max} and SIP increased by approximately 10%, while the relationship of SIP/P_{I,max} remained constant. Somewhat different results were found by Martyn and coworkers (50) when using the method of Nickerson and Keens (46). They found that the SIP was $52 \pm 6\%$ of P_{I,max} on the first trial. However, when subjects were asked to repeat the loads that they had previously failed, they were able to increase their SIP to $77 \pm 6\%$ of P_{I,max} (50).

Advantages. The attraction of the technique of Nickerson and Keens (46) has been that it provides a method for evaluating global respiratory muscle endurance in a one-session test, much like a pulmonary function test. There were no previous studies that defined a technique to establish sustainable pressure in a practical setting. Furthermore, the test is noninvasive and is tolerated relatively well, the equipment required is inexpensive and does not require a great deal of training or coordination for the subject, and the results are relatively independent of the mechanics of breathing because minute ventilation increases minimally.

Disadvantages. It is clear that subjects will adjust their breathing pattern as they attempt to breathe against any kind of large mechanical load, and they will learn to do this over time (51). This effect may have been underestimated by Nickerson and Keens (46) as discussed by Martyn and coworkers (50). Relatively small changes in duty cycle (52), inspiratory flow rate (20, 52), and tidal volume (13) can have relatively large effects on endurance measures. Therefore, it would seem appropriate to control the pattern of contraction against the load during the test. However, it is likely that a naive subject will be able to achieve longer T_{lim} values when allowed to breathe spontaneously. Artificially imposing a breathing pattern may not be appropriate for body size, vital capacity, or CO₂ production. Furthermore, chest wall configuration, and therefore respiratory muscle recruitment, are quite different when inspiring against “target” respiratory patterns, when agonists and antagonists are simultaneously recruited (52), as compared with spontaneous or maximum uncontrolled inspirations (13). Nevertheless, the effects of the pattern of contraction and recruitment on T_{lim} result in an inherent measurement variability between subjects and in the same subject over time (50). It is likely that this problem could be overcome to some extent by measuring \dot{P}_{mo} and \dot{W}_{ext} , because they are likely to be the most dominant determinants of T_{lim}, regardless of the pattern of breathing. However, this has not been measured systematically in available clinical studies using maximum sustainable threshold loading.

Having subjects begin with endurance trials at the highest pressure loads can be exhausting, uncomfortable, and time-consuming for the patient. The test generally requires a minimum of 2 hours, as was originally described (46).

Maximum Incremental Threshold Loading

Methodology. The incremental threshold loading technique was described in the late 1980s (8, 50, 53). In concept, it was designed to resemble a Bruce protocol, which is popular for

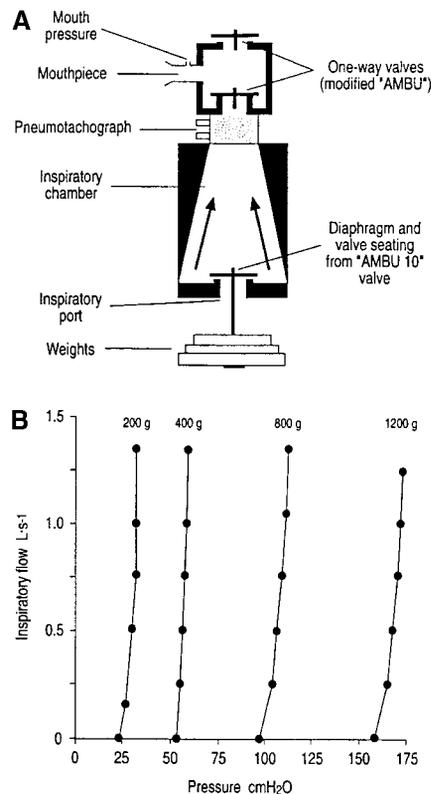


Figure 7. (A) An example of a threshold loading device built from a commercially available positive end-expiratory pressure valve (Ambu PEEP valve; Life-Assist, Rancho Cordova, CA). (B) Typical pressure–flow characteristics of the device, showing the relative flow independence of the threshold pressure. Reprinted by permission from Reference 49.

incremental, whole body exercise testing. Before the study, the patient's P_{I,max} is measured by standard techniques (see PRESSURE MEASUREMENTS in Section 2 of this Statement). The subjects inspire from a threshold valve, as described previously, beginning with initial threshold pressures of approximately 30–40% of P_{I,max}. The threshold pressure is then increased by a unit of weight (e.g., 100 g) added to the outside of the valve, resulting in a change in pressure of approximately 5–10% of P_{I,max}, until the load cannot be tolerated for 2 minutes. The maximum inspiratory mouth pressure that can be tolerated for the full 2-minute interval is considered the peak pressure (P_{peak}) (8). This technique has generally been applied to the measure of inspiratory muscle endurance.

Normal values. Normal values obtained by this technique have not been thoroughly described. Small sets are displayed in Table 2. Results are relatively consistent between laboratories, particularly for the peak PTI that can be achieved in the last stage (PTI_{peak}, 0.25 to 0.32). Older subjects appear to demonstrate less initial strength (P_{I,max}) but an ability to achieve higher relative PTI_{peak} values (8), which may be consistent with chest wall adaptations to aging (54).

Advantages. The incremental threshold test holds strong appeal as a measure of inspiratory muscle function because it is well tolerated and provides a clear outcome variable that is somewhat easier to define than sustainable efforts. Furthermore, it appears to be sensitive to disease states and clinical treatment (3, 8, 9, 55). The test has been described by the original authors as more reproducible than the technique of Nickerson and Keens (46); as being tolerated well by naive subjects, who give results similar to those of trained subjects; and

having an overall outcome that is little affected by the breathing pattern (56). However, subsequent testing by Eastwood and coworkers (57), using similar techniques, found that normal subjects demonstrate a considerable learning effect from the first to the third trial.

An interesting observation is that a peak \dot{V}_{ext} reaches its highest value and then falls precipitously before attaining P_{peak} , while oxygen consumption and pressure development are still rising (50). This means that efficiency is falling during the final stages of the test. It is promising that peak \dot{V}_{ext} may be a useful measurement of the capacity of the muscles of the chest wall to perform external work, a value that may be as important clinically as the measure of endurance. A second interesting finding is that some subjects are able to achieve higher P_{peak} values during this test than they can attain during $P_{1,max}$ maneuvers (50, 53, 57), a phenomenon attributed to the fact that some subjects are unable to maximally activate their inspiratory muscles during $P_{1,max}$ testing (58).

Disadvantages. Unfortunately, the extent to which the results from incremental tests represent endurance or strength is not entirely clear. Strictly speaking, it is not a test that has been proven to be a direct measure of endurance, just as an incremental exercise test is not generally considered an endurance test. However, when individuals are asked to attempt to sustain the maximum threshold pressure previously reached with the incremental method, the average T_{lim} they can maintain is approximately 6 minutes (53). This suggests that although the maximum incremental threshold pressure is not sustainable, it is certainly approaching the asymptote of a typical inspiratory muscle endurance curve. Another suggestion that the threshold test is approximating an endurance measurement is the fact that the maximum PT_{Imo} in the last stage is approximately 0.22–0.32 (50, 57), which is similar to sustainable pressures described for the rib cage muscles (2) and the inspiratory muscles working in synergy in a normal range of duty cycles and low flow (13).

Of some concern is the tendency for hypoventilation and desaturation during the test (57). Although modest desaturation is unlikely to affect the measurement appreciably in normal subjects (57, 59), hypercapnia may contribute to a loss of function, unrelated to endurance characteristics (60, 61). Finally, as the intensity of the load increases, subjects consistently decrease end-expiratory lung volume to maximize the length and configuration of their inspiratory muscles (57). This is something of a disadvantage for testing, because the capacity of the muscles to contract against the load is changing during the test. However, it is likely that such changes in configuration are typical of patient responses to many types of high inspiratory mechanical or ventilatory loads and is not a problem unique to incremental loading. Finally, the recruitment patterns of the respiratory muscles may vary during incremental loading and may not totally reflect the endurance characteristics of breathing against constant submaximal loads.

Repeated Maximum Inspiratory Pressures

Methodology. McKenzie and Gandevia (6, 62, 63) have developed a technique that uses 18 repeated $P_{1,max}$ maneuvers. The test begins with measurement of $P_{1,max}$ and practice efforts using visual feedback of airway opening pressure. Three different breathing patterns have been described (6, 62). The most practical appears to be a series of 18 $P_{1,max}$ contractions lasting 10 seconds each, with 5 seconds of rest between contractions (duty cycle = 0.67) (62). A similar approach has been used to measure expiratory and limb muscle endurance (6). The only equipment required is a manometer for measuring airway opening pressure. This technique has been generally used to measure inspiratory muscle endurance.

Normal values. In normal young subjects ($n = 12$), with a duty cycle of 0.67, the average inspiratory mouth pressure attained in the last contraction is $87 \pm 3\%$ of $P_{1,max}$ (mean \pm SD) (6). The PT_{Imo} at this point is approximately 0.58. Using a similar protocol, but with a slower frequency, pressures dropped to approximately 77% (6). Interestingly, when the duty cycle is reduced to 0.5, no drop in pressure generation is observed across the 18 contractions in normal subjects (6). The PT_{Imo} is then 0.25, which may be just below the threshold for fatigue for the rib cage muscles (2, 43).

Advantages. The technique provides a measurement that is entirely independent of lung and chest wall mechanics, as well as mechanical work of breathing, making it potentially useful for understanding endurance properties of the respiratory muscles without interference from chest wall or lung mechanics. It appears to be sensitive to the influence of lung disease (6), is simple to perform, and lends itself to the potential for a pulmonary function testing environment.

Disadvantages. Potential disadvantages include the fact that the endurance characteristics may reflect the anaerobic capacity of the muscles to sustain force, rather than aerobic endurance, because it is likely that blood flow is largely occluded to the muscles during the prolonged contractions. It also does not appear that in 18 contractions a sustainable level of pressure is fully attained (62). Furthermore, patients with severe lung disease may find it difficult to perform such extended maximum inspiratory maneuvers without discomfort or dyspnea. This technique has yet to be independently tested in patients.

Maximum Sustainable Isoflow

Methodology. The isoflow method allows subjects to inspire with $P_{1,max}$ against a device that provides a constant inspiratory flow rate to the lungs (14, 64) (Figure 8). In this way, it resembles the repeated $P_{1,max}$ technique but the lungs are inflated and the inspiratory muscles are allowed to shorten at a relatively constant rate. The method was modeled after isokinetic testing devices commonly used in limb muscle evaluation. Visual feedback of inspiratory pressure, over time, is provided from an oscilloscope. Breathing pattern is generally set such that the subjects hyperventilate during the test. The inspiratory airflow is humidified, and P_{ETCO_2} is maintained at eucapnia with supplemental CO_2 . For routine measurements, inspiratory flow is maintained, at approximately 1 L/second, inspiratory time at 1.5 seconds and total breath period at 3.5 seconds (duty cycle = 0.42). Many other breathing patterns have been used with this technique (14, 64, 65); however, for normal subjects this pattern has been shown to be well tolerated. Subjects continue to inspire maximally with each breath for 10 minutes. Airway opening pressures generally decline exponentially during this period until a "sustainable" pressure is obtained (Figure 8). Using curve-fitting techniques, it has been shown that sustainable pressures in normal subjects can be calculated within 5% with only 5 minutes of endurance testing (64).

To roughly calculate the additional inspiratory pressure used to overcome lung and chest wall impedance, the isoflow apparatus can be modified to inflate the subject's lungs during complete relaxation (13). This additional positive pressure can be added to active inspiratory pressures developed during each breath to estimate the total inspiratory muscle pressure (P_{mus}).

The isoflow apparatus consists of a large and well-regulated pressure source providing inspiratory flow across an extremely high resistance (13, 64). The pressure drop across the resistance is so high (8,000 to 14,000 cm H_2O) that any additional inspiratory pressures developed by the subject at the airway opening have negligible effects on flow rate. Flow is

TABLE 2. PREDICTED VALUES FOR INCREMENTAL THRESHOLD LOADING*

Author (Ref.)	Age (yr)	Subjects No. (M/F)	P _{peak} /P _{i,max} [†] (%)	PTI _{peak}	Notes on End Point
Martyn (50)	33 ± 2	14 (9/5)	88 ± 10	NR	P _{peak} determined from highest load over 1 min
McElvaney (53)	31 ± 5	10 (5/5)	Trial 1: 84 ± 17 Trial 2: 87 ± 21	~0.22 ± 0.07 ~0.25 ± 0.08	Highest P _{peak} tolerated for full 2 min
Morrison (56)	67 ± 4	8 (5/3)	80 ± 17	~0.32 ± 0.12	Highest P _{peak} tolerated for full 2 min
Eastwood (57)	30 (28–41) [‡]	7 (5/2)	Trial 1: ~75 ± 20 Trial 3: ~94 ± 21	NR 0.26 ± 0.11	Highest P _{peak} tolerated for 30 s

Definition of abbreviations: F = female; M = male; NR = not reported; P_{i,max} = maximum inspiratory pressure; P_{peak} = peak threshold pressure achieved during incremental loading under conditions stated in Notes on End Point column; PTI_{peak} = peak pressure–time index achieved during incremental loading under conditions stated in Notes on End Point column.

* Results represent means ± SD.

[†] P_{i,max} was measured at residual volume.

[‡] Mean (range).

initiated by negative mouth pressures of -2 to -3 cm H₂O and turned off at $+2$ to $+3$ cm H₂O by an electrical triggering circuit. Subjects are protected from the high-pressure source by breathing from a nonbreathing valve, which will ensure that flow bypasses the mouth if there is no active inspiration. End-tidal CO₂ is monitored continuously, and additional CO₂ is bled into the inspiratory line to maintain P_{ET,CO₂} at eucapnia. This technique has been used primarily to measure inspiratory muscle endurance.

Normal values. Normal values have not been well described over a wide range of subjects. However, in 15 normal subjects (8 males and 7 females; age, 26 ± 6 years) with breathing patterns described above, the peak airway pressure dropped to $70 \pm 7\%$ of their initial pressures (measured with inspiratory flow of 1 L/second), and $61 \pm 12\%$ of P_{i,max} by the end of 10 minutes of repeated contractions (64). The sustainable PTI with the pattern of contraction described above was 0.18 ± 0.04 . There is a small but significant training effect between the first and fourth trials with the procedure (64).

Advantages. The isoflow technique has the advantage that most of the important parameters influencing respiratory endurance measurements are controlled. For example, P_{ET,CO₂} (and therefore arterial oxygen saturation), breath timing, inspiratory flow, and tidal volume are fixed. Furthermore, lung and chest wall mechanics can be accounted for at a first approximation (13). An additional strength is the fact that it is possible to measure the inspiratory muscle strength under similar conditions used in the endurance test. This avoids the difficulty of comparing pressure measurements under static contractions (P_{i,max}) with contractions under dynamic conditions, where changes in length and velocity of contraction affect pressure development (13, 64). Furthermore, because subjects are performing maximal contractions, the fatigue process develops rapidly and the sustainable pressures can be obtained in a few minutes of testing. The decay of inspiratory pressure over time is an additional variable that can be helpful in distinguishing effects on the fatigue process, independent of sustainable pressure development (61). The test is noninvasive and is tolerated well by naive subjects.

Disadvantages. As yet, the isoflow technique has not been used to test patient populations and therefore its utility has not been determined in the clinical setting. It has, however, been shown to be useful for studying mechanisms of fatigue (13, 59, 61, 65). One potential problem with applying the tech-

nique on patients is the difficulty with imposing the same breathing pattern used on normal subjects. For example, normal subjects have relatively high ventilatory requirements during the test to assure maintenance of ET_{CO₂}, whereas patients with lung disease may not be able to physically perform such high levels of ventilation. Furthermore, the method also depends on subject cooperation, and one cannot be certain of the relative contributions of the rib cage or the diaphragm during contractions. Finally, the equipment used for the isoflow technique is not available commercially, although it is not particularly ex-

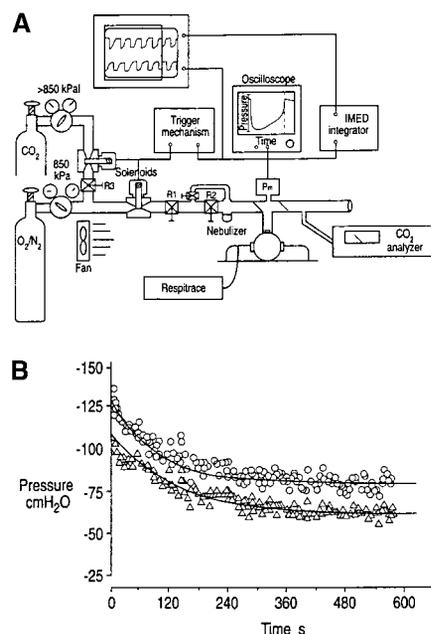


Figure 8. (A) Equipment used for the isoflow loading device. The tanks and regulators on the left provide a high-pressure source through an extremely high resistance. Flow is activated by a pressure-triggering device. The oscilloscope provides visual feedback, so that the subjects can perform maximally. CO₂ is maintained at a constant value by supplementing the inspiratory gas. (B) A typical endurance curve from an isoflow test. *Open circles:* The peak pressure developed during inspiration. *Open triangles:* The average pressure generated during inspiration per breath. Reprinted by permission from Reference 64.

pensive to create from basic equipment in most physiology laboratories.

In summary, at the present time, for clinical applications, the most promising and practical technique for evaluating the endurance qualities of the global inspiratory muscles against external loads appears to be the incremental threshold loading technique, originally described by Martyn and coworkers (50) and refined by later studies (8, 53, 56, 57). However, because of the uncertainties with regard to its specificity for endurance, we recommend that the term "maximum incremental performance" be used to describe its outcome measures until further information is available. The usefulness of the technique will be advanced by careful quantification of \dot{P}_{mo} , \dot{W}_{rs} , and $\dot{V}_{O_{2rs}}$ during the tests and by consistent recording of the maximum values that can be maintained for the full 2-minute increments. Further work needs to be done to define predicted values in the normal population.

Other methods described here are of considerable value under experimental conditions and should be considered as options, particularly for specific experimental designs where careful control of the variables is critical. Whenever possible, with any of these techniques, the goal should be to define the sustainable level of \dot{P} and \dot{W}_{rs} . Further studies in patient populations will be required to determine the comparative usefulness of these techniques in a clinical environment.

All of the external loading techniques are more likely to reflect the endurance qualities of the rib cage muscles as compared with the diaphragm (44, 57, 66). This should be kept in mind with regard to their clinical implications.

ENDURANCE OF THE DIAPHRAGM

Rationale

To specifically load the diaphragm requires the subject to attempt to generate a target transdiaphragmatic pressure rather than a target mouth pressure. This is because it is possible to generate inspiratory pressures at the airway opening by the rib cage muscles in the absence of significant diaphragm contribution. Furthermore, pressure development by the diaphragm is not only distributed against the rib cage but is used to contract against the abdominal contents as well.

Methodology

Roussos and coworkers (45) tested for the maximal sustainable, transdiaphragmatic load. Subjects sustained a given Pdi until they could no longer reach the target pressure. There were no requirements on breathing frequency or duty cycle. They found that approximately 40% of Pdi,max could be sustained for 60–90 minutes. A higher Pdi lasted for a shorter time.

A more precise technique for measurement of diaphragm endurance in humans was developed by Bellemare and Grassino (1, 67). Subjects are instrumented with an esophageal and gastric balloon as described in PRESSURE MEASUREMENTS in Section 2 of this Statement. Maximum transdiaphragmatic pressure is determined and then subjects proceed to inspire through a variable inspiratory flow resistance with a set breathing pattern by watching an oscilloscope (Figure 9). Two target pressures are displayed on the oscilloscope screen: Pdi and gastric pressure (Pga). Tidal volume and duty cycle (T_i/T_{tot}) are monitored as well. The subject generates a target Pdi by actively inspiring against a variable resistance and a target Pga of approximately 50% of Pdi. Runs with Pdi of 0.2 to 0.8 and T_i/T_{tot} of 0.2 to 0.7 were tested. The product of $Pdi/Pdi,max \times T_i/T_{tot}$ was found to be the best predictor for endurance. Values of 0.15 to 0.18 or smaller could be sustained for more than 1 hour. Values

above 0.18 were sustainable for shorter periods. This work proposed the concept of PTIdi as a consistent index to predict development of fatigue and failure. Accomplishing this requires active contraction of the abdominal muscles during inspiration, resulting in the diaphragm generating approximately equal but opposite pressures against the abdomen and rib cage. The choice of using a Pga of 50% of Pdi was arbitrary and may not have been a critical variable. A procedure for quickly determining a sustainable pressure load has not been developed. Bellemare and Grassino (1, 67) have used this technique primarily to understand the determinants of diaphragm fatigue by performing repeated endurance trials with varying Pdi targets and did not intend its use as a clinical test.

The equipment required for this technique is shown in Figure 9. It is possible that the use of a threshold resistance may be of benefit for controlling esophageal pressure (Pes) during inspirations rather than an orifice-type resistance, thus eliminating the need for controlling both Pdi and abdominal pressure (Pab) with visual feedback.

Normal Values

Measurements of diaphragm endurance have not been routinely performed in a large number of normal subjects. However, Bellemare and Grassino (1) described the normal sustainable PTIdi to be in the range of 0.15–0.18 when tidal volume remained approximately 0.75 L (Figure 2A). Therefore, at a duty cycle of approximately 0.4, normal subjects can sustain approximately 40–50% of Pdi,max.

Advantages

The technique described by Bellemare and Grassino (1) is the only method that has been identified for specifically loading the diaphragm and ensuring that it fatigues during endurance measurements. By limiting tidal volume and contracting the abdominal muscles (i.e., diaphragm antagonists), changes in diaphragm shortening with contraction are reduced to a minimum. This means that the energetics of diaphragm contraction are uniquely dependent on Pdi and not \dot{W}_{di} because the diaphragm is doing little mechanical work against the rib cage or abdomen.

Disadvantages

Because of the need for invasive instrumentation and the requirement of the subject to coordinate a rather unnatural pattern of abdominal and thoracic expansion, the technique has not been applied extensively to the clinical environment. PTIdi was measured in patients being weaned from a ventilator. It shows that patients developing a PTIdi higher than 0.18 failed the weaning trial. The same patients were tested at a later date with favorable evolution and had a PTIdi below 0.15, and they could be weaned (68). One potential complication lies in the fact that diaphragm blood flow may be determined in part by the relative negative or positive pressures on its surface. For example, Buchler and coworkers (30) demonstrated that blood flow is obstructed more by high positive abdominal pressures than by similar Pdi values obtained by negative pleural pressures. This would suggest that by contracting the abdominal antagonist muscles simultaneously with inspiration, there may be reduced blood flow to the diaphragm, resulting in a greater probability of fatigue and a lower endurance.

In summary, for a specific measure of diaphragm endurance, the technique of Bellemare and Grassino (1) remains the only method currently available. The methodology may become more accessible in the clinical environment as techniques develop for rapidly attaining a measure of sustainable

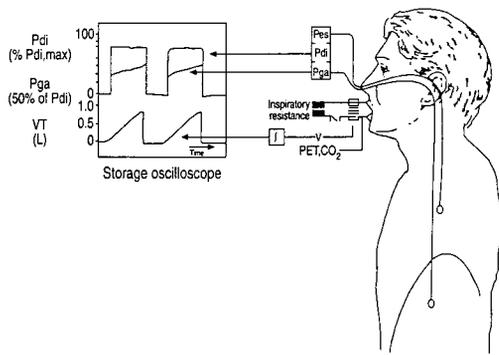


Figure 9. The method for measuring diaphragm endurance. Pdi = Transdiaphragmatic pressure; Pdi,max = maximum transdiaphragmatic pressure; Pga = gastric pressure; \dot{V} = respiratory flow from a pneumotachograph; P_{ET,CO_2} = end-tidal carbon dioxide pressure; V_T = tidal volume. Redrawn by permission from Reference 1.

PTIdi, using incremental or maximum effort approaches similar to those described for global inspiratory muscle function. This technique remains in the domain of clinical research. Few studies are available.

CONCLUSION

This Section of the Statement has explored the available techniques to assess respiratory muscle endurance. The measurements and techniques include the following:

1. Pressure–time product (PTP): The integration of inspiratory pressure swing over time. Pressure can be esophageal, Pdi, or mouth pressure (if an external resistance is added to the circuit). PTP of the expiratory muscles can also be measured. If pressure is normalized to a fraction of the maximum pressure, the value obtained is the pressure time index (PTI). A PTI of 0.15–0.18 is the upper limit that can be sustained indefinitely by the diaphragm in humans and as high as 0.3 for the rib cage muscles. The PTI thresholds are lower if inspiratory flow is high.
2. Work of breathing: Calculated by the integration of pressure on tidal volume, measures work against an external inspiratory or expiratory load and is a useful test for measuring endurance as a function of workload. Values of work of breathing relate well to oxygen consumption over a wide range of ventilations. This measurement is limited to respiratory research and could benefit from computerized equipment to facilitate measurement and analysis in the clinical setting.
3. Ventilatory endurance tests: Maximal sustainable ventilation (MSV) expressed as a percentage of 12 seconds of maximum voluntary ventilation. Two techniques are available to determine MSV: the maximum effort technique (the subject seeks to sustain ventilation at a target level of 70–90% MVV for 8 minutes) and the maximum incremental technique (starting at 20% MVV, the target ventilation is increased by 10% every 3 minutes). There are limited normal data for MSV and these show considerable variability. Each laboratory should develop its own normal values. MSV can be difficult to interpret (e.g., in patients with COPD). The incremental technique may prove to be of value in the clinical setting. To date, most studies of ventilatory endurance have been undertaken within a research context.
4. Endurance of external loads applied to the airway: The external load can be resistive (the pressure required depends

on flow), elastic (pressure depends on tidal volume), threshold (finite pressure required to open the valve, which is independent of flow and volume), or an isoflow load (flow rate held constant). The most widely used technique is that of threshold loading. Either the maximum sustainable threshold load or the maximum incremental threshold load can be measured. The incremental threshold loading test, which uses the same principles as an incremental exercise test, is the most commonly undertaken, and there are limited normal data available. It is not clear to what extent the test reflects respiratory muscle strength rather than endurance.

5. Repeated maximum inspiratory pressures: In this test the subjects undertake 18 repeated $P_{i,max}$ maneuvers, each effort lasting 10 seconds with a 5-second rest between contractions. Pressure drops to 87% of $P_{i,max}$ in young normal subjects over the run. Equipment is simple, and only a manometer and stopwatch are required. Few data from studies in patients are available.
6. Maximal sustainable isoflow: In this test the subject breathes against a high impedance (air tank) providing a constant flow (1 L/second). The subject develops maximal pressure at a T_i/T_{tot} of 0.40. Maximum pressure declines exponentially to a sustainable level of 61%, yielding a PTI of 0.18. This technique has not yet been tested in large populations. It has potential as a method of training the inspiratory muscles as well as documenting their endurance.
7. Endurance of the diaphragm: This has been studied in normal subjects by measuring Pdi and T_i/T_{tot} , which were kept constant by following a pattern of pressure and timing displayed on an oscilloscope. A PTI of 0.20–0.30 resulted in task failure at an earlier time. The technique was developed as a physiologic study designed to measure the use of TTIIdi as a parameter to evaluate the development of diaphragm fatigue.

Of the tests of ventilatory endurance available, the most promising, in a clinical context, appears to be the maximum incremental ventilation test. To specifically assess the endurance of the inspiratory muscles, relatively independently of lung and chest wall mechanisms, the incremental threshold loading test appears to be most useful.

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5. Assessment of Respiratory Muscle Fatigue

The purpose of this Section is to outline a potential diagnostic strategy to assess the development of respiratory muscle fatigue in humans. At the outset, it is important to note that there is evidence suggesting that human respiratory muscle fatigue may develop in pathophysiological states associated with the development of respiratory failure (i.e., respiratory loading induced by lung disease) (1). It is also important to recognize that fatigue is defined as a loss of the capability to generate skeletal muscle force and/or velocity that is accompanied by recovery during rest (2). As a result, a single measurement of force is inadequate to detect fatigue: rather, muscle force generating or shortening capability must be demonstrated to fall during serial measurements over time. It could further be argued that a demonstration that force subsequently rises if muscle contraction is stopped and a rest period is provided would be necessary to fully satisfy the definition of fatigue and to exclude the possibility that a given fall in force did not represent muscle injury (the latter condition, by definition, does not improve with short periods of rest). It follows that muscle “fatigue” can therefore be distinguished from muscle weakness (i.e., a reduction in the level of force generation at a given point in time) and muscle injury (i.e., a slowly reversible or irreversible decrement in muscle contractility).

This Section is divided into a brief discussion of (1) the present theories regarding the genesis of muscle fatigue and the different types of muscle fatigue, and (2) a review of the various tests available with the potential to detect the development of fatigue in normal subjects and patients.

TYPES OF FATIGUE

On an operational level, it has proven convenient to classify fatigue into different types, with these different forms of fatigue representing different biophysical mechanisms of fatigue development and with each type having different physiological characteristics (3). Several such classification schemes are possible, but a widely employed convention is to classify fatigue as either (1) central fatigue, (2) peripheral high-frequency fatigue, or (3) peripheral low-frequency fatigue. We review each of these types of fatigue in turn.

Central Fatigue

“Central fatigue” refers to a condition in which muscle force generation during sustained or repetitive contraction becomes limited owing to a decline in motoneuronal output. Central fatigue is judged to be present when a truly maximum voluntary effort produces less force than one generated by direct electrical stimulation.

A number of experiments have suggested that a form of central diaphragmatic “fatigue” may develop during respiratory loading (3–11). A study by Bellemare and Bigland-Ritchie (5) provided evidence that such a phenomenon can occur during the application of external resistive loads to normal human subjects. This study measured transdiaphragmatic pressure generation over time before, during, and after inspiratory resistive loading, and employed superimposed electrical phrenic stimulation at various times during the experiment to determine whether subjects were capable of fully “activating” the diaphragm. This approach makes use of the observation that it is possible for well-motivated individuals to fully activate rested skeletal muscle during volitional contractions when making a maximal effort (i.e., superimposed elec-

trical stimulation of muscle during such maximal maneuvers does not result in an increase in force generation above that achieved volitionally) (3) (*see TWITCH OCCLUSION* in Section 2 of this Statement). Although achievement of such “maximal” activation is difficult, and usually cannot be achieved with every attempted contraction even in motivated individuals, one study found that all research subjects could achieve at least one maximal contraction of a limb muscle (6). As a result, evidence that maximal activation of a given muscle during a maximal volitional effort can never be achieved after a period of exercise (i.e., the superimposed electrical stimulation can always evoke an increase in force generation) constitutes evidence of “central” fatigue.

At the start of the study by Bellemare and Bigland-Ritchie, no superimposed force could be detected during the imposition of electrical stimuli on maximum volitional efforts, indicating that these subjects were capable of maximally activating the diaphragm before respiratory loading. During the course of loading, however, the extent to which the diaphragm could be activated decreased progressively. Evidence of the development of central diaphragmatic fatigue during repeated maximal and submaximal diaphragmatic contractions has also been reported in a study by McKenzie and coworkers (7).

Other work has suggested that “central fatigue” may be the result of a decrease in central respiratory motor outflow in response to opioid elaboration in the central nervous system, with the latter generated, in turn, as a consequence of the stress of loaded breathing (4, 8, 9). In support of this concept, Santiago and coworkers (8) have shown that naloxone restores the load compensatory reflex in patients with chronic obstructive pulmonary disease in whom it is initially absent. Subsequently, this group demonstrated that resistive loading in unanesthetized goats resulted in a progressive reduction in tidal volume, which was partially reversed by administration of naloxone (4).

In keeping with the results of these animal studies, an experiment involving patients with asthma found that naloxone pretreatment alters the response to methacholine challenge. In these individuals, in whom methacholine induced severe reductions in FEV₁, naloxone pretreatment resulted in an increased breathing frequency, occlusion pressure, and mean inspiratory flow rate when compared with saline pretreatment (10). It has been postulated that similar central limitations of respiratory motor outflow may occur in patients with diseases that chronically load the respiratory system, contributing to the development of chronic hypercapnia.

High-Frequency Peripheral Fatigue

Central fatigue is a failure to generate force as a result of a reduction in motor output from the central nervous system. Peripheral fatigue refers to failure at the neuromuscular junction or distal to this structure and is judged to be present when muscle force output or velocity falls in response to direct electrical stimulation. Peripheral fatigue can result because of alterations in the neuromuscular junction, changes in propagation of the action potentials along the sarcolemmal membrane or into the t-tubules, changes in excitation–contraction coupling, or because of other alterations within the muscle cell (e.g., alterations in metabolism, changes in contractile proteins). Peripheral fatigue can be further classified into high-frequency and low-frequency fatigue on the basis of the shape of the postfatigue muscle force–frequency relationship. If fa-

tigue results in depression of the forces generated by a muscle in response to high-frequency electrical stimulation (e.g., in humans, 50–100 Hz) then high-frequency fatigue is said to be present, whereas a reduction in force generation in response to low-frequency stimuli (i.e., 1–20 Hz) is taken as an indication of low-frequency fatigue. Studies have suggested that loss of force at low frequencies represents an impairment of muscle excitation–contraction coupling (i.e., a reduction in contractile protein activation in response to a given nonimpaired sarcolemmal action potential) (12). Reduction in high-frequency force generation is thought to indicate either an alteration in neuromuscular junction transmission, a reduction in sarcolemmal membrane excitability, or a reduction in action potential propagation into the t-tubular system (13, 14). Low-frequency fatigue can occur in isolation, but high-frequency fatigue is invariably associated with some alterations in muscle force generation at lower frequencies.

High-frequency fatigue has been demonstrated in the diaphragms of normal humans after a trial of high-intensity inspiratory resistive loading (this was demonstrated using high-frequency electrical phrenic stimulation) (15). In this study high-frequency fatigue resolves extremely quickly after cessation of strenuous muscle contractions (i.e., after removal of the inspiratory resistive load; see Figure 1).

Low-Frequency Peripheral Fatigue

In the presence of pure low-frequency fatigue, force generation in response to high-frequency stimulation is unimpaired, indicating that the contractile proteins are capable of generating maximal force provided that sufficient calcium is released by the sarcoplasmic reticulum (SR). As a result, impaired force generation at submaximal frequencies of stimulation may represent either a reduced level of calcium availability due to alterations in SR function or a reduction in the calcium sensitivity of the myofilaments at submaximal calcium concentrations. Both changes have been demonstrated experimentally (16, 17). Reduced myofilament calcium sensitivity can be produced experimentally by increasing hydrogen and phosphate ions (18). The explanation for impaired calcium release by the SR during contractions is less well understood, and a number of theories have been proposed to account for this phenomenon (16, 19–21).

Low-frequency fatigue has been demonstrated in the diaphragm and sternocleidomastoid muscles of normal subjects breathing against high resistive loads (17, 22). Low-frequency fatigue has also been shown to develop in the diaphragm of normal subjects asked to sustain maximum voluntary ventilation for 2 minutes (23).

Implications of Different Types of Fatigue for Diagnosis

Although it is convenient to discuss the characteristics of central, peripheral high-frequency, and peripheral low-frequency fatigue separately, it is likely that these various phenomena do not occur in isolation during muscle activation. All three processes may be operating simultaneously when the respiratory muscles confront an excessive workload, with the relative importance of each depending on the duration of respiratory loading and other physiological variables (i.e., arterial pressure, arterial blood gas concentrations, nutritional state). Whereas all three processes may participate in the acute response to loading, both central and high-frequency fatigue resolve rapidly once fatiguing levels of muscle contraction cease, and only low-frequency fatigue is likely to persist over minutes to hours.

Because muscle fatigue is a complex phenomenon, a test that is well suited to detect one form of fatigue may be incap-

able of detecting another. Moreover, the necessity to make serial measurements of an index of muscle force generation over time to detect fatigue is a particularly difficult endeavor for the respiratory system, because a large number of variables (i.e., lung volume, thoracoabdominal configuration, muscle interaction) can vary over time. All these factors can influence the relationship between muscle force and pressure generation.

As an example, consider the utility of measuring maximum inspiratory pressure ($P_{i,max}$) serially to detect respiratory muscle fatigue. This parameter is highly effort dependent, and time-dependent reductions could represent lack of motivation, central fatigue, peripheral high-frequency fatigue, or simply an alteration in lung volume and a resultant mechanical change in the transduction of muscle force into pressure. In addition, failure of the $P_{i,max}$ to change does not exclude the development of fatigue, because this test would not be suitable to detect low-frequency fatigue. As a result, one must keep in mind the potential limitations of a given test for the detection of muscle fatigue. Most tests are suitable for detecting the presence of only one component of muscle fatigue, and complete characterization of fatigue requires a complex series of assessments.

TESTS OF RESPIRATORY MUSCLE FATIGUE

Breathing Pattern: Tidal Volume and Breathing Frequency

Rationale. Rapid shallow breathing, characterized by high breathing frequency and low tidal volume, commonly develops in progressive respiratory failure or in unsuccessful attempts to wean from mechanical ventilation. These conditions are associated with an increased ventilatory load and/or a reduced respiratory muscle capacity and may therefore potentially lead to respiratory muscle fatigue (see PREDICTION OF WEANING in Section 10 of this Statement).

Methodology and equipment. Breathing frequency can be easily counted at the bedside and should be included in standard monitoring. Tidal volume measurements of intubated patients are commonly accomplished with the flow sensors built into modern ventilatory equipment and can be displayed on a breath-by-breath basis by these machines. Volume measurements can also be made with Wright respirometers and other spirometric devices via a mouthpiece in nonintubated patients, albeit mouthpiece placement can artifactually alter tidal volumes and respiratory patterns. To avoid such artifacts, it is possible to noninvasively monitor tidal volume by respiratory inductance plethysmography. Use of this and similar methods is described in DEVICES USED TO MONITOR BREATHING: PNEUMOGRAPH, MAGNETOMETER, AND RESPIRATORY INDUCTIVE PLETHYSMOGRAPH in Section 6 of this Statement.

Advantages. Monitoring changes in breathing frequency and tidal volume is simple and noninvasive.

Disadvantages. The relationship between fatigue and breathing pattern is complex. Moreover, rapid shallow breathing is most likely a reflex response to an increase in the respiratory workload (24) and not the consequence of respiratory muscle fatigue per se (25). Thus, although rapid shallow breathing may accompany respiratory muscle fatigue (2), it cannot be considered a specific marker of fatigue.

Applications. Monitoring breathing frequency and tidal volume represents a part of the routine respiratory surveillance of patients, but these parameters should not be used as specific indicators of the development of respiratory muscle fatigue (see BREATHING PATTERN in Section 10 of this Statement).

Thoracoabdominal Motion

Rationale. The analysis of breathing movements gives some insight into the level of recruitment and function of the respiratory

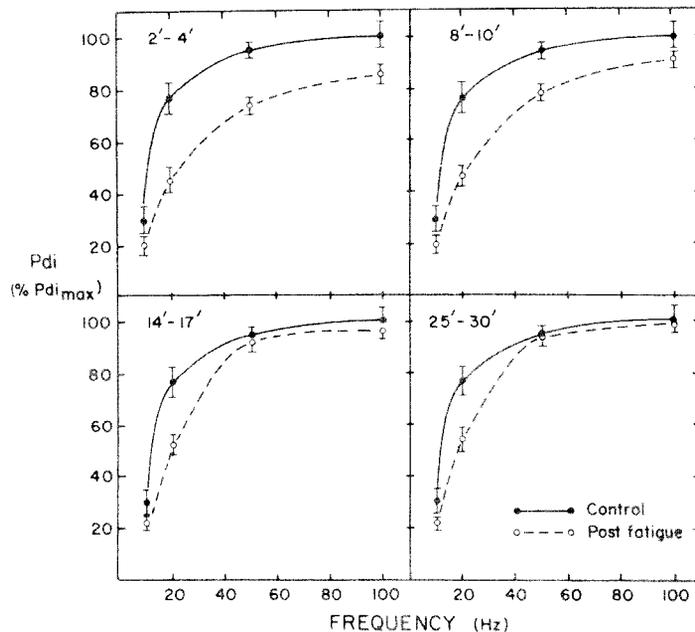


Figure 1. Pressure–frequency relationships for the human diaphragm at various time points after a loaded breathing trial (i.e., a breathing trial in which an external resistive load was applied to increase the work done by the diaphragm and simulate the effects of lung disease). Diaphragm pressure generation was measured by determining the transdiaphragmatic pressure gradient (Pdi) generated in response to electrical stimulation of the phrenic nerves; Pdi is shown on the y axis and phrenic stimulation frequency is shown on the x axis. The time at which each set of curves was obtained is shown in the upper left-hand corner of each panel. For reference, each panel contains both a postload pressure–frequency curve obtained at the designated time (dashed line), and a preload pressure–frequency curve (solid line). At 2–4 minutes postloading, there was a large decrement in pressure generation in response to phrenic stimulation of 20–100 Hz (top left panel), indicating diaphragm fatigue. Over time, the pressures generated in response to high-frequency stimulation increased so that at 25–30 minutes postloading, pressure generation in response to 50- and 100-Hz stimulation had returned to preloading levels (bottom right panel). In contrast, however, response to 20-Hz stimulation remained depressed 25–30 minutes after loading. In effect, both low- and high-frequency peripheral diaphragm fatigue was present 2–4 minutes after loading, with rapid resolution of the high-frequency component of fatigue and persistence of the low-frequency component at 25–30 minutes. Reprinted by permission from Reference 15.

muscles (in particular of the diaphragm, the rib cage inspiratory muscles, and the abdominal muscles). Two unusual patterns of muscle recruitment may be observed in healthy subjects subjected to fatiguing inspiratory loads (26). The first is an increased variability in compartmental contribution to tidal volume, with breaths characterized by clear rib cage predominance alternating with other breaths in which abdominal motion predominates. This pattern reflects alternatively predominant recruitment of the inspiratory rib cage muscles and of the diaphragm. Because fatigue may develop separately in the diaphragm and in the inspiratory rib cage muscles (27), such alternation may represent a way to postpone respiratory muscle failure. The second pattern is frank paradoxical movement of one compartment, generally the abdomen, that is, an inward movement of the abdominal wall during inspiration. Abdominal paradox indicates weak, absent, or inefficient contraction of the diaphragm. These two patterns may also be observed in patients showing signs of diaphragmatic fatigue during weaning trials from mechanical ventilation (2) (see Figure 5 in Section 6 of this Statement).

Methodology. Most anomalies of thoracoabdominal motion can be detected by visual inspection by a trained observer. This assessment is facilitated by placing the patient in a recumbent position and conducting a visual inspection for several minutes. Quantitative measurements of rib cage–abdominal motion can also be performed (see ESTIMATION OF VENTILATION BASED ON CHEST WALL MOTION: KONNO–MEAD DIAGRAM in Section 6 of this Statement).

Advantages. Visual inspection provides a simple bedside means of detecting alterations in respiratory muscle use.

Disadvantages. The abnormal patterns of thoracoabdominal motion described above are not specific for respiratory muscle fatigue. Indeed, respiratory alternans and abdominal paradox can appear immediately after the institution of loaded breathing and these abnormalities do not appear to become accentuated with the development of fatigue. Furthermore, these patterns can also occur, albeit to a lesser degree, during the application of low, nonfatiguing respiratory loads (28). Thus, abnormal thoracoabdominal motion should be viewed as reflecting an increased ventilatory load, which in itself may or may not induce respiratory muscle fatigue.

Applications. Analysis of thoracoabdominal motion is most useful to detect either specific forms of respiratory muscle dysfunction (e.g., diaphragmatic paresis) and/or an increase in the ventilatory load. This assessment is, therefore, of some routine clinical use, but lacks specificity for detecting respiratory muscle fatigue (see BREATHING PATTERN in Section 10 and DEVICES USED TO MONITOR BREATHING: PNEUMOGRAPH, MAGNETOMETER, AND RESPIRATORY INDUCTIVE PLETHYSMOGRAPH in Section 6 of this Statement).

Pressure–Time Index of Inspiratory Muscles

Rationale. In several investigations, skeletal muscle fatigue was found to occur when a muscle generated more than 15% of its maximal force during sustained contraction. This work has led to the concept that a fatigue threshold exists, with fatigue occurring only when the level of pressure–time generated exceeds this threshold level. Additional work on this concept has shown that the fatigue threshold is higher during intermittent contractions and depends on the relative duration of contraction and relaxation. The same holds true for the inspiratory muscles of subjects submitted to external inspiratory loads. The pressure–time index of the diaphragm is defined as

$$PTdi = (Pdi/Pdi,max)(T_i/T_{tot})$$

where Pdi is the mean transdiaphragmatic pressure generated per breath, Pdi,max is maximal transdiaphragmatic pressure, T_i is inspiratory time, and T_{tot} is total breath time. When breathing is accomplished predominantly with the diaphragm, the critical PTdi is 0.15–0.18. Below this threshold, breathing can be sustained for more than 1 hour without evidence of fatigue. Above this threshold, task failure occurs after a time limit that is inversely related to PTdi (29) (see Figure 2). In most situations in which inspiratory loads are applied, the spontaneous breathing pattern is characterized by predominant recruitment of inspiratory rib cage muscles other than the diaphragm, resulting in augmented rib cage expansion and abdominal paradox. Under these circumstances, the pressure–time index of the inspiratory rib cage muscles is defined as

$$PTrc = (Ppl/Ppl,max)(T_i/T_{tot})$$

where P_{pl} is mean pleural pressure generated per breath and $P_{pl,max}$ is maximal pleural pressure (equivalent to MIP). With this breathing pattern, the critical PT_{rc} is 0.30. Above this threshold, task failure occurs after a time limit that is inversely related to PT_{rc} (30).

Methodology and equipment. The measurement of esophageal pressure is required to compute PT_{rc} , and the measurement of both esophageal and gastric pressures is required to compute PT_{di} . This is most commonly performed with balloon-catheter systems, as described in PRESSURE MEASUREMENTS in Section 2 and in Figures 8 and 9 in Section 4 of this Statement.

Advantages. In principle, PT_{di} and PT_{rc} characterize the operational conditions of the inspiratory muscles with respect to their fatigue threshold. These indices may allow the assessment of the risk of fatigue before actual task failure occurs.

Disadvantages. The critical values of PT_{di} and PT_{rc} were established in healthy subjects breathing against external loads. The critical thresholds may be different in clinical circumstances, in which a number of pathological factors (e.g., levels of tissue perfusion, presence of hypoxemia) may influence muscle performance. Second, pressure-time index assessment is dependent on accurate measurement of maximal muscle pressure generating capacity (i.e., the $P_{di,max}$ of the diaphragm, $P_{pl,max}$ for the inspiratory rib cage musculature), which is often difficult in patients. Third, shortening velocity of muscle fibers strongly influences muscle energetics and the metabolic consequences of contraction. As a result, the critical PT_{di} and PT_{rc} that can be tolerated are also a function of inspiratory flow patterns, with lower values for these parameters at high inspiratory flows. Fourth, some clinical conditions (malnutrition, steroid myopathy) change muscle fiber populations, altering the relationship between muscle strength and fatigability. Conditions that result in a shift to a greater concentration of slow fibers in muscle may well result in a better tolerance of a given absolute level of the pressure-time index and an increase in the critical pressure-time index for the diaphragm and rib cage muscles. The critical pressure-time index in most patients remains to be measured.

Applications. The pressure-time index should be considered a conceptual framework within which to gauge the level of muscle function rather than an instrument for the clinical diagnosis of fatigue. Fatigue thresholds have been reported in patients with chronic obstructive pulmonary disease (31, 32); however, it remains largely untested in other pathologies.

Volitional Maximal Pressures

Rationale. Skeletal muscle fatigue has been defined as a loss of capacity to develop force in response to a load that is reversible by rest (12). In accordance with this definition, respiratory muscle fatigue can, potentially, be documented by measuring a decrease in volitional maximal respiratory pressures, with demonstration of recovery with rest. As a consequence, to detect fatigue of the inspiratory muscles, one could measure either maximal static inspiratory pressure, maximal transdiaphragmatic pressure, or maximal sniff pressure.

Maximal inspiratory pressure. Methodology and equipment. $P_{I,max}$ is measured at the mouth as described in VOLITIONAL TESTS OF RESPIRATORY MUSCLE STRENGTH in Section 2 of this Statement.

Advantages. The measurement of $P_{I,max}$ is noninvasive. Fatigue of inspiratory muscles as a whole has been documented by a transient fall of $P_{I,max}$ after breathing against external loads (12), maximal voluntary hyperpnea (33), marathon running (34, 35), or labor (36).

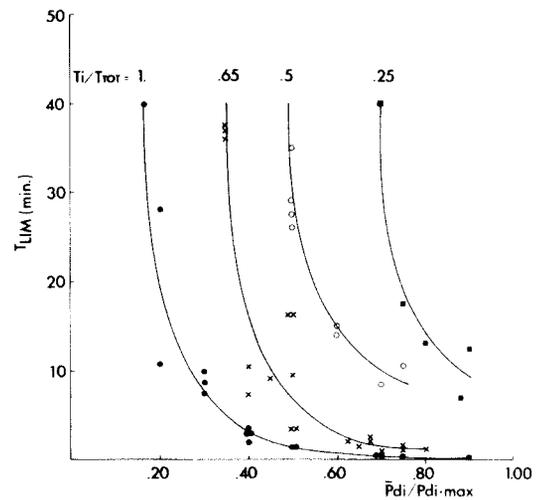


Figure 2. Data obtained from human subjects generating a variety of levels of transdiaphragmatic pressure ($P_{di}/P_{di,max}$) with various inspiratory durations (T_i/T_{tot}) during breathing trials. Each point represents the results from a single breathing trial that was performed at a targeted $P_{di}/P_{di,max}$ (x axis) and with a pattern of breathing that resulted in a predetermined inspiratory duration (T_i/T_{tot} isopleths of 1, 0.65, 0.5, and 0.25). Subjects continued breathing trials until they were unable to sustain the targeted pressure level; the duration each trial could be sustained was defined as T_{lim} (shown on the y axis). This graph shows that the time breathing could be sustained (T_{lim}) was a function of both the pressure developed ($P_{di}/P_{di,max}$) and the inspiratory duration (T_i/T_{tot}). For a given T_i/T_{tot} isopleth, T_{lim} was shorter when pressure generation was higher and, for a given pressure generation level, T_{lim} was shorter when inspiratory duration was increased. Reprinted by permission from Reference 29.

Disadvantages. The major limitation of $P_{I,max}$ as a test of fatigue is a lack of specificity, which is due to its total dependence on the subject's maximal volitional effort. Although $P_{I,max}$ is reliable in highly motivated subjects, a maximal volitional effort cannot be obtained with certainty in patients. Another drawback of $P_{I,max}$ is a potential lack of sensitivity for fatigue. Because a maximal static effort is associated with a high neuronal firing frequency, it reflects mainly high-frequency fatigue and may be a poor indicator of long-lasting low-frequency fatigue (see MAXIMAL STATIC INSPIRATORY AND EXPIRATORY PRESSURE in Section 2 of this Statement).

Applications. Measurement of $P_{I,max}$ can be used to detect inspiratory muscle fatigue in motivated volunteers, but has limited use in patients for this purpose because of difficulties in ensuring maximality of effort. Twitch interpolation techniques provide a potential means of solving this latter problem (see TWITCH OCCLUSION in Section 2 and see Section 1 of this Statement).

Maximal transdiaphragmatic pressure. Methodology. $P_{di,max}$, measured with balloon-catheter systems, is described in TECHNIQUES FOR PRESSURE MEASUREMENTS in Section 2 of this Statement).

Advantages. This test measures specifically the strength of the diaphragm. Diaphragmatic fatigue has been documented by a transient fall in $P_{di,max}$ after breathing with diaphragm emphasis against external loads (6), voluntary hyperpnea (33), or high-intensity exercise (37).

Disadvantages. The measurement of $P_{di,max}$ is invasive and, moreover, shares the same type of limitations as $P_{I,max}$ for detecting fatigue. Because the physical maneuver that patients must carry out for reliable measurement of $P_{di,max}$ is even more complex than that required to measure the $P_{I,max}$, it cannot be recommended for assessing diaphragmatic fatigue in clinical settings.

Applications. Pdi,max can be used to detect inspiratory muscle fatigue in motivated volunteers, but probably should not be used for this purpose in patients.

Maximal sniff pressures. Methodology. Diaphragmatic strength can be assessed by maximal sniff Pdi (38), and global inspiratory muscle strength by maximal sniff esophageal pressure (Pes) (39) or maximal sniff nasal inspiratory pressure (SNIP) (40, 41), as described in SNIFF TESTS in Section 2 of this Statement.

Advantages. The sniff is a volitional maneuver that is easily performed by almost all subjects and patients. The SNIP is noninvasive and often yields higher pressures than the P_{i,max} (39).

Disadvantages. The potential usefulness of measuring a fall of maximal sniff pressures to detect inspiratory muscle fatigue in patients remains to be established.

Applications. Although maximal sniff pressures are of established value for measuring inspiratory muscle strength, it is a test still under development for documenting fatigue.

Relaxation Rate

Rationale. On cessation of contraction, skeletal muscles relax at a rate determined by their relative proportion of fast and slow fibers. When muscles fatigue, their relaxation rate declines as a result of a slower uptake of calcium previously released from the sarcoplasmic reticulum. During various types of intermittent contractions, the rate of decay of Pes and of Pdi reflects the relaxation rate of inspiratory muscles and of the diaphragm, respectively. When fatigue is induced by breathing against external loads, the inspiratory muscle relaxation rate falls early and then stabilizes, following a time course similar to that of the change in electromyogram (EMG) power spectrum. Thus, relaxation rates typically decline before the occurrence of muscle failure at about the same rate as the center frequency of EMG does. On cessation of loading, the relaxation rate recovers quickly and reaches baseline values within 5 to 10 minutes (42, 43).

Methodology. The relaxation rate of Pes or Pdi can be measured during intermittent contractions against loads (42), during sniffs with airway occlusion (43) or without airway occlusion (44), and during phrenic nerve stimulation (43). The most useful and simple maneuver is the unoccluded sniff, which is easy to perform for most subjects and provides large and consistent changes in relaxation rate after fatigue (45).

Standard balloon-catheter systems are used to measure Pes and gastric pressure (Pga), from which Pdi is obtained. The maximal relaxation rate (MRR) of Pes or Pdi is calculated as the first derivative of pressure with respect to time (dP/dt) over the first half of the relaxation curve. This is obtained by drawing a tangent to the steepest portion of the pressure curve. Because the MRR increases with the amplitude of the pressure swing, it is usual to normalize the MRR and to express it as a percentage of the pressure fall in 10 milliseconds (42, 45). When the natural logarithm of pressure is plotted as a function of time, a straight line appears over the lower 60–70% portion, indicating a monoexponential decay. The reciprocal of the slope of this line represents the time constant (τ) of this exponential decay, which may be used as another measure of muscle relaxation, usually expressed in milliseconds (42, 45) (see Figure 3). Thus, a slower muscle relaxation is documented by a decline in the MRR and by an increase in τ . Inspiratory muscle relaxation rate can be assessed in a less invasive manner by measuring the MRR of nasopharyngeal or mouth pressure during sniffs with balloons positioned in these locations (44). An entirely noninvasive measure of inspiratory muscle MRR can be obtained by using SNIP (46). These less

invasive techniques have been validated only in normal subjects. Transmission of brief pressure swings from the alveoli to the upper airways is likely to be dampened in patients with abnormal lung mechanics.

Equipment. The pressure measurement system required for sniffs is described in Section 2 of this Statement. Analysis of the MRR is best done with a computer program (46).

Advantages. The measurement of inspiratory muscle relaxation rate is relatively simple and requires minimal cooperation from subjects. The sniff maneuver is easily performed by most subjects and patients and does not need to be perfectly "maximal," provided that the MRR is expressed as percentage pressure fall per 10 milliseconds. Sniffs should, however, be performed as near to the maximal as possible, because the MRR is effort dependent below 60% of maximal pressure (47). The muscle relaxation rate slows at an early stage during fatiguing contractions and may therefore indicate that inspiratory muscle fatigue is incipient.

Disadvantages. The relationship between changes in relaxation rate and force loss during fatigue is not understood. For instance, the degree of force loss does not correlate with the changes in relaxation rate and therefore cannot be inferred from this parameter (45, 47). The rapid recovery of this index with rest also poses practical problems of measurement in clinical settings. The range of normal values for the MRR and τ is wide, with overlap between fresh and fatigued states. Serial measurements are thus required to detect the onset of inspiratory muscle fatigue in an individual (45). Finally, some clinical conditions (e.g., asthma) have been reported to elicit activation of inspiratory muscles during expiration (postinspiratory inspiratory muscle activity). Under such circumstances, persistent activation of some muscles or portions thereof would

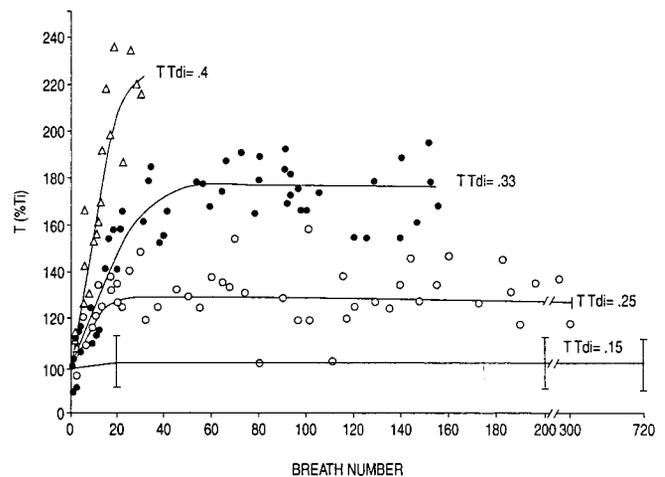


Figure 3. The time constant of respiratory muscle relaxation, τ , as a function of breath number during a series of breathing trials against respiratory loads. Each curve represents the results from a single breathing trial, with individual points on each curve representing relaxation time constants calculated on single breaths during the trial. Each trial is annotated with the pressure–time index (TTdi, equivalent to the pressure–time index using the nomenclature in the present document) achieved during the trial. During a trial with a high pressure–time index of 0.4 (uppermost curve), relaxation slowed dramatically, with a large increase in the relaxation time constant, τ , within a few breaths. In contrast, with less intense respiratory loading, that is, lower pressure–time indices, there was less slowing of relaxation and smaller increases in the relaxation time constant. At the lowest pressure–time index (0.15, lowest curve), there was essentially no slowing of relaxation and no increase in the time constant during the breathing trial. Reprinted by permission from Reference 42.

be expected to alter measured relaxation rates, distorting the relationship of alterations in the MRR to cellular events and to the development of muscle fatigue.

Applications. Measurement of the relaxation rate can be used with confidence as an early sign of fatigue in subjects subjected to high external inspiratory loads (42–45) or to high-level hyperpnea (46). The inspiratory muscle relaxation rate can also be used to detect fatiguing contractions during exercise in patients with chronic obstructive pulmonary disease (48) or during weaning trials from mechanical ventilation (49). Because interpretation of changes in relaxation rate is not straightforward, this test can be considered useful only for clinical research.

Electromyography

Time domain analysis. Rationale. For the respiratory muscles, as for any other skeletal muscles, a nearly linear relationship may be found between the pressure and the electrical activity they generate. The slope is related to force and the length of the diaphragm. As a result, for a given muscle length, a decrease in the ratio of respiratory muscle pressure to the integrated electromyographic activity of the muscle generating that pressure should, in theory, indicate a decrease in muscle contractility and the development of fatigue. Furthermore, it has been suggested that a decrease in this ratio indicates an alteration in excitation–contraction coupling (50). This point is also discussed in INFERRING DIAPHRAGM ACTIVATION AND ELECTROMECHANICAL EFFECTIVENESS FROM EMG in Section 6 of this Statement.

Methodology. The methodology required for electromyographic assessment is reviewed in detail in EMG EQUIPMENT AND DATA ANALYSIS in Section 3 of this Statement.

Advantages. In theory, this is a useful approach for separating changes in pressure-generating capacity caused by neural or neuromuscular transmission factors from changes caused by peripheral muscular factors (51). One potential major advantage of this test is the possibility to detect fatigue during spontaneous breathing (52), because no special efforts are required by patients.

Disadvantages. For this index to be valid, other factors affecting respiratory muscle contractility, such as muscle length, chest wall configuration, or lung volume, should be controlled or kept constant (53). The applicability of this particular method to the respiratory system is limited by the difficulty of recording the activity of all the muscles involved in normal or augmented breathing that contribute to the measured pressure. Their relative contribution to the generated pressure is known to change during fatigue development (6, 28), and a reliable recording of the activity of a selective respiratory muscle group is regarded as difficult by some (54). Section 3 of this Statement offers a more optimistic view. In practice, the diaphragm, the neck accessory muscles, and the abdominal muscles are most amenable to this form of testing because their electrical activity can be more easily recorded without interference from other muscles and their force production (sternomastoid) or pressure output (diaphragm and abdominals) can also be recorded in relative isolation.

When interpreting results, one must also recognize that the relationships between integrated EMG activity of the respiratory muscles and the pressure they generate may not be perfectly linear (49).

If special precautions are not taken, EMG signals (particularly those recorded from the diaphragm with an esophageal electrode) can be subject to artifactual changes caused by variations in lung volume or chest wall configuration (55). Luckily, reports provide techniques that exclude many of the artifacts associated with esophageal diaphragmatic recording. Specifically,

work by Sinderby, Grassino, and others provides a means of recording and analyzing electromyographic signals so as to exclude electrocardiogram (ECG), electrode motion, noise, and esophageal peristalsis artifacts (56–59). This latter work has also shown that it is possible, by using a multielectrode array, to reliably measure the diaphragm EMG amplitude and power spectrum in such a way that these variables are not affected by chest wall configuration and/or diaphragm length (56). Note, however, that even if EMG activity can be accurately recorded respiratory muscle pressures must also be reliably assessed for the pressure-to-integrated EMG ratio to be meaningful.

Applications. The theoretical value of time domain electromyographic assessment in patients is that it can provide a means of determining whether observed reductions in respiratory muscle pressure-generating capacity are due to alterations in action potential transmission or to intrinsic alterations in peripheral muscle function (i.e., alterations in excitation–contraction coupling or contractile protein myofilament function). Although this technique is principally of value for experimental applications at the present time, ongoing efforts are being made to improve the reliability of this form of testing, and this type of measurement may assume a broader clinical role in the future.

Frequency domain analysis. Rationale. Frequency domain analysis of EMG signals from the respiratory muscles has been proposed as a test to detect the occurrence of respiratory muscle fatigue in humans (60), because the power spectrum of skin surface-recorded EMG signals typically shifts to lower frequencies during fatiguing contractions (see Figure 4).

Several indices of the power spectrum have been used for this purpose, including an assessment of the “center” or “centroid” frequency of the power spectrum and a “power ratio” of a high-frequency band over a low-frequency one. Both of these indices appear to decrease with fatigue and increase with recovery. With appropriate instrumentation, these analyses can be obtained “on line” in spontaneously breathing subjects or patients. Shifts in the EMG power spectrum indicative of diaphragmatic fatigue have been documented during severe whole body exercise (61) and during loaded breathing in normal subjects, in female patients during delivery (39), as well as in ventilator-dependent patients having weaning problems (2).

Methodology. The methodology required for electromyographic assessment is reviewed in detail in EMG EQUIPMENT AND DATA ANALYSIS in Section 3 of this Statement.

Advantages. Studies of normal subjects have shown a good correlation between EMG power spectrum shifts and force or pressure losses at high stimulation frequencies (high-frequency fatigue) but not with force loss at low stimulation frequencies (low-frequency fatigue) (62). High-frequency fatigue is typically associated with failure at the neuromuscular junction or at the sarcolemma. In line with these predictions, a good correspondence has been found for the human diaphragm between the rate of power spectrum shift, the pressure–time product (63), and the changes of the shape of the action potential wave form measured during phrenic nerve stimulation.

Disadvantages. The etiology of power spectral shifts with fatigue is still controversial. Possible mechanisms include a slowing of muscle fiber conduction velocity, a widening of the action potential waveform, a decrease in motor unit discharge rate, or synchronization of motor units firing (64). None of these can be directly linked to a fatiguing process at the sarcomere level. Power spectrum shifts are therefore related to central motor control, or reflex pathways, or changes in electrolyte or metabolite concentrations within the muscles.

In addition, power spectrum shifts are rapidly reversed on rest or with reduced activity even though the muscle may remain in a fatigued state. Power spectrum analysis of an EMG,

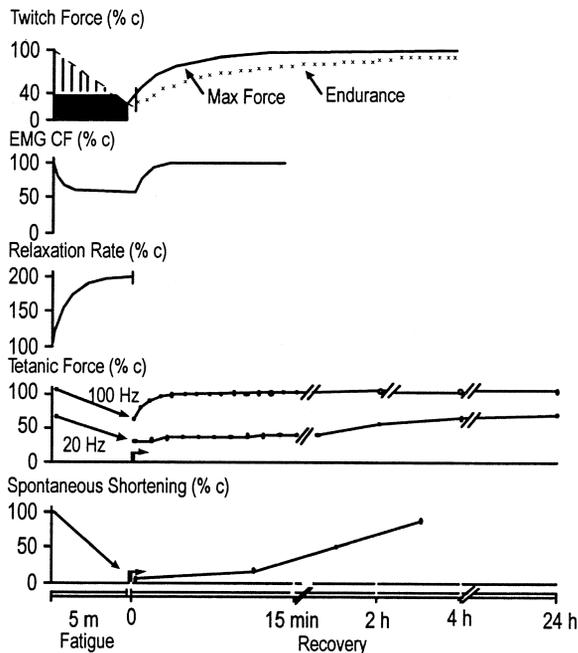


Figure 4. Time course of various parameters during an isometric contraction held at 40% of maximal force (task) until failure. From the top: *Maximal force*: voluntary maximal electrical supramaximal pulses of the nerve. The *vertical lines* are pressure swings obtained by electrical stimulation, showing a progressive loss of maximal force. The time elapsed from the start until task failure is known as the time limit, or endurance. The exercise is defined as a fatiguing task, because there was loss of maximal force. Regaining the ability to develop maximal force takes a few minutes. Regaining the ability to perform the same task again, however, takes hours. This panel shows the time course of the central frequency (CF) of the EMG obtained via surface electrodes and fast Fourier transforms in the same exercise. Decay of CF is fast, and is a forewarning of task failure. This parameter is an expression of membrane potential conduction velocity. *Relaxation rate*: The time course of relaxation time (if the contraction is interrupted). Control values are the same as in a rested muscle. This parameter is linked to failure at the sarcomere level, mainly related to calcium coupling and release from troponin. *Tetanic force*: The decrease in force during an electrical stimulation at 100 or 20 Hz, and its ensuing rate of recovery. Recovery from fatigue is faster when the muscle is probed with 100 Hz than with 20 Hz; the former is proposed to be caused by conduction mechanisms, whereas the latter is mediated by contraction mechanisms. *Spontaneous shortening*: Spontaneous shortening of the diaphragm before (100%) and after task failure, and time of recovery. Figure used by permission from Dr. A. E. Grassino.

therefore, cannot provide an indication as to the state of the contractile system or the excitation–contraction coupling process, or how these may change with fatigue. As mentioned previously, because of the close association of these indices with neural or sarcolemmal events, power spectral shifts recover quickly with rest (within 5 minutes). As a result, these indices can be markedly affected by the breathing pattern (63) and the breathing strategy employed (29), which in turn may cause a high breath-to-breath variability.

Applications. Because of the problems listed above, this test cannot be taken as a reliable global index of the development of muscle fatigue. The principal utility of this test is that demonstration of an EMG spectral power shift in a working muscle may provide some clue to the development of an alteration in neuromuscular transmission.

Muscle Responses to External Stimulation

Pressure–frequency relationships. Rationale. Fatigue, defined as a decrease in the pressure- or force-generating capacity of a

muscle under loaded conditions, can be most specifically detected by recording the pressure– or force–frequency curve of that muscle in response to artificial motor nerve stimulation. Of the respiratory muscles, the diaphragm (16, 65) and the sternomastoid (66) muscles are most amenable to this form of testing. Low-frequency fatigue has been documented for these muscles in normal subjects during loaded breathing (16) as well as during intense exercise (67).

Methodology. The methodology required for phrenic nerve stimulation and sternomastoid stimulation is reviewed in detail in Section 2 of this Statement.

Advantages. This technique overcomes many of the difficulties associated with volitional or spontaneous breathing efforts. Indeed, the responses are not complicated by possible variations in the level of effort expended. The response of a particular muscle can also be studied in isolation, free from the activity of other muscles. Changes in the shape of the pressure– or force–frequency curves also give indications as to the underlying mechanism of fatigue. For example, a decreased pressure or force at high stimulation frequencies may be indicative of impairment at the neuromuscular junction or at the sarcolemma, whereas a decreased force or pressure at low stimulation frequencies may suggest a possible impairment of excitation–contraction coupling.

Disadvantages. This is a difficult test to perform. Tetanic stimulation can also be painful and it may be necessary to anesthetize the skin near the electrodes. To overcome this problem, partial pressure–frequency curves may be constructed by using twin pulses and by varying the intervals between the pulses (68, 69). These are better tolerated than tetanic stimulation and can provide comparable information regarding the presence of high- and low-frequency fatigue. Because of a large intersubject variability in the responses to artificial stimulation, fatigue can be reliably detected by these techniques only when a subject serves as his/her own control. A possible exception concerns the ratio of the force or pressure developed at a low stimulation frequency (i.e., 20 Hz) over that at a high stimulation frequency (i.e., 100 Hz), for which some critical value may be recognized below which low-frequency fatigue may be said to be present (16, 65, 66, 68).

Application. Although this test provides a means of directly detecting the development of muscle fatigue, applicability of this approach is limited by (1) patient discomfort associated with high-frequency stimulation, (2) equipment expense and complexity, and (3) the need to carefully control for variation in body position, lung volume, and the electrode–nerve interface. Advances in magnetic stimulation techniques may allow a variation of this form of testing to reach more widespread clinical application in the future, but this test is currently limited to research applications.

Single twitch stimulation. Rationale. As an alternative to tetanic or twin pulse stimulation, recording of muscle twitches in response to single nerve shocks can be employed to detect the presence of low-frequency fatigue (68). Twitch responses are much easier to obtain but are more variable than tetanic responses and are subject to additional variations caused by phenomena such as twitch potentiation (70).

Methods and equipment. The methodology required for phrenic nerve stimulation is reviewed in Section 2 of this Statement.

Advantages. This technique is nonvolitional, eliminating concerns about patient effort in the interpretation of obtained results. In addition, because only single twitches are evoked when employing this technique, much less patient discomfort is involved when compared with that produced by construction of the force–frequency relationship. Because a single shock is, by definition, a “low-frequency” stimulus, this approach also pro-

vides a means of detecting the development of low-frequency fatigue, whereas measurement of maximal voluntarily produced pressure does not. In addition, the magnitude of the compound action potential evoked during single twitches can be measured and monitored over time; correlation of this assessment with force generation over time may provide a means of detecting alterations in neuromuscular transmission.

Disadvantages. The application of these tests has been largely limited to scientific investigations in normal subjects and patients with lung (71) or neuromuscular diseases (72). Their application in clinical settings is more difficult, partly because of the factors already mentioned but also because of the many pieces of equipment that are required to perform these tests. In the case of the diaphragm, these difficulties are compounded by the necessity of stimulating the phrenic nerves bilaterally. In addition, it is critical that supramaximality be attained during electrical stimulation for this test to be useful. Unless electrical current is sufficiently high (i.e., increased to a level 150% of that required to initially attain a maximal signal), alterations in the compound action potential over time may simply reflect local, axonal changes. The introduction of magnetic stimulation (73) and of phonomyography (74) may help overcome some of these difficulties.

Applications. Although this technique holds promise, more work is needed before this test can be used in the clinical arena. Because of the technical problems detailed above, it is difficult to use present stimulation techniques to accurately evaluate the time course of fatigue, and this approach is currently better suited for evaluation of the effect of an intervention or treatment on muscle function. Once standardization of this technique is achieved, it probably offers the greatest promise to provide an objective index of the development of muscle fatigue.

CONCLUSION

This Section of the Statement has reviewed the complex process of muscle fatigue and has discussed the available direct and indirect measurements relevant to the assessment of fatigue of the respiratory muscles.

Although a variety of measures and indices have been employed to assess the development of respiratory muscle fatigue in research, there is no well described technique that has been successfully developed and tested to permit precise identification of respiratory muscle fatigue in the clinical setting. Of the tests reviewed, breathing pattern analysis and measurement of thoraco-abdominal motion are nonspecific indices that do not directly measure fatigue. Analysis of the pressure-time index provides a useful conceptual framework, but not a specific test of fatigue.

In the research environment, serial measurement of maximal voluntary respiratory pressures, assessment of maximum relaxation rates, frequency domain EMG analysis, and measurement of respiratory muscle pressures in response to electrical or magnetic nerve stimulation are all techniques that can be used to assess the evolution of respiratory muscle fatigue. Of these techniques, serial measurement of respiratory muscle pressure generation in response to electrical or magnetic stimulation is arguably the best technique to directly assess the development of respiratory muscle fatigue at the present time, and it offers the greatest promise for future development into an objective test of respiratory muscle fatigue in the clinical arena.

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6. Assessment of Chest Wall Function

Mechanical properties and functions of the chest wall can be assessed by measurements of lung volume displacement, chest wall motion, and pressures measured at various locations in the chest wall. Respiratory muscle activation can be further characterized by electromyography (EMG). Techniques of pressure measurement are presented in Section 2 of this Statement. The framework for interpreting pressures in the chest wall is presented in this article.

PRESSURES IN THE CHEST WALL

In respiratory mechanics, it is important to distinguish between the two uses of the word “pressure.” In one case it denotes a pressure measured at a given location, as in “pleural pressure.” In the other case it denotes a difference in pressure between two points, usually on opposite sides of a structure, such as “transpulmonary pressure,” defined as the difference between pressure at the airway opening (P_{ao}) and pressure in the pleural space (P_{pl}). Pressures are usually measured relative to barometric pressure (i.e., they are taken to be zero when they are equal to barometric pressure).

Pressures at a point are usually assumed to be representative of the pressure in that space (see Figure 1 in Section 2 of this Statement). This simplification must be qualified when variations of pressure within a space are to be expected (1). In particular, gravity causes vertical gradients in pressure related to the density of the semisolid or liquid contents of a space: in the thorax, this gradient is approximately 0.2 cm H_2O/cm height and is affected by lung density; in the abdomen, the gradient is nearly 1 cm H_2O/cm height. Temporal fluctuations in pressure, as in tidal breathing, are little affected by gravitational gradients. Shear stress resulting from the deformation of elastic, shape-stable organs can cause local variations in pressure, such as those that occur just below the diaphragm when it displaces the liver during a large forceful contraction (2).

Pressure differences across structures, as opposed to pressures measured at a point, are relevant for characterizing those structures. The schematic drawing in Figure 1 of Section 1 of this Statement shows relationships among locations where pressures can be measured (within circles) and intervening respiratory structures and equipment (within rectangles). Pleural and abdominal pressures are usually estimated by measuring esophageal and gastric pressures (P_{es} and P_{ga}), respectively. Table 1 and Figure 1 in Section 2 of this Statement list pressures measured at a point and pressure differences across structures. These differences are usually taken in a direction such that positive pressure differences expand the structure (e.g., lung). An exception to this rule is transdiaphragmatic pressure (P_{di}), which has been defined both as pleural pressure minus abdominal pressure, $P_{di} = P_{pl} - P_{ab}$, and as its reverse, $P_{di} = P_{ab} - P_{pl}$. The complicating effects of gravity must be considered when pleural pressure is estimated from esophageal pressure (P_{es}) and abdominal pressure is estimated from gastric pressure (P_{ga}). When the diaphragm itself is completely relaxed and the actual pressure difference across the diaphragm is nil, the measured transdiaphragmatic pressure has a minimum value, usually approximately 10 cm H_2O , which is attributed mostly to the gravitational hydrostatic difference between esophageal and gastric pressures. This hydrostatic transdiaphragmatic pressure, which changes only slightly with breathing (3), is usually subtracted from reported measurements of P_{di} .

A pressure difference between two points may characterize two or more different structures or groups of structures. For example, the pressure difference between the pleural space and the body surface in a spontaneously breathing person is both the transthoracic (transchest wall pressure, P_{cw}) and the negative of transpulmonary pressure ($-P_L$).

ASSESSMENT OF THE PROPERTIES OF THE RELAXED HUMAN CHEST WALL: RAHN DIAGRAM

Scientific Basis

Pressure differences across viscoelastic, plastoelastic structures such as the lungs and chest wall depend on the structure's volume, volume history, and rate of change of volume. Accordingly, pressure differences across respiratory structures are often represented as characteristic pressure-volume (PV) curves (4). For the relaxed respiratory system, transpulmonary, transthoracic, and transrespiratory pressures are usually plotted against lung volume in a Rahn diagram (Figure 1). The PV characteristics shown in Figure 1 are of a relaxed subject slowly inflated or deflated by a pressure source at the airway opening. All the passive structures show an increase in volume with an increase in the pressure difference across them. When two pneumatic structures are in series, for example, the lung and the chest wall, the pressure difference across both structures (the transrespiratory pressure) is the sum of the pressure differences across each, and the volume displacements of the whole are equal to the volume displacements of each part. The PV curve can be locally described by the volume at a given pressure and the slope (compliance) at that point. The compliance of a passive structure at a given volume is the ratio of volume change to pressure change (i.e., the slope of the characteristic PV curve at that volume).

Methodology

Lung volume displacements and pressures are measured as described in Sections 1 and 2 of this Statement. The following properties of the chest wall and lung are found by analysis of Rahn diagrams:

1. In trained subjects, the static PV characteristic of lung compliance is obtained from transpulmonary pressure ($P_L = P_{ao} - P_{es}$) during an interrupted exhalation from total lung capacity (TLC) to residual volume (RV) with the glottis held open. The quasistatic deflation curve is similar, and is measured during a slow exhalation (expiring at flows less than 0.3 L/second). For subjects who cannot satisfactorily perform these maneuvers, P_L can be measured during intermittent airway occlusions, 2–4 seconds long, in an expiration from TLC to RV, or during interrupted deflation of the respiratory system with a supersyringe, valve, or other device.
2. The PV characteristic of the relaxed chest wall (P_{cw}) is obtained from esophageal pressure (P_{es}) during a slow relaxed exhalation through pursed lips or other high resistance from TLC to functional residual capacity (FRC) and during passive inhalation with relaxation against an intermittently occluded airway between RV and FRC. Alternatively, it can be measured during exhalation from TLC to RV with periodic airway occlusions with relaxation. Relaxation above FRC, however, may be difficult for untrained subjects, and relaxation below FRC can usually be achieved

only by highly trained subjects. Normal compliance at FRC is approximately 0.2 L/cm H₂O.

3. The PV characteristic of the relaxed respiratory system is obtained by plotting Pao versus V_L during the maneuvers described above (Prs = Pao - Pbs [body surface pressure]). Normal values are approximately 0.1 L/cm H₂O at volumes of 40–60% of the vital capacity (VC).

Advantages

The Rahn diagram is useful for describing the elastic properties of passive systems. Each curve reflects the pressure difference developed by this structure for a range of volumes. Static compliance determined from these curves can be used for diagnosis. For example, the compliance of the lung is decreased in interstitial lung disease and increased in emphysema. Chest wall compliance is decreased in ankylosing spondylitis and obesity.

Disadvantages

Whereas the lungs' PV characteristic (i.e., the plot of elastic recoil pressure of the lung, P_{L,el}, versus lung volume) is relatively easy to obtain in untrained subjects, the elastic recoil pressure of the chest wall (P_{cw,el} versus V_L) is difficult to measure because it requires complete relaxation of the respiratory muscles at various lung volumes. Relaxation can be monitored via surface EMG of the chest wall. Failure to relax the respiratory muscles is also revealed when repeated measurements of passive PV curves of the chest wall are not identical. In subjects who can achieve relaxation at FRC but not at volumes above FRC, a relaxation curve can be approximated by extending a line from the relaxation point, assuming a normal chest wall compliance of 0.1 L/cm H₂O. The chest wall compliance can also be estimated in untrained subjects by the weighted spirometer technique (5). These estimations may, however, be unreliable in hyperinflated patients (e.g., in chronic obstructive pulmonary disease) who never reach a true (static) relaxation volume even when they are relaxed during exhalation. This is a well-established test, although it is seldom used for clinical diagnosis.

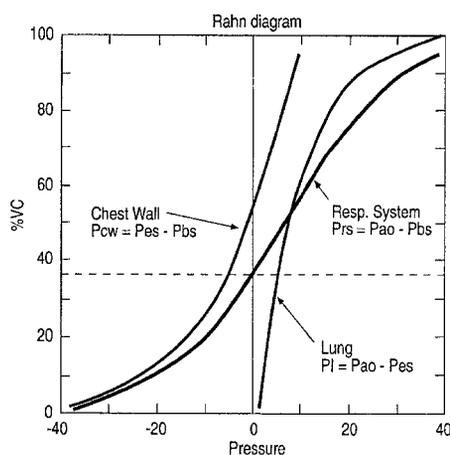


Figure 1. The Rahn diagram shows the pressure–volume relationships of the relaxed chest wall (P_{cw}), lungs (P_L), and the total respiratory system (Prs). Ordinate: Lung volume expressed as a percentage of vital capacity (VC). Abscissa: Pressures, each defined by the respective equations. Horizontal dashed line: Relaxation volume of the respiratory system. Pes = esophageal pressure; Pbs = body surface pressure; Pao = airway opening pressure. Modified from Campbell EJ, Agostoni E, Davis JN, editors. The respiratory muscles: mechanics and neural control, 2nd ed. Philadelphia, PA: W.B. Saunders; 1970. p. 55.

ASSESSMENT OF THE FUNCTION OF THE ACTIVE CHEST WALL: CAMPBELL DIAGRAM

Scientific Basis

To evaluate respiratory muscle action, a Campbell diagram, in which lung volume on the ordinate is plotted against pleural pressure on the abscissa, can be constructed. In this diagram, pleural pressure has differing significance depending on the maneuver. Consider a subject who is slowly inflated and deflated passively by a syringe connected to the airway while the respiratory muscles are relaxed (passive inflation; Figure 2). The pleural pressure, which is equal to transthoracic pressure, rises and falls, describing the characteristic PV curve for the relaxed chest wall, which is the same as that in the Rahn diagram (Figure 1). Alternatively, during active slow inhalation and exhalation with an open glottis, the pleural pressure (in this case equal to transpulmonary pressure with a negative sign) becomes more subatmospheric as the lungs inflate (active inflation; Figure 2), describing the lungs' characteristic PV curve, which appears as a mirror image of the lungs' curve in Figure 1. In the Campbell diagram the two curves intersect at relaxation volume at a pleural pressure of about -5 cm H₂O. The intersection represents the equal and opposite elastic recoils of the lung and chest wall.

During inhalation, the pleural pressure is the pressure across the active chest wall. The pressure generated by the inspiratory muscles is simply the pressure difference between the active chest wall characteristic and the relaxed chest wall characteristic. Work done by the inspiratory muscles,

$$\int P_{ms} dv,$$

is represented by the hatched area in Figure 2. The horizontally hatched area represents the work done to overcome elastic recoil of the lung and chest wall. Additional pressure is necessary to overcome airway resistance and lung tissue resistance; this work is shown with vertical hatching. Total work is therefore the sum of elastic and resistive work per inhalation, and is usually multiplied by breathing frequency and expressed as g · cm/ml. Work of breathing was found to average 2.2 ± 0.92 g · cm/ml at a respiration frequency of 15 breaths/minute (6), and was independent of age or sex. This is a test of great physiological interest and is widely used in research. It is seldom used for clinical evaluations. Reference 6 gives a full account of the complexities of how the work is done by the coordination of the various respiratory muscles.

Figure 3 shows a Campbell diagram with the addition of maximal static inspiratory pressure (MIP) and maximal expiratory pressure (MEP) during efforts against an occlusion (outer dashed lines). The MIP is greatest (most subatmospheric) at low lung volumes, whereas the MEP is greatest (most positive) at high lung volumes, largely because of the length–tension characteristics of the inspiratory and expiratory muscles. At high lung volume, the diaphragm and other inspiratory muscles are shorter, whereas expiratory muscles are longer (4). The inner dashed and dotted line in Figure 3 indicates the pleural pressure required to balance the elastic recoil of the lungs. TLC is at the intersection of these lines, where maximal inspiratory pleural pressure is balanced by the lungs' elastic recoil. The innermost loop represents resting breathing at FRC, as is shown for inspiration only in Figure 3.

The pressure–volume relationship during a maximal forced inspiration and expiration are shown as the inner solid line loop in Figure 3. Pressures at every volume are reduced from maximal static pressures because the muscle is shortening. The loss of maximal inspiratory pressure (the difference in pressure between the dashed and solid lines at a given lung volume in

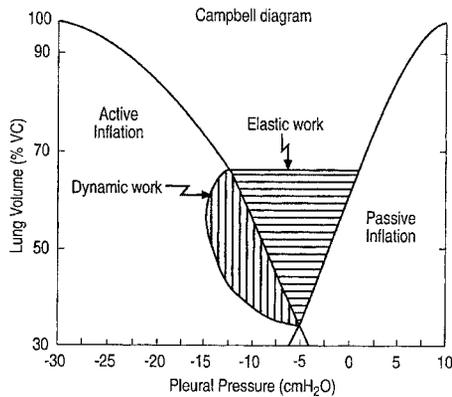


Figure 2. Campbell diagram. Graphical analysis of the work done during a breathing cycle by the inspiratory muscles. *Vertical hatching:* Work done to overcome flow resistance of the lungs. *Horizontal hatching:* Work done to overcome elastance of the lungs and chest wall. Modified by permission from Macklem PT, Mead J, editors. Handbook of physiology. Vol. 3: The respiratory system, Part 3. Bethesda, MD: American Physiological Society; 1986. p. 495.

Figure 3) was estimated to be approximately 7%/L/second of flow at a volume of FRC + 1 L (7). The muscle pressure at this volume represents the maximal capacity (P_{cap}) of the inspiratory muscle to generate pressure while shortening maximally. During submaximal exercise, for example, healthy subjects may require esophageal pressures in the range of -30 cm H_2O to ventilate the lungs, or approximately 40% of P_{cap} . When pressures in that range are achieved while breathing for several minutes with a duty cycle of 0.5, muscle fatigue may result (see Section 5 of this Statement). At higher levels of ventilation (maximal voluntary ventilation), at which peak flow can reach up to 10 L/second, there is a decrease in maximal inspiratory muscle pressure within 15–20 seconds, attributed to fatigue.

Equipment

Measurements of pressure and volume are described in Sections 1 and 2 of this Statement.

Applications

The following properties of the chest wall and lung are found by analysis of Campbell diagrams:

1. The quasistatic (or static) PV characteristic of the lung is obtained from esophageal pressure ($P_{es} = -P_{L,el}$) during a slow (or halting) inhalation and exhalation with the glottis held open.
2. The PV characteristic of the relaxed chest wall is described above as in the Rahn diagram.
3. Pressure generated by respiratory muscles (P_{mus}) is the horizontal distance (i.e., change in pressure) between the relaxation characteristic of the passive chest wall and the active one.
4. The Campbell diagram is also used to depict the maximal static inspiratory pressure (MIP) and maximal static expiratory pressure (MEP) measured with the airway occluded. The values of MIP in healthy young males are shown as the dashed outer loop in Figure 3. Section 2 of this Statement discusses the technique used to perform the MIP test and gives normal values in health and disease.

Advantages

The Campbell diagram is a convenient tool for calculating the elastic and resistive work of inspiratory and expiratory mus-

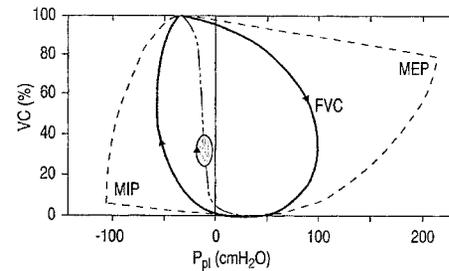


Figure 3. Campbell diagram with reduced scale to show maximal static inspiratory pressures (MIP) and maximal static expiratory pressures (MEP) at various lung volumes (*dashed lines*), pressures during maximal dynamic inspiration and expiration in a forced vital capacity (FVC) maneuver (*outermost loop*), and spontaneous breathing at rest (*innermost loop*).

cles. The relationship between work and oxygen consumption makes it possible to calculate the efficiency of respiratory muscles (see Figure 3 in Section 4 of this Statement). The difference between maximal static inspiratory pressures and peak actual pleural pressure measured during breathing indicates the muscle force reserve, an index that helps assess the likelihood of fatigue. This is a well-established method, often used in clinical research.

Disadvantages

To infer respiratory muscle action, the pleural pressure must be referred to the PV curve of the “relaxed” chest wall as in the example above. For example, a given positive pleural pressure may reflect either expiratory muscle activity at FRC or slight inspiratory muscle activity at a high lung volume. Furthermore, difficulties in measuring the relaxation characteristic in untrained subjects can make estimates of P_{mus} uncertain. Although the Campbell diagram is easy to plot, its interpretation requires some practice.

ESTIMATION OF VENTILATION BASED ON CHEST WALL MOTION: KONNO-MEAD DIAGRAM

Scientific Basis

Quantitative measurements of respiratory system motion are usually based on measurements of lung volume and displacements of chest wall structures, including the abdominal wall. Because the tissues of the chest wall are essentially incompressible, volume changes (displacements) of the chest wall surfaces are nearly equal to volume changes of the lungs and can be used to “noninvasively” estimate lung volume, without the need for a mouthpiece, mask, or other connection to the airway. (Changes in intrathoracic blood volume cause differences between chest wall and lung volume displacements, but these are usually negligible.) The relevance of noninvasive measurements of ventilation is shown in BREATHING PATTERNS in Section 10 of this Statement.

During quiet breathing in a subject at rest, the surface of the chest wall moves in a predictable way as lung volume increases and decreases. Various dimensions of the chest wall have been measured to estimate changes in chest wall (or lung) volume. The “chest pneumogram” is a record of changes in thoracic circumference that provides a qualitative measure of ventilation. However, because the major compartments of the chest wall, the rib cage and abdomen, move independently in most conscious subjects, measuring overall chest wall displacement accurately usually requires two or more simultaneous measurements of displacement.

Advantages. The RIP is easy to use. Because the belts encircle a large part of the rib cage and abdomen, integumental mobility and cross-sectional shape distortions are less problematic than with magnetometers, and therefore the RIP is often used during sleep or exercise. The RIP is more accurate than magnetometers in estimating lung volume change (15), perhaps because its signal varies with cross-sectional area and samples a larger part of the moving chest wall than do magnetometers.

Disadvantages. The RIP measures changes relative to an unknown baseline, and its accuracy depends on lung volume calibration at the time of study (see below). In addition, movement of the belts or changing body position can affect calibration.

Calibration of RIP and magnetometers. Numerous methods for calibrating the magnetometer and RIP signals for estimating lung volume displacement have been described. All methods determine coefficients for rib cage and abdominal signals, and most require simultaneous spirometric measurements of lung volume change during periods of breathing in which the contributions of rib cage and abdomen to tidal volume vary. In the method described by Konno and Mead (Figure 4), the volume–motion coefficients of rib cage and abdomen are established by having subjects perform an isovolume maneuver at two volumes that differ by a known amount. Volume calibration is accomplished by extending the isovolume lines to the axes, where they indicate the known volume difference. Calibration can also be accomplished by using statistical techniques based on tidal breathing without isovolume maneuvers, and semiautomated procedures and computer programs incorporated into some commercial devices can simplify calibration in practice. Alternatively, one can assume a standard ratio of the volume–motion coefficients of rib cage and abdomen instead of finding the ratio experimentally, and calibrating the combined signal with a spirometer (16). The use of a standard gain ratio when measuring tidal volume is probably as accurate as more elaborate methods of calibration and, importantly, avoids extreme errors in calibration that can occur with untrained subjects. We recommend use of standard ratios for measuring tidal volume, especially in untrained subjects.

Methodology: Respiratory Area Flux Meter

Another device, the respiratory area flux meter, also uses expandable coils that surround the rib cage and abdomen, but in this case the subject must also lie within large fixed-field coils mounted in a frame (17).

Advantages. The principal advantage of the area flux meter is that it measures the cross-sectional areas of the rib cage and abdomen accurately.

Disadvantages. Although promising, this technique has not yet been widely applied. The necessity for large field coils may relegate this device to research applications.

OPTICAL DEVICES USED TO MEASURE CHEST WALL MOTION

A variety of optical techniques using lasers or small lamps and multiple video cameras can track the three-dimensional position of numerous points on the torso with high precision and temporal resolution. Optical reflectance motion analysis is one of these methods (18).

Advantages

These techniques can measure displacements accurately for estimation of lung volume change and can provide detailed kinematic data for chest wall mechanics (*see below*). They are excellent for studying distortion of the chest wall.

Disadvantages

Like other techniques described above, optical techniques are subject to artifacts from soft tissue movement. Most optical techniques are expensive and time-consuming, so they have been limited to research.

INFERRING RESPIRATORY MUSCLE CONTRIBUTION TO BREATHING FROM CHEST WALL MOTION

Scientific Basis

Thoracoabdominal displacements such as those displayed on a Konno–Mead diagram demonstrate the action, dysfunction, or paralysis of specific respiratory muscles. For example, with diaphragmatic paralysis there may be “paradoxical” inward motion of the abdominal wall during early inhalation (Figure 4, mainly rib cage). As the active rib cage expands, pleural pressure decreases, and without diaphragmatic contraction pleural pressure is transmitted to the abdominal compartment, where it causes a passive inward movement of the abdominal wall. Likewise, rib cage muscle paralysis causes characteristic paradoxical movement of the rib cage during inhalation.

Patients with lung disease often have abnormal chest wall motions, as well. In patients with chronic obstructive pulmonary disease, alternation between rib cage breathing and abdominal breathing (“respiratory alternans”) and paradoxical motion of the abdomen during inspiration can herald inspiratory muscle fatigue and impending respiratory failure (19). This is not, however, pathognomonic of fatigue, because it can be elicited voluntarily. Furthermore, abdominal pain can trigger such patterns after upper abdominal surgery.

The Konno–Mead diagram is only one possible motion–motion diagram of the chest wall, and other plots such as anteroposterior–transverse diameter plots can give additional information about specific respiratory muscle use and describe distortions of rib cage shape that occur with contraction of specific respiratory muscles. For example, inspiratory efforts made principally with the cervical accessory muscles of inspiration can cause the lower rib cage cross-section to become more elliptical (19). Compared with normal breathing, contraction of the diaphragm by itself causes predominance of abdominal wall over rib cage displacement, increased ellipticity of the lower rib cage, and predominance of lower over upper rib cage anteroposterior displacement (16).

Advantages

Chest wall motion is easy to measure and provides information about respiratory muscle activity.

Disadvantages

Motion–motion plots such as Konno–Mead diagrams, when used by themselves to infer specific muscle action, can be ambiguous, because a given motion may be produced by several different muscular actions. For example, paradoxical motion of the abdominal wall in inspiration is not necessarily an indication of diaphragm paralysis because of the influence of the zone of apposition (20) on abdominal displacements (*see subsequent passages*). When the rib cage expands in a normal inhalation, the outward displacement of the lower rib cage, which is part of the abdominal container, tends to lower abdominal pressure and draw the abdominal wall inward even when the diaphragm is shortening normally (21). Therefore, small paradoxical inward motions of the abdominal wall during inhalation do not necessarily indicate diaphragmatic paralysis (Figure 4). Conversely, diaphragm paralysis may be missed if one uses only motions to infer muscle action. The paradoxical in-

ward motion of the abdominal wall expected during inhalation with a paralyzed diaphragm may be abolished if inspiration occurs with simultaneous relaxation of abdominal muscles that were activated during expiration (22). Unambiguous evidence of muscle action is best achieved by combining displacement and pressure measurements.

Actions of specific rib cage muscles are difficult to infer from rib cage motions, because numerous muscles have specific actions at numerous sites on the rib cage. Furthermore, the simultaneous activity of inspiratory and expiratory muscles can obscure effects of individual muscles. Therefore, assessing the actions of specific rib cage muscles usually involves electromyography and measurements of several rib cage dimensions and pressures (*see INFERRING RESPIRATORY MUSCLE CONTRIBUTION TO BREATHING FROM PRESSURE–VOLUME RELATIONSHIPS and INFERRING DIAPHRAGM ACTIVATION AND ELECTROMECHANICAL EFFECTIVENESS FROM EMG*).

INFERRING RESPIRATORY MUSCLE CONTRIBUTION TO BREATHING FROM THE ESOPHAGEAL–GASTRIC PRESSURE RELATIONSHIP: MACKLEM DIAGRAM

Scientific Basis

Decramer and Macklem introduced a method for inferring respiratory muscle action by measuring esophageal and gastric pressures (23). For example, inhalations made with rib cage muscles alone (as in diaphragm paralysis) result in decreases in both esophageal pressure, which is normal, and in gastric pressure, which is not, whereas diaphragmatic inhalations result in increased gastric pressure and a negative swing in P_{es} (lung inflation) (Figure 5).

Advantages

This technique is useful and informative when esophageal and abdominal pressures are recorded.

Disadvantages

Using chest wall pressures by themselves to infer muscle actions leaves some uncertainty, as does the use of displacements already described here. Macklem's method of analysis assumes that abdominal muscles are relaxed. When they are not, pressure changes are ambiguous and difficult to interpret. Nevertheless, this remains an interesting research tool and has potential for development.

INFERRING RESPIRATORY MUSCLE CONTRIBUTION TO BREATHING FROM PRESSURE–VOLUME RELATIONSHIPS

Scientific Basis

Pressure–volume measurements of rib cage and abdominal compartments can provide the basis for mechanical analysis of the diaphragm, rib cage, and abdominal muscles, allowing inferences about which muscles contribute to a particular breath or respiratory maneuver. Whereas the Campbell diagram can be used to infer inspiratory and expiratory activity of all the respiratory muscles, other PV diagrams can be used to infer action of specific respiratory muscles. Pressure–volume diagrams of rib cage and abdomen were introduced by Konno and Mead (24), who showed their respective relaxation characteristics. By comparing pressure–volume data during breathing with those obtained during relaxation, these diagrams can be used to infer the action of specific respiratory muscles when pressure data alone or volume data alone could be misleading. An example of the pressure–volume diagram for the abdomen is shown in Figure 6. Contraction of the abdominal muscles

tends to displace the abdominal wall inward and increase abdominal pressure. Therefore, a movement down and to the right of the relaxation line in Figure 6 reliably indicates abdominal muscle contraction. Similarly, diaphragm contraction (or paralysis) can be inferred from deviations of the diaphragm's PV data in relation to its relaxation characteristic. If the diaphragm shortens or remains relatively isometric and transdiaphragmatic pressure increases, the diaphragm must be actively contracting. For examples of the use of such plots, see Goldman and coworkers (25) and Mead and coworkers (26).

The rib cage presents a challenge in pressure–volume analysis because no single pressure difference characterizes the pressures acting on the whole structure. The internal pressure applied to the lung-apposed surface of the rib cage can be characterized by pleural (esophageal) pressure, but pressure in the caudal rib cage apposed to abdominal viscera and diaphragm (the “zone of apposition”) is closer to abdominal (gastric) pressure than pleural pressure. In addition, the diaphragm itself can have an inspiratory effect on the lower rib cage when it contracts. Therefore, the pressure acting on or contributed by the rib cage is generally neither pleural nor abdominal pressure but some combination of the two (27). This complication can be handled by more elaborate analysis of chest wall motion and pressures (28).

Advantages

PV data can provide unambiguous evidence of diaphragm and abdominal muscle activity and, with careful analysis, evidence of rib cage muscle inspiratory and expiratory action.

Disadvantages

Inferring contributions of specific rib cage muscles generally requires the addition of electromyographic data and a more complex analysis. The method remains, however, a powerful research tool, which can be perfected.

INFERRING DIAPHRAGM ACTIVATION AND ELECTROMECHANICAL EFFECTIVENESS FROM EMG

The Rahn, Campbell, Konno–Mead, and Macklem diagrams allow the inference of respiratory muscle activity via departures from the relaxed pressure–volume, motion–relaxation, or pressure–pressure relationships. The major limitation of

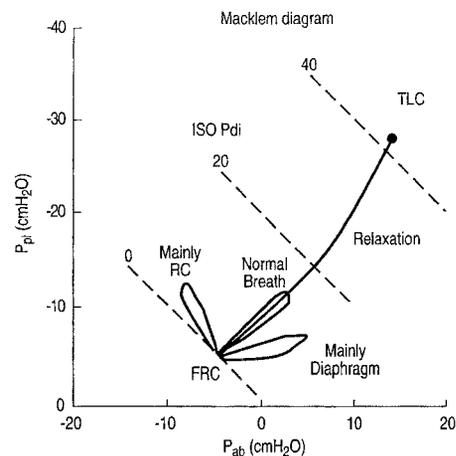


Figure 5. Macklem diagram. The pleural pressure–abdominal pressure relationship for a variety of breaths is shown, emphasizing the use of certain chest wall muscles: mainly rib cage (RC) muscles (upper girdle, intercostals), normal breath, or mainly diaphragm contraction. Dotted lines: Iso Pdi isopleths show loci of constant transdiaphragmatic pressure.

these methods is that both esophageal and gastric pressures are affected by the action of many muscles, and the analysis of their individual actions is indirect and qualitative. "Relaxation" is often difficult to obtain.

The use of the electromyogram (EMG) displayed in the time domain allows the evaluation of the level and timing of activation of an individual muscle (28–31). The frequency domain analysis of the EMG allows the evaluation of center frequency or centroid parameter sensitive to changes in the velocity of conduction of membrane potentials. Center frequency decreases when the muscle fatigues (32, 33) (and see FREQUENCY DOMAIN ANALYSIS in Section 3 of this Statement).

Simultaneous measurement of integrated EMG of the diaphragm (Edi), the Pdi, and muscle configuration (length) allows the estimation of activation pressure ratio, as shown in Figure 7 (28, 31, 34). The strength of Edi can be measured as the root mean square (RMS) (34). Because absolute RMS values are subjected to many variables, normalization is done to the maximal voluntary RMS obtained by holding an inspiration at TLC. This test could be used to evaluate the relative activation during resting breathing. It was found that the percentage of RMS swings measured during resting breathing was 8% of maximal in healthy subjects and 43% in chronic obstructive pulmonary disease, whereas there were nonsignificant differences in Pdi swings (34).

From studies of normal subjects, it was established that the RMS, expressed as a percentage of its maximal activation at TLC, varies as a function of chest wall configuration as measured by a Konno–Mead diagram (28, 31). The RMS/Pdi ratio has the highest slope at lung volumes near TLC (short muscle) and smaller slopes at low lung volumes, at which the diaphragm is contracting against active abdominal muscles. The force of the diaphragm (for a given percentage of maximum RMS) is strongly dependent on its length and configuration (Figure 7).

Advantages

The advantage of this method is that it makes possible the evaluation of the effectiveness of the muscle, that is, amount of force generated per stimulation units.

Disadvantages

The disadvantage of this method is the rather complex method of EMG analysis, which may be made easier by multielectrode recording technology (33). In addition, this method requires evaluation of the configuration of the diaphragm via the Konno–Mead method, as well as the velocity of shortening. This method is still under development, and remains an interesting research tool.

CONCLUSION

This Section of the Statement has considered the mechanical properties and function of the chest wall, assessed by volume

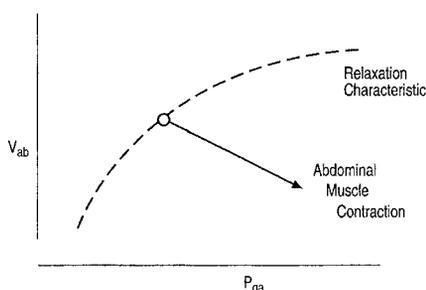


Figure 6. Abdominal displacement (V_{ab}) gastric pressure (P_{ga}) characteristic during relaxation and contraction of abdominal muscles.

displacements, chest wall motion, and respiratory pressures. Important techniques include the following:

Assessment of the passive properties of the chest wall (Rahn diagram): the chest wall is a contractile musculoskeletal structure that changes volume to accommodate the ventilatory function of the lung. Its passive characteristics are those of an elastic body, and have been defined by Rahn diagram (the relationship between the passive relaxation pressure at the closed mouth and lung volume). The relaxation characteristics of the lung are measured by the relationship between volume and esophageal pressure. By subtraction, the passive relaxation properties of the chest wall are calculated. The Rahn diagram is of considerable conceptual importance, although seldom constructed outside a research context.

Assessment of the active chest wall (Campbell diagram): lung volume is plotted against pleural pressure and the diagram permits calculation of respiratory muscle work, both elastic and resistive. The measurement of work and oxygen consumption helps calculate muscle efficiency. If pressure data from maximum efforts against a closed airway ($P_{i,max}$, $P_{E,max}$), across the range of lung volume, are plotted on the Campbell diagram a useful comparison can be made with the pressures achieved during maximum dynamic inspiration and expiration or resting ventilation.

Estimation of ventilation by chest wall motion (Konno–Mead diagram): the technique allows noninvasive measurement of ventilation and the assessment of the contribution of the diaphragm and rib cage to tidal volume. The diagram plots rib cage and abdomen diameters (magnetometers) or perimeters (respiratory inductive plethysmograph). If calibrated, the technique can measure tidal volume without the need

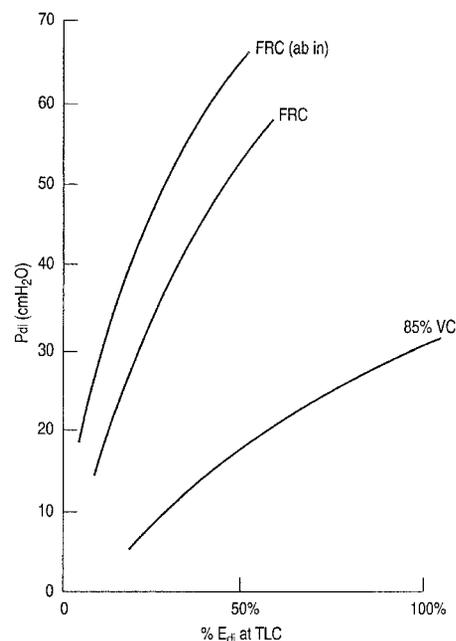


Figure 7. Static progressive contraction of the diaphragm held at three configurations, as shown in Figure 4 (solid circles). The transdiaphragmatic pressure is plotted against the integrated electrical activity of the diaphragm, obtained from the crural region via an esophageal electrode and an RC integrator. FRC: The contraction held at FRC configuration. 85% VC: Notice a considerable loss of Pdi per percent Edi (shorter diaphragm). FRC volume and abdominal muscle contraction [FRC (ab in)]: Notice the increase in Pdi for any given level of Edi (longest diaphragm). The slopes are an index of the effectiveness of the diaphragm to convert stimulation to pressure. Reprinted by permission from Reference 28.

of a mouthpiece. Initially magnetometers, and later RIP, have allowed the concept embodied in the Konno–Mead diagram to develop into a clinically useful and widely used noninvasive measure of ventilation.

Inferring respiratory action from esophageal and gastric pressures (Macklem diagram): the diagram plots esophageal against gastric pressure and allows breaths that are achieved mainly by rib cage muscles or diaphragm to be distinguished.

Assessing activation and electromechanical effectiveness of the diaphragm from EMG (Edi/Pdi diagram): At FRC the diaphragm can generate much more Pdi for a given Edi than at high lung volumes. EMG is measured with an esophageal electrode and activity is expressed as a percentage of EMG at active TLC. At rest, patients with chronic obstructive pulmonary disease have much higher Edi/Pdi ratios than normal subjects.

The measurements listed above have been widely used in clinical research and have advanced importantly our understanding of chest wall function. However, relatively little work has been undertaken in the clinical arena, an important challenge to be met.

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7. Imaging Respiratory Muscle Function

This Section of the Statement covers imaging techniques that pertain to assessment of the function of the muscles of respiration that change the volume of the thorax. It does not consider modalities for imaging muscles responsible for maintaining the patency of the upper airway.

TRANSMISSION RADIOGRAPHY

Radiography remains the most used technique for evaluating the position and movement of the diaphragm. Postero-anterior (P-A) and lateral views of the thorax at total lung capacity can be supplemented by radiographs at other static lung volumes and movement of the hemidiaphragms as assessed by fluoroscopy.

Limitations

As shown by three-dimensional reconstruction techniques using other imaging techniques, the shape of the human diaphragm is complex (1–3) (Figure 1), so transmission radiography, even with two views, can provide only qualitative estimates of shape. The silhouette of the diaphragm revealed by transmission radiography represents the most cephalad portion of the diaphragm apposed to the lung, rather than the chest wall from one side to the other in P-A views and from dorsal to ventral in lateral views. The most cephalad portion of the diaphragm, for example, the P-A view, may not lie in the same dorsal–ventral plane and, furthermore, may not even represent a contiguous line over the surface of the diaphragm. It clearly does not represent the curvature of a bundle of muscle in the diaphragm or necessarily any region of the diaphragm muscle. Furthermore, attempts to use radiographic changes at different lung volumes to assess changes in the length of the diaphragm require assumptions about the relative contribution of the central tendon and muscle. Parallax distortion and the necessity for exposure to ionizing radiation also cause difficulties with this technology.

Applications

Bearing in mind these important limitations, radiography has been used to assess diaphragm position and motion in clinical assessment and to derive estimates of diaphragm length in research studies. In addition, estimating lung volumes from P-A and lateral radiographs at full inflation may indirectly assist assessment of the diaphragm.

Position of Hemidiaphragm Domes at Total Lung Capacity

Normal subjects. In ~ 95% of normal adults the level of the dome of the right hemidiaphragm on postero-anterior radiographs taken standing at full inflation (total lung capacity) is projected in a plane ranging from the anterior end of the fifth rib to the sixth anterior interspace; and in only 5% is it at or below the level of the seventh rib (4). The height of the right dome tends to be higher in women, in subjects of heavy build, and in those older than 40 years of age. The plane of the right diaphragmatic dome tends to be about half an interspace higher than the left, although in ~ 10% of normal subjects both are at the same height or the left is higher than the right (5).

Disease. In bilateral diaphragm paralysis both domes are elevated at total lung capacity (and radiographic lung volume is reduced). This change is indistinguishable from volitional failure to fully inflate the lungs. In unilateral paralysis, elevation of the paralyzed dome is obvious. When there is an ac-

quired enlargement of total lung capacity, as in severe emphysema, the domes are lower (the level of the right dome at the anterior end of the seventh rib or lower) with flattening and a larger radius of curvature, visible on both P-A and lateral radiographs. If a line is drawn on a P-A radiograph from the vertebral angle to the costophrenic angle, the maximum curvature of the dome, assessed at 90° to this line, should normally be at least 1.5 cm. In the most severe disease the domes may be flat or even inverted with loss of the zone of apposition, allowing visualization on the P-A radiograph of the insertions of the diaphragm into the lower ribs.

Excursion of hemidiaphragm domes during tidal breathing. High-speed cassette changers or video fluoroscopy can provide dynamic information. In a study of inspiratory–expiratory radiographs obtained during quiet tidal breathing in the erect position from 350 subjects, 30–80 years of age, and without evidence of respiratory disease, the mean tidal excursions of the domes of the right and left hemidiaphragms were found to be 3.3 and 3.5 cm, respectively (6). Tidal diaphragmatic movement averaged 0.5 cm less in women than in men. Despite similar mean values, unequal movement of the two hemidiaphragmatic domes in an individual subject is common, most commonly being greater on the right (5).

In bilateral diaphragm paralysis individuals may breathe by active expiration below relaxation volume followed by passive inhalation, during which the diaphragm may descend, at least during early inspiration, leading to erroneous conclusions about diaphragm function (6, 7). Because relaxation volume decreases in the supine position, subjects are less likely to be able to breathe by active expiration below the relaxation volume and passive descent of diaphragm during inspiration is less likely to occur.

Unilateral diaphragm paralysis is easier to detect because there is paradoxical motion during tidal inspiration, with ascent of the paralyzed dome, contrasting with descent of the normal hemidiaphragm; this contrast can be amplified by the sniff test, which induces a vigorous, short-lived contraction in the normal hemidiaphragm. Because of normal variations in movement of the two diaphragms, relative weakness of one hemidiaphragm (such as after cardiothoracic surgery) is difficult to detect radiographically.

Estimates of Change in Diaphragm Length from Radiographs at Different Lung Volumes

The length of the silhouette of the diaphragm domes, length of the diaphragm apposed to the lateral rib cage between the costophrenic angle and a skeletal landmark corresponding to its insertion, and the internal diameter of the rib cage can all be read on a P-A radiograph (8, 9). As discussed above, the silhouette may be formed from the dome in several dorsal–ventral planes, and therefore these measurements do not give the actual length of the diaphragm in a transverse section. But it has been argued that changes in these measurements in radiographs obtained at different lung volumes may still give a reasonable estimate of changes in diaphragm length (8). Similar measurements can also be made with a set of lateral radiographs. To estimate muscle fiber shortening, further assumptions must be made about the uniformity of shortening and the contribution of the central tendon to the total length. Using P-A radiographs at several lung volumes, estimated diaphragm shortening as lung volume increases in normal subjects has been predicted by a modified piston-and-cylinder model that

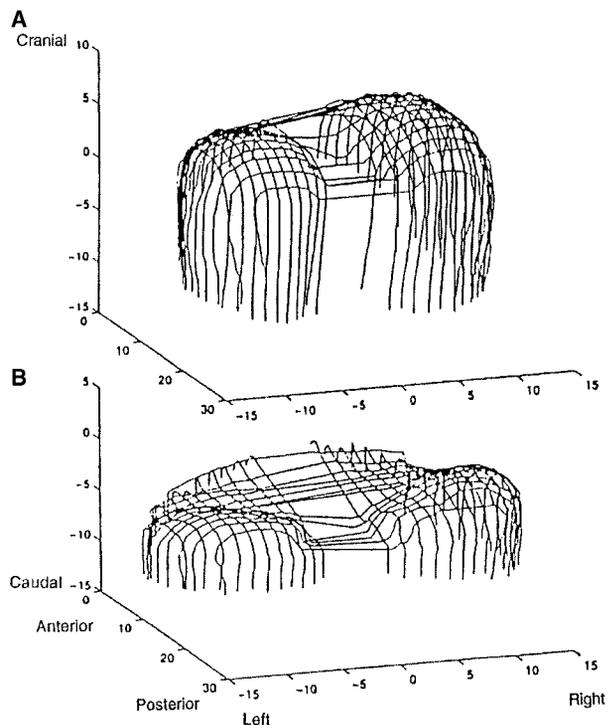


Figure 1. Three-dimensional reconstruction, using spiral computed tomography, of diaphragm contour at supine functional residual capacity in a normal subject (A) and a patient with hyperinflation due to chronic obstructive pulmonary disease (B). The silhouette of the domes projected on a transmission radiograph may arise from different planes. Scale in centimeters. Reprinted by permission from Reference 3.

allows for inspiratory expansion of the lower rib cage but neglects change in shape of the domes (9). Radiographic changes in diaphragm length over the vital capacity have been estimated in patients with chronic obstructive pulmonary disease (10–12). Nonradiographic methods can be used to measure the internal diameter of the rib cage (calipers or magnetometers, with chest wall thickness measured by ultrasound) and the length of the zone of apposition (ultrasound; *see below*); the accuracy of estimates of change in the diaphragm length by nonradiographic methods therefore will be influenced by whether the dome shape remains reasonably constant (or its change can be predicted) over the vital capacity (11, 12).

ULTRASOUND

Diaphragm

Ultrasound can be used to image the diaphragm when there is little or no air intervening between the probe and the muscle. The normal diaphragm, in common with other skeletal muscles, is poorly echogenic and identification depends on bright echoes reflected from the attached parietal pleural and peritoneal membranes (13); a further, less bright and irregular echo may be visible, arising from the layer of connective tissue and vessels running through the middle of the muscle (14).

Applications

Dome movement. Ultrasound has been used to monitor displacement of the dome of the diaphragm during respiratory maneuvers, with craniocaudal excursions of the posterior dome measured either with a transducer on the lateral chest wall (15) or with a probe placed on the upper abdomen and directed toward the dome (16, 17). Visualization of the right

dome is usually better than the left because of the underlying liver, in contrast to the gastric and intestinal gas adjacent to the left dome. Diaphragm displacement measured by these techniques compares favorably with simultaneous fluoroscopic estimates (18), but the diaphragm is shown as a brightly echogenic arc with poorly defined borders whose thickness can be as much as 10 mm; the pleural and peritoneal membranes cannot be distinguished. In this application a 3.5-MHz vector transducer with considerable penetration but lower resolution is used in the time-motion mode (M-mode).

Zone of apposition. Ultrasound has also been used to assess the length and thickness of the zone of apposition against the rib cage; although dynamic changes in length can be assessed by fluoroscopy (19) this entails considerable radiation exposure. Most of the more recent ultrasound studies have concentrated on this application; because the costal part of the diaphragm is relatively close to the skin surface, it is possible to use a 7.5- or 15-MHz transducer, which has less penetration but superior resolution. High-resolution M-mode ultrasound has been used during tidal breathing (20); with two-dimensional (B-mode) ultrasound the two outer echogenic layers of parietal pleura and peritoneum can be clearly visualized (14) (Figure 2). In these applications a small ultrasound transducer is held firmly in a lower intercostal space in the mid- or anterior axillary line (usually on the right side) perpendicular to the chest wall; if the angle of incidence changes significantly from perpendicular, resolution is lost. The measurement is rapid and shows good repeatability in most subjects, but may be difficult in obese individuals.

With this technique the thickness of the zone of apposition during relaxation at different lung volumes (14, 21), tidal breathing (20), and static inspiratory efforts (14) has been measured.

Because the diaphragm is identified by its enveloping membranes and there is scattering, ultrasound tends to overestimate diaphragm thickness. However, estimates of the average thickness of the costal diaphragm in normal untrained subjects during relaxation at FRC have been in the range of 1.7–3.3 mm (14, 20, 22–24), with larger values in men than women (22), and lower values in children (24, 25). Healthy newborn infants have also been studied (26). There appears to be a thicker diaphragm in individuals with greater inspiratory strength (27). Unilateral diaphragm paralysis is associated with a thinner costal diaphragm (28), and Duchenne muscular dystrophy is associated with increased echogenicity (25).

Most measurements have been made in the right anterior axillary line and little is known about variations in thickness at different sites in the zone of apposition.

Diaphragm thickening with increasing lung volume should be inversely proportional to reduction in length; the thickening found as lung volume is increased (14, 21) is compatible with this relationship, but thickening during tidal breathing (20, 29) and maximal inspiratory efforts (14) has been greater than anticipated from the expected shortening. Whether this is an artifact or is caused by enhanced thickening close to diaphragm insertions into the ribs (as has been shown in dogs) is not yet known.

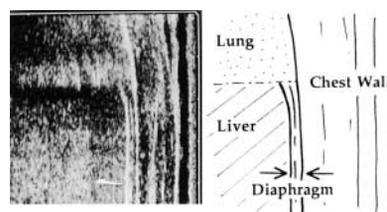


Figure 2. B-mode ultrasonogram of the normal diaphragm in the zone of apposition (between the two arrows) visualized through a lower right intercostal space. Scale division on x and y axis is 10 mm. Reprinted by permission from Reference 14.

TABLE 1. RADIOGRAPHY

Name of Test	Information Provided	Diagnostic Purposes	How to Perform
Standard P-A (and lateral) chest radiograph at TLC	Position of diaphragm domes at TLC (radiographic estimate of TLC)	Unilateral/bilateral diaphragm paralysis Emphysema	Standard radiographic techniques
Fluoroscopy or rapid-radiography technique during tidal breathing and sniffs	Movement of right and left domes: paradoxical motion exaggerated by brisk contraction of normal dome during sniffs	Unilateral or bilateral diaphragm paralysis	Fluoroscopy or rapid-cassette change radiography
Set of radiographs at different lung inflation between RV and TLC	Silhouette of domes, internal diameter of rib cage, and estimates of length of zone of apposition to derive change in diaphragm length as lung volume changes	Relationship between diaphragm length and function, e.g., emphysema pre- and post-lung volume reduction surgery	Standard radiographic techniques with spirometric control. (Rib cage diameter can alternatively be obtained with calipers or magnetometers and ultrasound; length of zone of apposition with ultrasound)

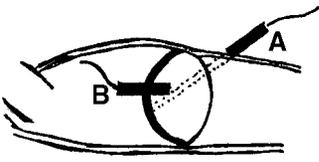
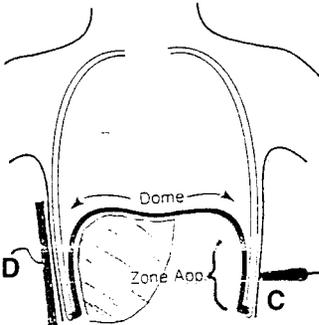
Definition of abbreviations: P-A = postero-anterior; RV = residual volume; TLC = total lung capacity.

Potential further applications include the simple assessment of diaphragm involvement in neuropathy (30) and myopathy, severe acute illness, after cardiothoracic surgery (31), and changes with rehabilitation and training programs (32). Skeletal muscle mass is related to force generation. The muscular cross-sectional area of the diaphragm in the zone of apposition has been estimated from measurements of the internal circumference of the lower rib cage and measurements of diaphragm thickness (27).

Ultrasound has also been used to detect displacement of the upper border of the zone of apposition of the costal diaphragm to the rib cage when lung volume changed (8); this

makes use of the loss of diaphragm echo complex, because of the intervention of aerated lung as lung volume increases. The length of the zone of apposition can also be estimated by identifying the rib into which the diaphragm is inserted and/or measuring its upper border at total lung capacity (19). In this application a longer ultrasound probe is placed craniocaudally across several ribs and intercostal spaces (again perpendicular to the chest wall), usually in the anterior axillary line; because the probe cannot be placed so close to the diaphragm and the image is lost beneath the ribs, resolution usually is less good with this technique.

TABLE 2. ULTRASOUND

Name of Test	Information Provided	Diagnostic Purposes	How to Perform
Diaphragm			
Dome ultrasound	Movement of right (or left) dome	Unilateral or bilateral diaphragm paralysis	Ultrasound probes with sufficient penetration (3 or 3.5 MHz) placed over abdomen (A) or over lateral rib cage (B). M-mode
			
Zone of apposition ultrasound	Thickness at different lung volumes, relaxed or contracted	Detect contraction during tidal breathing or inspiratory efforts Effects of pulmonary or neuromuscular disease, training, and disuse Placement of intramuscular electrodes	High-resolution probe with less penetration (7.5 MHz) over intercostal space, usually in anterior axillary line. B- or M-mode (C)
	Length at different lung volumes	Estimates of diaphragm length and swept volume	Linear probe in craniocaudal plane over lateral rib cage. B-mode (D) Both measurements are usually made on the right side
Other Respiratory Muscles			
Ultrasound of neck, rib cage, or abdominal muscles	Thickening during respiratory maneuvers	? Contraction during tidal breathing or inspiratory efforts	High-resolution probe (7.5 MHz) over appropriate muscles. B-mode
	Distance from overlying skin	Placement of intramuscular electrodes	

Other respiratory muscles. Intercostal muscles, parasternal (33) (and cervical inspiratory) muscles, as well as abdominal muscles (34–36), which are difficult to image by other techniques, can all be imaged with ultrasound, reliance being placed on echoes from the surrounding fascia. If the relationship between thickness and shortening were known, ultrasound could be used to assess the pattern of intercostal and abdominal muscle contraction during breathing maneuvers. Ultrasound imaging of these muscles (and the diaphragm) is useful in the accurate placement of intramuscular electrodes to record electrical activity (28).

VOLUMETRIC IMAGING

Volumetric computed tomography scans (2, 3, 37–39) and magnetic resonance imaging (1, 40, 41) can determine the configuration of the thoracic cavity. Both methods can be used to determine the detailed shape of the diaphragm (Figure 1), the rib cage, and ribs in normal (1, 2, 38, 39) and emphysematous (3, 42–44) subjects. Such data have been used with engineering analysis to determine the distribution of tension in the canine diaphragm from measurements of transdiaphragmatic pressure (37). To date, use of these methods has been limited to research and few measurements of diaphragm thickness have been made. Clinical use of both imaging methods is still limited by the expense of data acquisition and the laborious data analysis. Computed tomography scans are complicated by radiation exposure and magnetic resonance imaging is complicated by prolonged data acquisition times, which must assemble average data over numerous breaths; both can be applied only in horizontal postures.

NUCLEAR MEDICINE

Both single-photon emission computed tomography (SPECT) and positron emission tomography (PET) scans provide volumetric information, which can be used to identify the surface of ventilated or perfused lungs. Because the outer surface of the lung is apposed to the rib cage and diaphragm, the configuration of the diaphragm and rib cage can also be determined by these methods. Both techniques offer poor spatial and temporal resolution and there are no published data in which they have been used to analyze respiratory muscle function.

SUMMARY

Radiographic techniques are widely used to assess respiratory muscle function (summarized in Table 1). Ultrasound is increasingly used, particularly to assess the diaphragm (Table 2). Volumetric imaging (computed tomography and magnetic resonance imaging) has limited research application.

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8. Tests of Upper Airway Function

The upper airway is surrounded by skeletal muscles that exhibit respiratory-related activity (Figures 1 and 2) (1–4). The mechanical effects of respiratory-related upper airway muscle activation are very different from those of the respiratory pump muscles. Laryngeal muscles regulate the size of the valvelike glottic aperture. Loss of innervation to the intrinsic laryngeal muscles can cause stridor leading to respiratory arrest. Pharyngeal muscles stiffen and dilate this potentially collapsible segment of the upper airway. Changes in upper airway muscle activity can alter upper airway caliber and thereby influence the mechanical effects of respiratory pump muscle activation. Motor output to upper airway muscles is state dependent. The suppression of upper airway muscle activity during sleep is felt to play an important role in the pharyngeal airway closure during sleep in patients with obstructive sleep apnea. Electromyography, measurements of upper airway resistance, and upper airway imaging can be used to directly or indirectly evaluate upper airway muscles. Specific tests are of use in the clinical evaluation of specific disorders such as extrathoracic airway obstruction and stridor. Evaluation of the upper airway in the awake patient with obstructive sleep apnea (OSA) can identify the presence of anatomic abnormalities; however, upper airway evaluation during wakefulness is of limited value in determining airway function during sleep.

ELECTROMYOGRAPHY

Rationale

The upper airway serves as a common conduit of the respiratory, digestive, and phonatory systems. Whereas respiration requires patency of the upper airway throughout the respiratory cycle, swallowing and phonation are dependent on upper airway closure. During swallowing, upper airway muscles close the velopharyngeal sphincter and create a peristaltic-like constriction of the collapsible pharyngeal airway to propel the food bolus into the esophagus. Activation of upper airway muscles during phonation constricts valvelike structures at the velopharynx and glottis. To maintain airway patency during respiration, activation of upper airway muscles during inspiration dilates and stiffens the airway. Loss of upper airway muscle activity during sleep is felt to predispose to pharyngeal airway closure in patients with OSA (Figure 3). Electromyography has been used extensively in research studies to determine the respiratory-related activation of upper airway muscles and their role in the pathogenesis of OSA. In particular, information on time domains, coordination among muscles, and relative amounts of activity (integration) represents the parameters often used (*see* ELECTROMYOGRAPHY in Section 3 of this Statement).

Methodology

The techniques used to record the electrical activity of upper airway muscles are similar to those described in ELECTROMYOGRAPHY in Section 3 of this Statement. Hooked-wire electrodes can be inserted directly into the muscle of interest. A peroral approach is used to insert the electrode wires into muscles in the oral cavity and soft palate (5–11). A transcutaneous approach through the cricothyroid membrane is used to insert electrode wires into the cricothyroid and thyroarytenoid muscles (12, 13). A retractable needle catheter advanced through a fiberoptic scope has been used to insert electrodes into upper airway muscles that are not easily accessible through a peroral or transcutaneous approach (14, 15).

Given the complex anatomy of upper airway muscles and their relatively small size, it is important to verify the correct placement of the electrodes by having the subject perform voluntary maneuvers associated with activation and/or suppression of the particular muscle. The following maneuvers can be used to confirm correct electrode placement in some specific upper airway muscles: genioglossus, activation during tongue protrusion; pharyngeal constrictors, activation during swallowing; levator palatini, activation on the explosive “p” during phonation of repetitive “pa” sounds; thyroarytenoid, activation during a prolonged “e” sound or Valsalva maneuver; posterior cricoarytenoid, suppression during a prolonged “e” sound or Valsalva maneuver and phasic activation on inspiration.

Surface electrodes can be applied on the skin or mucosa overlying the muscle of interest. Surface electrodes can be applied to the skin in the submental area to record genioglossus activity and over the cartilaginous portion of the nose to record alae nasi activity (16, 17). Given the overlapping nature of upper airway muscles and their relatively small size, surface electrodes are likely to record electrical activity from more than one muscle (18). In contrast, intraoral mucosal surface electrode recordings of genioglossus muscle activity are very similar to those obtained from hooked-wire electrodes (19).

The electromyogram (EMG) can be analyzed to determine the presence or absence of respiratory-related activity by comparing it with a signal, such as flow or pressure, that indicates the phases of respiration (Figure 3). The moving average signal is used to quantify respiratory-related activity (20). As summarized by Platt and coworkers (20), the EMG ideally reflects global activity in a pool of motor neurons of the muscle. The moving average signal tracks a scaled version of the envelope of the raw EMG signal. This process is called amplitude demodulation. The moving average is readily interpretable as a continuous indication of the total electrical activity of the muscle, and digitization of this slow-output waveform requires much less storage space than the original raw signal. Peak activity is the maximum activity during a respiratory cycle above electrical zero. Tonic activity is the minimum activity during a respiratory cycle above electrical zero. Phasic activity during a respiratory cycle is peak minus tonic activity. Measurements are expressed in arbitrary units, as a percentage of control, or preferably as a percentage of the maximal activity obtained during a particular intervention or during the entire study.

Equipment

The equipment required for EMG recordings of upper airway muscles is similar to that described in EMG EQUIPMENT in Section 3 of this Statement.

Advantages

Electromyographic recordings provide an indirect assessment of efferent motor output to upper airway muscles. Numerous research studies have used upper airway electromyography to determine the role of upper airway muscles in the control of breathing. Electromyography allows the investigation of individual upper airway muscles. The pharyngeal airway is surrounded by 20 or more skeletal muscles. Electromyographic recordings have been obtained from only a minority of these muscles because of their relative inaccessibility. The genioglossus is the most frequently recorded upper airway muscle because of its easy accessibility. However, significant differences exist in the electromyographic activation of upper airway mus-

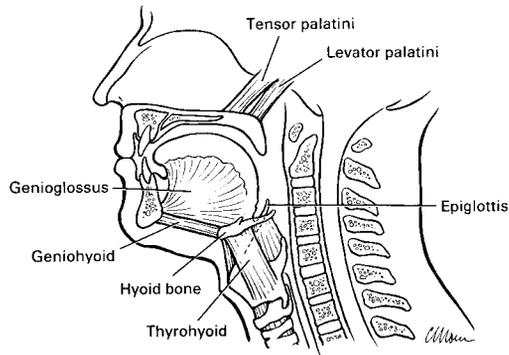


Figure 1. Some muscles that influence the pharyngeal airway. Contraction of muscles attaching to the hyoid bone can displace the anterior pharyngeal wall ventrally, helping to increase airway size. Muscles attached to the soft palate help regulate the route of breathing.

cles, and genioglossus activity may not always be representative of motor output to other upper airway or even pharyngeal muscles. For example, during quiet breathing, the pharyngeal constrictors rarely exhibit respiratory-related activity, whereas the posterior cricoarytenoid, a vocal cord abductor, uniformly exhibits phasic inspiratory activity, and the thyroarytenoid, a vocal cord adductor, exhibits phasic expiratory activity (7, 13, 21).

Disadvantages

Upper airway EMGs are technically difficult given the complex anatomy of these relatively small muscles combined with their often conflicting respiratory and nonrespiratory functions. Electromyography of a specific upper airway muscle does not reveal the mechanical effects of this electrical activation or how the electrical activation of a particular upper airway muscle interacts with the simultaneous electrical activation of other upper airway muscles to influence upper airway function. For example, during quiet breathing in wakefulness, the posterior cricoarytenoid, a vocal cord abductor, is tonically active throughout the respiratory cycle and exhibits phasic activity on inspiration. In contrast, the thyroarytenoid, a vocal cord adductor, is also tonically active throughout the respiratory cycle but exhibits phasic activation on expiration. Electromyography does not reveal the net effect of these simultaneously active counteracting muscles on vocal cord position. This example further emphasizes that electromyography of one specific upper airway muscle is not necessarily representative of others.

Another general weakness of electromyography is the inability to calibrate the recordings. As a result it is very difficult to compare EMG results from a specific muscle between days or between subjects (22). Some studies have attempted to circumvent this problem by expressing the data as a percentage of maximum activation (10, 11). Such comparisons, however, are problematic. Assuming that filtering and gains are fixed, EMG recording is affected by factors such as electrode site, distance between electrodes, and skin resistance (surface electrode) (22).

Normalization techniques are commonly used in muscle research to make comparisons across nonrespiratory muscle groups (22–26). However, in this regard, important differences exist between limb muscles and upper airway muscles. Limb muscles are attached to bone at both ends and as such, muscle length and orientation can be fixed so that the contractions are isometric. In addition, EMG studies of limb muscles generally normalize the data to known EMG–force relationships. Using wire electrodes to record from the biceps brachii, Komi and Biskirk (27) examined reproducibility within days with the wires unchanged and across days with reapplication of the

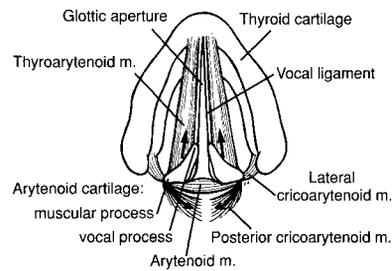


Figure 2. Intrinsic laryngeal muscles attached to the arytenoid cartilage help regulate the size of the glottic aperture.

wires. Reproducibility for the wire electrodes was 0.62, and this dropped to 0.22 when the electrodes were reapplied. Jonsen and Komi (28) also found poor reproducibility in the recorded EMG signal among four pairs of wire electrodes implanted in the same brachioradialis muscle.

Comparative studies of upper airway function during respiration have frequently used the genioglossus as a representative upper airway muscle (11, 22, 29). However, the genioglossus is fixed at only one end, with many degrees of freedom of movement. During protrusions against a balloon transducer to measure force, control of tongue length and orientation cannot be assured. Likewise, it cannot be assumed that the contraction during voluntary maneuvers is isometric or even consistent from trial to trial.

Applications

The clinical indications for electromyography of upper airway muscles are limited, and in general the technique should be reserved for research studies. Submental surface electrodes are used to record muscle activity as a qualitative signal during polysomnograms to stage sleep. Vocal cord EMG recordings are routinely performed in many centers to assess vocal cord paralysis. By contrast, in general, EMG of the upper airway muscles in research studies is the subject of a more quantitative evaluation and measurement.

UPPER AIRWAY RESISTANCE

Rationale

Changes in upper airway muscle activity can influence upper airway caliber (16, 30). Therefore, measurements of upper airway resistance can be used to indirectly assess changes in upper airway muscle activity. However, upper airway resistance is also influenced by changes in mucosal vasculature, body position (e.g., supine versus prone), head position (e.g., extended versus flexed), lung volume, and application of continuous positive airway pressure (31, 32). Upper airway resistance also has a direct but nonlinear relationship with flow.

Methodology

Resistance is calculated by measuring the pressure drop across the airway at a given flow. The upper airway includes the larynx, pharynx, and nasal and oral cavities. Upper airway resistance can be measured during oral or nasal breathing. Determination of total upper airway resistance requires measurement of the pressure drop between the subglottic airway and the nares or mouth. Resistance across the nasal, pharyngeal, or laryngeal segments of the upper airway can be determined by measuring the pressure drop across the particular segment of interest (33). Measurement of subglottic pressure requires the percutaneous or transnasal placement of a catheter attached to a pressure transducer into the extrathoracic trachea (34). Because of the technical difficulty of both methods, most studies of upper airway resistance exclude the laryngeal airway from their measurements.

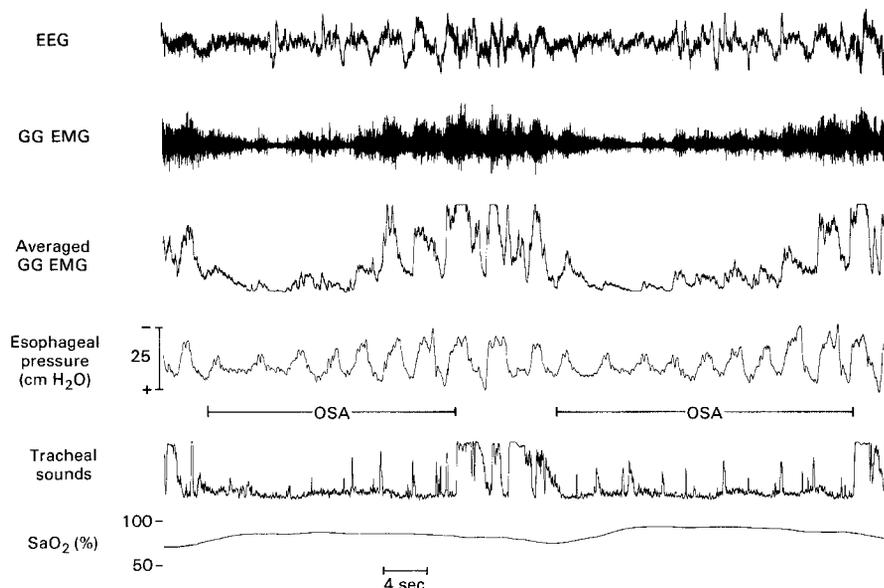


Figure 3. Electromyogram (EMG) of the genioglossus (GG) muscle during two obstructive apneas (OSAs) in nonrapid eye movement sleep. Airway closure (horizontal lines) is associated with a decrease in GG activation. GG activation progressively increases during the obstructive, apneas but airway reopening, as evidenced by the resumption of tracheal breathing sounds, does not occur until there is a large burst of GG activity. The time constant of the oxygen saturation signal delays the appearance of the oxygen saturation nadir until after airway reopening. EEG = electroencephalogram; SaO₂ = arterial oxygen saturation.

Supraglottic airway resistance is the pressure drop from the level of the epiglottis to the airway opening (mouth or nose) at a given flow (Figure 4). A face mask connected to a pneumotachograph is attached via an airtight seal to the individual to measure flow. Mask pressure, that is, pressure at the nares or mouth, is measured from a port in the mask. The intraluminal airway pressure measurement requires an invasive procedure. After topical anesthesia of one nasal passage, a catheter attached to a pressure transducer is advanced to the level of the epiglottis and secured at the nose. To eliminate the influence of kinetic energy, the pressure is measured from a side port near the sealed tip of the catheter. Because changes in the position of the catheter can influence the measurements, studies should be designed so that the control and experimental recordings are obtained without repositioning or removing the catheter. The catheter can be filled with air or water. An air-filled catheter has the potential to become occluded with fluid. Once in position, pressure from the water-filled catheter at zero flow must be obtained to determine the contribution of hydrostatic pressure to the measurements. Pressure transducer-tipped catheters have also been used to measure pharyngeal pressure. However, these catheters work best in a completely dry or fluid environment such as the intravascular space and esophagus. The repetitive wetting and drying of the transducer surface in the pharynx frequently results in an unacceptable drift of the signal.

Upper airway resistance is calculated by dividing the pressure drop across the airway at a particular flow by that flow. The units of measurement are cm H₂O · L⁻¹ · second⁻¹. It is important to state whether the measurements are obtained during inspiration or expiration as, even at the same flow, upper airway resistance during inspiration is not the same as upper airway resistance during expiration. Measurements on different breaths should also be obtained from the same portion of inspiration or expiration as the pressure–flow relationships during each of the two respiratory phases may show hysteresis.

An alternative method used to quantify upper airway resistance is to describe the entire pressure–flow curve on inspiration or expiration by fitting the pressure and flow data to a second-order equation. Numerous equations have been used, including the Rohrer equation: $P = K_1V + K_2V^2$ (Equation 1), where P is pressure, V is flow, and K_1 and K_2 are constants. The presence of two constants in this equation makes statistical comparisons difficult and, therefore, another frequently

used equation is: $P = KV^2$ (Equation 2). Changes in upper airway resistance can be assessed indirectly by measuring total pulmonary resistance with the passage of an esophageal balloon. This method is valid if resistance across the lower airways remains constant. Therefore, these measurements must be obtained at a given lung volume.

The measurement of upper airway resistance requires two pressure transducers to measure the pressure drop across the airway and a pneumotachograph connected to a differential pressure transducer for the measurement of flow. Pressure is calibrated in cm H₂O and flow in L · second⁻¹. As the measurements are obtained under dynamic conditions, the three signals should remain in phase up to a frequency of 10 Hz.

Advantages

When properly controlled, measurements of upper airway resistance can provide a global assessment of the effect of changes in upper airway muscle activity on upper airway function.

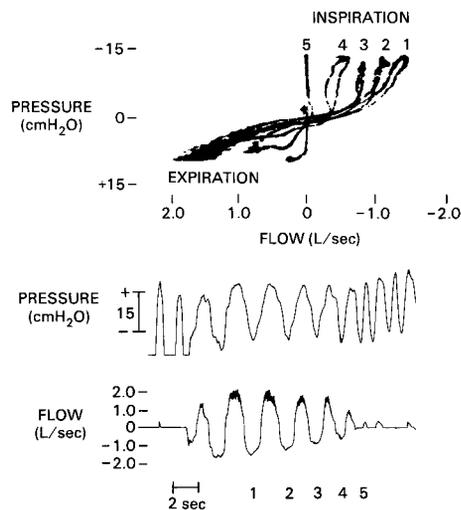


Figure 4. Changes in upper airway resistance in the breaths preceding an obstructive apnea in nonrapid eye movement sleep. The supraglottic pressure–flow plot shows a progressive increase in inspiratory resistance, i.e., narrowing of the pharyngeal airway, on the four breaths preceding complete airway closure on inspiration (breath 5).

Disadvantages

Upper airway resistance is only an indirect measurement of upper airway muscle activity. Measurements must be carefully controlled as upper airway resistance can be affected by many other factors (*see* previous sections). Measurement of upper airway resistance requires an invasive procedure that is of low morbidity.

Applications

The determination of upper airway resistance is a clinical research technique that has been used to assess the effect of changes in chemical drive and sleep-wakefulness states on upper airway size and muscle activity. Nasal rhinometry, the measurement of nasal airway resistance, is used by ear, nose, and throat physicians to assess the patency of the nasal passages.

INDIRECT LARYNGOSCOPY

Rationale

Visualization of the glottis by indirect laryngoscopy can confirm vocal cord paralysis resulting from the loss of intrinsic laryngeal muscle innervation. All the intrinsic laryngeal muscles, except the cricothyroid, are innervated by the recurrent laryngeal nerve. Loss of motor innervation from the recurrent laryngeal nerve, as may occur secondary to a mediastinal tumor or as a complication of thyroidectomy, results in vocal cord paralysis and hoarseness. With bilateral vocal cord paralysis, the cords are positioned close to the midline and show no abduction during inspiration. Audible stridor is almost invariably present. Stridor also occurs during the laryngospasm and/or laryngoedema that can be encountered immediately after removal of an endotracheal tube.

Methodology

Indirect laryngoscopy is performed in the awake patient by advancing a small angled mirror through the open mouth to the soft palate while protruding the subject's tongue. Illumination of the angled reflecting surface allows visualization of the glottic aperture through the oral cavity. Topical anesthesia of the soft palate can help minimize the gag reflex. As the cords are being visualized, the patient is instructed to vocalize an "e" sound that normally adducts the vocal cords. Failure of one cord to adduct indicates ipsilateral vocal cord paralysis. In the case of bilateral vocal cord paralysis, both cords are close to the midline and show no abduction during inspiration and may even show paradoxical movement with respiration due to the effects of changes in intraluminal pressure on inspiration and expiration. Direct laryngoscopy is performed under general anesthesia. With the advent of fiberoptic scopes, this latter technique is rarely indicated in adults to assess the presence or absence of vocal cord paralysis.

Advantages

Indirect laryngoscopy is an easy technique that requires little equipment. It is performed in awake patients. It provides a direct visual assessment of vocal cord movement and is the technique of choice for confirmation of vocal cord paralysis if a fiberoptic instrument is not available.

Disadvantages

As a visual assessment of intrinsic laryngeal muscle activity, indirect laryngoscopy is limited to determining the presence or absence of motor innervation. Bilateral but asymmetrical movement of the vocal cords is difficult to quantify. This finding may suggest vocal cord paresis but can also arise from other conditions.

FIBEROPTIC IMAGING

Rationale

Fiberoptic imaging can be performed in place of indirect laryngoscopy for detection of vocal cord paralysis. In clinical research, fiberoptic imaging is used to evaluate the mechanical effects of laryngeal and pharyngeal muscle activation on upper airway size. Fiberoptic imaging has also been used in research laboratories to assess upper airway mechanics in the absence of upper airway muscle activity (35, 36).

Methodology

Fiberoptic imaging is an invasive procedure that provides direct visualization of the upper airway. However, it is easily performed in the awake adult patient and is associated with very little discomfort. After topical anesthesia of one nasal passage, the fiberoptic scope is advanced through the nares and along the floor of the nasal passage into the pharyngeal airway. Depending on the outer diameter of the scope, prior application of a nasal decongestant may be of benefit. The glottic aperture is easily visualized from the hypopharynx. No attempt should be made to touch or pass through the unanesthetized glottis during this visual examination.

Equipment

Application as a diagnostic technique requires a fiberoptic nasopharyngoscope, optimally with an outer diameter of 4 mm or less, attached to a light source. Physicians performing the procedure should be specially trained in this technique.

When using fiberoptic imaging as a research technique to quantify changes in upper airway dimensions, it is necessary to have a camera attached to the fiberoptic scope to obtain videotape recordings. Individual frames of the videotape can then be analyzed offline, ideally with a personal computer frame grabber and digitizing software. Methods have been described to calibrate the measurements in metric units (36, 37).

Advantages

Compared with indirect laryngoscopy, fiberoptic examination of the upper airway allows a more thorough examination of the upper airway. If a video camera is available, the physical findings can be documented on videotape. This technique is used for clinical diagnostic purposes.

Disadvantages

The fiberoptic equipment is expensive. Standardized techniques should be instituted to sterilize the scope between procedures. Passage of the fiberoptic scope may be associated with a vasovagal reaction associated with hypotension and loss of consciousness. Adequate supportive care should be available in the event of this complication.

Use of fiberoptic imaging of the upper airway in clinical research is laborious even with computer-assisted analysis. In addition to difficulties with calibration of measurements in metric units, the lack of depth perception on the videotape images makes it particularly difficult to detect the edge of the pharyngeal airway that should be measured. Movement and clouding of the scope are other technical difficulties frequently encountered during research studies.

COMPUTED TOMOGRAPHIC SCANNING

Rationale

Computed tomographic (CT) scanning allows imaging of the upper airway size and anatomy (38, 39). The technique may

also demonstrate related structural abnormalities, which may impinge on the upper airway.

Equipment

Routine CT scanners are used (*see* Section 7 of this Statement). Three-dimensional reconstruction may be helpful.

Advantages

Computed tomography is widely available, it is noninvasive, and it provides images of the whole upper airway.

Disadvantages

The subject receives radiation exposure. Subjects are usually studied awake, whereas the object of investigation is often the site of upper airway narrowing during sleep.

Applications

Computed tomography is of limited value in determining the site of obstruction of the upper airway, as this must be done during sleep; the site of maximal narrowing during wakefulness may not be the site of occlusion during sleep. Faster acquisition CT scanners hold the promise of providing not just structural images of the upper airway but also the ability to assess upper airway function.

MAGNETIC RESONANCE IMAGING

Rationale

Magnetic resonance imaging (MRI) scanning allows imaging of the upper airway size and anatomy (40). The technique may also demonstrate related structural abnormalities that may impinge on the upper airway (41–43).

Equipment

Routine MRI scanners are used (*see* Section 7 of this Statement).

Advantages

MRI is widely available. It is noninvasive and provides images of the whole upper airway. It is not ionizing and can identify adipose deposits around the airway.

Disadvantages

Slow scanning times on many scanners mean that several breath cycles are averaged. Subjects are usually studied awake, whereas it is the site of upper airway narrowing during sleep that is often the object of investigation.

Applications

Magnetic resonance imaging is of limited value in determining the site of obstruction of the upper airway, as this must be done during sleep; the site of maximal narrowing during wakefulness may not be the site of occlusion during sleep. Like CT, MRI holds the promise of providing not just structural images of the upper airway but also the ability to assess upper airway function.

ACOUSTIC REFLECTION

Rationale

Acoustic reflection allows quantification of upper airway caliber by noninvasive means. The subject breathes through a mouthpiece attached to a microphone that emits sound waves. The reflected impulse is analyzed to provide a plot of the cross-section of the upper airway as a function of distance from the mouth (44, 45).

The system requires a loudspeaker, microphone, wave tube, mouthpiece shutter system, and personal computer. Commercial systems are available.

Advantages

Acoustic reflection is noninvasive, nonirradiating, inexpensive, compact, and can be performed rapidly. It can be used in large numbers of subjects in a variety of different body postures (46).

Disadvantages

Acoustic reflection cannot be used to visualize the retropalatal airway and cannot be used during sleep.

Applications

Acoustic reflection is applicable to population or physiological studies of upper airway size. It is of little value to individual patients.

FLOW-VOLUME LOOPS

Rationale

Flow-volume loops have the potential to be used to detect upper airway obstruction during wakefulness as a predictor of airway occlusion during sleep.

Equipment

Recording of flow-volume loops requires a body plethysmograph, rapid response spirometer, or pneumotachograph (*see* Section 1 of this Statement).

Advantages

Flow-volume loops can be measured quickly. The equipment is widely available and measurements can be made during wakefulness.

Disadvantages

Flow-volume loops cannot usefully distinguish patients with sleep apnea from others (47, 48).

Applications

The only clinical role is as a quick method of assessing whether a gross mass lesion is present around the upper airway. It is not of routine value.

POLYSOMNOGRAPHY

Rationale

Polysomnography is the study of several physiological variables during sleep, including the recording of sleep itself. The precise items recorded will vary but usually include electroencephalography, electro-oculography, electromyography, respiratory pattern, snoring, oxygen saturation, transcutaneous carbon dioxide tension, electrocardiography, and body posture (49–51). This allows the recognition of events that occur during sleep and offers the advantage over other techniques that sleep can be identified with certainty.

In patients with marked respiratory muscle weakness, detection of respiratory movement during obstructive events from external sensors may be very difficult or impossible. Indeed, true obstructive events may be scored even by skilled observers as “central.” There are three ways around this problem. First, esophageal pressure may be recorded during polysomnography in all such patients (52, 53). Second, flattening of the flow-time curve during these events in sleeping subjects may be helpful (54). Third, some centers have adopted the approach that patients with multiple “central” apneas should be treated with continuous positive airway pressure to determine whether these events respond to continuous positive airway pressure.

Equipment

Computerized systems are generally used, which allows the recording of the all-night data on to optical or compact disk formats. Detection of fluctuation in nasal pressure during inspiration and expiration reflects changes in inspiratory and expiratory airflow and therefore is a promising method for the detection of hypopneas (50, 55). Studies have shown that nasal pressure is more sensitive than thermal sensors for detecting hypopneas and that the square root of the pressure signal improves the estimate of airflow (56, 57).

Advantages

Polysomnography allows identification of sleep. It can detect coincidence of different events, such as respiratory change and sleep disturbance. It is possible to identify the extent of decline in arterial oxygen saturation (SaO_2) during different sleep stages. The sequelae of hypoventilation due to respiratory muscle insufficiency during sleep can be identified.

Disadvantages

Polysomnography is expensive relative to limited sleep study equipment, both in terms of capital and staff cost. Expert technical staff are needed to perform and analyze the studies.

Applications

Polysomnography is a valuable method of identifying sleep-related hypoventilation in patients with respiratory muscle problems and whether they have related sleep apnea-hypopnea syndrome as well. It is useful in some patients to monitor progress on treatment, such as noninvasive positive pressure ventilation.

MUSCLE BIOPSY

Rationale

Differences in upper airway muscle fiber composition have been reported in sleep apnea-hypopnea syndrome patients (58, 59).

Technique

Muscle biopsy is not generally performed as a diagnostic test, and is reserved for research examination of resected specimens.

Advantages

Muscle biopsy has no clinical applications.

Disadvantages

It is invasive and painful.

Applications

At present, applications are limited to research.

STRENGTH, FATIGUE, AND ENDURANCE OF UPPER AIRWAY MUSCLES

Rationale

It is not known whether strength, fatigue, and endurance of upper airway muscles are factors in sleep-related upper airway obstruction (54).

Equipment

A force transducer and EMG (*see above*) are required.

Disadvantages

The tongue is the only upper airway muscle for which force can be measured.

Applications

At present, applications are limited to research.

SITE OF PHARYNGEAL AIRWAY CLOSURE DURING SLEEP

Rationale

Loss of upper airway muscle activity during sleep is thought to have an important role in the pathogenesis of obstructive sleep apnea. However, because of the differences in upper airway muscle activity between wakefulness and sleep, studies of the upper airway during wakefulness are not capable of predicting the site of upper airway closure during sleep. Airway closure during sleep in patients with sleep apnea can occur at different sites in the pharyngeal airway (36, 60, 61). The primary site of closure is most frequently located in the velopharynx but can also occur in the oro- and/or hypopharynx. Determination of the site of airway closure is important, as studies indicate that it determines the outcome of uvulopalatopharyngoplasty (62, 63). Tests that determine the site of upper airway closure during sleep cannot be used to assess upper airway muscle function, as airway closure during sleep is also dependent on other factors, including the transmission of subatmospheric intrathoracic pressure into the pharyngeal airway and closing pressure (i.e., the pressure at which the pharyngeal airway closes in the absence of upper airway muscle activity and respiratory effort) (15, 27). Factors that narrow the pharyngeal airway raise closing pressure. Normally, closing pressure is subatmospheric. In patients with OSA, closing pressure is usually positive, that is, a positive intraluminal pressure is required during sleep to maintain pharyngeal airway patency. The site of airway closure can be determined during sleep with the placement of catheters attached to pressure transducers in the esophagus and at different levels in the pharyngeal airway (57). The site of pharyngeal airway closure during sleep can also be determined by imaging the upper airway with a fiberoptic scope or by fast acquisition MRI or computed axial tomography scans (36, 64).

CONCLUSION

Structurally, the upper airway consists of several valves (nares, mouth, soft palate, collapsible pharynx, epiglottis, and glottis) that are regulated in part by upper airway muscles. These valves allow airway closure during deglutition and phonation and regulate airway patency during respiration.

Two of the most important upper airway disorders affecting respiration are laryngeal narrowing and OSA. Laryngeal narrowing can result from laryngospasm and vocal cord paralysis. Tests of upper airway function that detect laryngeal narrowing and dysfunction include indirect laryngoscopy, fiberoptic imaging, electromyography, and flow-volume loops. The upper airway closure in the vast majority of patients with OSA occurs in the pharynx with suppression of upper airway muscle activity during sleep.

Although polysomnography is not a specific test of upper airway function, it is the accepted method to diagnose this repetitive closure of the pharyngeal airway during sleep. A plethora of techniques have been developed to assess respiratory-related upper airway structure and function, ranging from measurements of upper airway resistance to MRI. However, in general, these do not have a role in the clinical assessment of upper airway function and should be reserved for the research laboratory.

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9. Tests of Respiratory Muscle Function in Children

PHYSIOLOGY OF THE DEVELOPING RESPIRATORY PUMP

In early life the ventilatory response to loaded breathing is limited. Ventilatory failure can occur in newborns and infants due to immaturity of the chest wall and respiratory muscles, poor coupling between thoracic and abdominal movements, and upper airway dysfunction. Furthermore, infants spend a large proportion of time asleep, with full-term newborns spending more than 50% of their time in rapid eye movement (REM) sleep and premature infants an even higher proportion of time in REM (1).

At birth, the ribs extend almost at right angles from the vertebral column. As a result, the rib cage is more circular than in adults (2) and, consequently, lacks mechanical efficiency. In adults, the volume of the rib cage can be increased by elevating the ribs. In infants, the ribs are already elevated, and this may be one reason why motion of the rib cage during room air breathing contributes little to tidal volume (V_T) (3). The diaphragm appears flattened with a very wide angle of insertion on the rib cage, resulting in the absence of an area of apposition (4). The orientation of the ribs does not change substantially until the infant assumes the upright posture. Concurrently, there is progressive mineralization of the ribs. Between 1 and 2 years of age (3), rib cage contribution to tidal breathing reaches a value that approximates that reported in adolescents during non-REM (NREM) sleep (5). Changes in shape and structure with advancing postnatal age play a central role in stiffening the rib cage. A high chest wall compliance (C_{cw}) relative to lung compliance (C_L) is an inherent characteristic of the newborn mammal (6). In infants, outward recoil of the chest wall is very low. Consequently, the static passive balance of forces between the lung and the chest wall would dictate a very small functional residual capacity (FRC). There are compelling reasons to believe that dynamic end-expiratory lung volume in newborns and infants is substantially above the passively determined FRC. It has been shown that in newborns, in contrast to adults, expiration is terminated at substantial flow rates (7). In addition to foreshortened expiratory time, infants use postinspiratory activity of the diaphragm (8) and expiratory glottic narrowing to actively slow expiration (9). Dynamic elevation of end-expiratory lung volume above passive FRC persists until around the end of the first year of life (10).

With growth, there is a progressive increase in the bulk of respiratory muscles. There are also important changes in the fiber composition, fiber size, and oxidative capacity and contraction characteristics of the diaphragm (11). Mean cross-sectional area of all fiber types increases postnatally. Maximal pressures exerted by infants and even children are surprisingly high compared with adults (12–14). This is probably related to the small radius of curvature of the rib cage, diaphragm, and abdomen that, according to the Laplace relationship, converts small tensions into relatively high pressures (12). However, the inspiratory force reserve of respiratory muscles is reduced in infants with respect to adults because inspiratory pressure demand at rest is greater. High pressure demand in infants is due to high minute ventilation and to high weight-corrected metabolic rate (15–17).

Fatigability of neonatal respiratory muscles as compared with adult muscles remains a controversial issue. The paucity of fatigue-resistant Type I fibers, the high proportion of fatigue-susceptible Type IIc fibers, and low oxidative capacity of the neonatal diaphragm suggest that the muscle may be rela-

tively prone to fatigue. An *in vivo* study in rabbits found that diaphragmatic fatigue occurred more quickly in neonatal than adult animals (18). However, other *in vitro* and *in vivo* animal studies have shown the opposite (19).

Chest wall muscle contraction helps to stabilize the compliant infant rib cage, minimizing inward displacement of the rib cage by diaphragmatic contraction. However, when the stabilizing effect of intercostal muscles is inhibited, such as during REM sleep, paradoxical inward motion of the rib cage occurs during inspiration (20, 21). During REM sleep, the diaphragm dissipates a large fraction of its force in distorting the rib cage rather than effecting volume change. This increase in diaphragmatic work of breathing (22) represents a significant expenditure of calories, and may contribute to the development of diaphragmatic fatigue and ventilatory failure. Furthermore, acidosis and hypoxia, both of which increase muscle fatigability, are not uncommon in sick premature infants.

As in adults, upper airway muscles actively dilate and stiffen the airway during inspiration in infants and children. As cited above, laryngeal adduction is prominent during expiration in infants, effectively increasing the time constant for lung emptying. Upper airway muscles, except for the nasal and laryngeal abductors (alae nasi and posterior cricoarytenoid muscles), become atonic during REM sleep, predisposing the upper airway to collapse during inspiration and possibly resulting in decreased end-expiratory lung volume due to loss of laryngeal airflow braking. The sparing of active nasal and laryngeal dilation during inspiration in REM sleep presumably decreases the work of breathing by maintaining low airflow resistance in the upper airway. The negative pressure required to collapse the upper airway appears to be low in the neonate (23) (approximately -3 cm H_2O), increasing in children to about -20 cm H_2O (24) and returning to levels similar to those in early infancy with adulthood (25). Children and adults with obstructive sleep apnea exhibit airway collapse at pressures at or near 0 cm H_2O , suggesting that they have a more compliant upper airway than do normal subjects (24, 25).

TESTS OF RESPIRATORY MUSCLE FUNCTION

Equipment and Measurement Conditions

Maximal respiratory muscle pressures in infants and children are similar to those encountered in adults (*see* 26–28). The equipment used to measure respiratory muscle and chest wall function must be modified, however, to accommodate the smaller flow rate and V_T of infancy and childhood. The following equipment should be available: pressure transducers (flow, ± 2 cm H_2O ; esophageal pressure [P_{es}] and airway opening pressure [P_{ao}], ± 50 cm H_2O); transducer amplifiers; heated pneumotachographs (0–12 L/minute for neonates to 6 months, 0–30 L/minute for 3 months to 2 years); esophageal balloons; catheters (8F, internal diameter of 2 mm or 6F, internal diameter of 1.6 mm); face masks; timed shutter with pressure port; and multichannel strip chart recorder or computer screen, central processing unit, analog-to-digital converter, and printer. Because P_{es} may not adequately represent pleural pressure in the presence of high C_{cw} , all esophageal balloon and catheter measurements in infants should be validated by an “occlusion test” (29, 30). Equipment dead space should not exceed 1.5 ml/kg body weight.

For respiratory inductive plethysmography in children, the following are required: rib cage (RC) and abdominal (AB)

bands of a size appropriate for the subject's chest wall; a source of oscillatory current; signal processing equipment necessary to produce voltage output proportional to changes in RC and AB cross-sectional area. Also required is appropriate recording equipment such as strip chart, oscilloscope, or analog-to-digital converter with computer screen, central processing unit, and printer; or Respicomp, Respitrace PT (Non-Invasive Monitoring Systems [Miami Beach, FL], with computer hardware and analysis software integrated into system). Calibration of the respiratory inductive plethysmograph equipment is needed to measure V_T (spirometer or pneumotachograph). Frequency-amplitude response of respiratory inductive plethysmography has been shown to be flat to 13 Hz (31). The equipment necessary for the measurement of surface electromyograms (EMGs) in infants and children is identical to that used in adults (*see* EMG EQUIPMENT in Section 3 of this Statement).

At less than 5–7 years of age, children are not able to cooperate with lung function testing. For lung function testing of infants, a sedative such as chloral hydrate is usually administered. Therefore, the laboratory should be quiet, dimly lit, and conducive to sleeping. Sedation should not be given to infants with known upper airway obstruction. Continuous pulse oximetry should be measured in all sedated infants. Supplemental oxygen administration may be required, resuscitation equipment should be available, and personnel should be trained in pediatric cardiopulmonary resuscitation. Infants should not be discharged from the pulmonary function laboratory until fully awake.

For most tests in infants, the supine position is the position for which normal standards are defined. The neck should be in a neutral or a slightly extended position. The infant should be in clinically determined quiet sleep.

For tests in older children requiring maximal efforts, such as maximal respiratory muscle strength assessment, the technicians should be experienced in working with young children and in striking the right balance between exhorting the child to give his/her best effort, and not frightening the child. Other measurement conditions are identical to those for adult pulmonary function laboratories.

Chest Wall Compliance

Rationale. The high Ccw of infants influences FRC and ability to withstand respiratory loading. Certain disease states, e.g., neuromuscular disease, bony thoracic abnormalities, and intra-abdominal processes such as ascites, can alter Ccw.

Methods. Children greater than 7 years of age can probably understand the directions necessary for Ccw measurement as described for adults in Section 6 of this Statement, although passage of esophageal balloons in this age range is not routine. The measurement of passive Ccw in younger children and infants is technically difficult because of their inability to cooperate. To measure passive Ccw, the respiratory pump muscles must be inactive, or as close to inactive as possible. Several methods to achieve this have been described:

1. Passive Ccw has been measured under quasistatic conditions, during mechanical ventilation (MV) in preterm and full-term infants (32). Because during MV, pressure inside the chest wall is pleural pressure (approximated by an esophageal balloon or catheter), and pressure outside the chest wall is atmospheric (referenced to zero), the pressure difference across the chest wall is P_{es} . With an esophageal balloon in place, measurements of P_{es} at points of zero flow (end inspiration [$P_{I,ao}$], following a 1.0-second end-inspiratory hold and end expiration [$P_{E,es}$]) are made, and the difference is divided into that breath's V_T . Chest wall compliance is then measured as: $C_{cw} = V_T / (P_{I,ao} - P_{E,es})$.

2. Passive dynamic Ccw has been measured in spontaneously breathing sedated infants and toddlers (33). An anesthesia bag and mask is placed over the infant's mouth and nose, and gentle insufflations are given until the infant is no longer making respiratory efforts, as indicated by surface diaphragmatic EMG electrodes or by a conversion of P_{es} deflections from negative to positive during inspiration. With an esophageal catheter in place, C_L is calculated as: $C_L = V_T / [(P_{I,ao} - P_{I,es}) - (P_{E,ao} - P_{E,es})]$, where $P_{I,ao}$ and $P_{E,ao}$ are pressures at the airway opening during inspiration and expiration, respectively.
3. Respiratory system compliance (C_{rs}) is calculated as: $C_{rs} = V_T / (P_{I,ao} - P_{E,ao})$, and Ccw is calculated as: $1/C_{cw} = 1/C_{rs} - 1/C_L$.
4. Passive static Ccw has been measured in preterm infants (32). After an end-inspiratory occlusion, P_{es} rises to a plateau in parallel with P_{ao} , because the lung is at isovolume and transpulmonary pressure (P_{tp}) remains constant. After release of the occlusion, P_{es} decreases as lung volume decreases. Ccw is calculated as: $C_{cw} = dV / (P_{I,es} - P_{E,es})$, where dV is the change in lung volume.

This technique can be performed in spontaneously breathing infants, and relies on an intact Hering-Breuer reflex causing relaxation of the chest wall after an end-inspiratory occlusion.

Advantages and disadvantages of Ccw measurements. Measurements of chest wall mechanics are useful in assessing overall respiratory function in infants, because the chest wall is highly compliant in this age range. This leads to inefficient chest wall motion and predisposes to fatigue. These tests should probably be performed only in the research setting, because of their technical difficulty and requirement for absolute chest wall muscle relaxation to achieve interpretable results.

Normal values and alterations in disease. Chest wall compliance has been measured in preterm and full-term infants, toddlers up to the age of 3 years, school age children and adolescents, and in young adults (*see* Table 1). Because different techniques have been used in each age range, it is difficult to compare estimates of Ccw with growth. Size correction is also important; as with C_L , Ccw must be corrected for resting lung volume, or, if that is not available, for body weight. Another way that Ccw can be compared between different age groups is by comparison with C_L . The chest wall stiffens progressively with age. In preterm and full-term infants, Ccw is about three to six times greater than C_L (32–36); in school age children, Ccw is approximately twice C_L (37); in adolescents and adults, Ccw is approximately equal to C_L and in the elderly, Ccw is approximately half C_L (38) (Table 1). Chest wall compliance is abnormally increased in infants and toddlers with neuromuscular disease (39). In contrast, Ccw is abnormally decreased in adults with neuromuscular disease, possibly secondary to joint contractures due to years of low- V_T breathing (40). Although Ccw is presumably diminished in restrictive chest wall disorders such as scoliosis and asphyxiating thoracic dystrophy, physiologic measurements are few. Likewise, the effects of abdominal disorders such as obesity, ascites, and prune belly syndrome on Ccw are poorly understood.

Clinical application. Measurement of Ccw is not performed in routine clinical practice, but has been reported in clinical research.

Maximum Inspiratory and Expiratory Pressures

Rationale. Mouth $P_{I,max}$ and $P_{E,max}$ measurements are used to study respiratory muscle strength.

Methods. Accurate mouth $P_{I,max}$ and $P_{E,max}$ measurements can be obtained at approximately 6–7 years of age.

Children must be well instructed before the test. Pressures are measured with the child seated and wearing a noseclip. A cylindrical mouthpiece is recommended, as $P_{E,max}$ has been shown to be significantly lower when a scuba-type mouthpiece is used instead of a cylindrical one (41). A small leak, created by placement of a needle (1 mm in diameter by 15 cm long) in the mouthpiece, is recommended to eliminate glottic closure and artificially high $P_{I,max}$ (13, 42). Each effort should be maintained for at least 1 second. Simultaneous measurement of the lung volume at which maximal pressure is generated is recommended, using either a body plethysmograph or a spirometer. $P_{I,max}$ measurements at residual volume (RV) and $P_{E,max}$ measurements at total lung capacity (TLC) require two successive cooperation-dependent maneuvers. However, $P_{I,max}$ or $P_{E,max}$ at the end of a normal expiration, i.e., at FRC, requires only one cooperation-dependent maneuver, thereby limiting the potential for fatigue.

Advantages. Maximum inspiratory and expiratory measurements in children are simple and noninvasive.

Disadvantages. The disadvantages of $P_{I,max}$ and $P_{E,max}$ measurements in children are their variability and a learning effect. When fewer than five maneuvers were performed, the coefficient of variation (CV) was found to be 9% and was independent of maneuver, age, and sex (13). Studies in healthy children and in children with various respiratory disorders have shown a learning effect (43, 44). With multiple $P_{I,max}$ and $P_{E,max}$ determinations, i.e., more than 20 attempts, pressures were significantly higher than with a short $P_{I,max}$ and $P_{E,max}$ method, i.e., fewer than five attempts (43, 44). In routine practice, it is recommended to perform five measurements or more until two reproducible maximal values are obtained. In healthy children tested seated, $P_{I,max}$ and $P_{E,max}$ have been shown to be independent of the thoracoabdominal configuration assumed during the maneuver (45).

Normal values. Table 2 shows normal values of $P_{I,max}$ and $P_{E,max}$ in children and adolescents (13, 41, 42, 46, 47). In a number of studies the level of lung volume has not been controlled during the test. Only one study provides normal values for $P_{I,max}$ at FRC. Maximum inspiratory and expiratory pressures increase with age in children (15, 43), and are lower in girls than in boys even before puberty. However, the increase in $P_{I,max}$ and $P_{E,max}$ with age underestimates the increase in

net muscle force, i.e., the product of pressure and surface area over which the pressure is applied (13).

Clinical application. Measurements of $P_{I,max}$ and $P_{E,max}$ are useful in children and/or adolescents with neuromuscular disorders (48–50), with cystic fibrosis (51–55), and with chronic obstructive pulmonary disease (16). In the case of hyperinflation, $P_{I,max}$ and $P_{E,max}$ values have to be corrected for the absolute volume at which measurements were made (16, 53). $P_{I,max}$ and $P_{E,max}$ measurements may be useful in malnourished children (53). Maximum inspiratory pressure at FRC provides an assessment of the inspiratory maximal reserve of the respiratory muscles during quiet breathing in children (16, 55, 56). It has been proposed that inspiratory muscle strength be assessed by the measurement of the maximal pressure obtained while breathing 5% CO_2 at the time of weaning from MV in infants and children (57).

Nasal Sniff Pressures

Nasal sniff pressure ($P_{nas,sn}$) is an established test of inspiratory muscle strength in adults (see Section 2 of this Statement). The technique has been applied to children, normal values have been reported (58), and this simple noninvasive measure has considerable promise in pediatric practice.

Crying Pressures: Crying $P_{I,max}$ and $P_{E,max}$

Rationale. Mouth pressures generated during crying efforts may provide an index of respiratory muscle strength in awake infants.

Measurements. Firm application of a rubber cushion mask against the face is sufficient to elicit crying efforts in the awake infant (14). An artificial leak in the mask has been used to prevent glottic closure. Airway occlusions are performed at the end or at the beginning of a crying effort to measure crying $P_{I,max}$ and $P_{E,max}$, respectively. Only peak crying $P_{I,max}$ without a pressure plateau is available during crying. Crying $P_{E,max}$ can be measured at a pressure plateau sustained for 1 second.

Advantages. The main advantage is simplicity.

Disadvantages. Disadvantages include the following: (1) no determination of lung volume during the test; (2) gross potential pressure leaks around the mask; (3) artificially high peak crying $P_{I,max}$ if no needle leak in the mask to prevent glottic closure; and (4) relatively high CVs, 11 ± 4 and $9 \pm 3\%$ (mean \pm SD), respectively, as shown in one group of healthy infants.

Normal values. Normal values have been provided in a large group of healthy infants from the first month to the end of the second year of life (14). Peak crying $P_{I,max}$ was 118 ± 21 cm H_2O and independent of age and sex. However, overestimation of peak crying $P_{I,max}$ may have occurred because glottic closure was not prevented. Crying $P_{E,max}$ was 125 ± 35 cm H_2O and was related to body weight.

Clinical application. Crying pressures may be useful in infants with neuromuscular disease (59).

Crying Pressures: Crying Transdiaphragmatic Pressure

Rationale. Crying transdiaphragmatic pressure (P_{di}) measurements allow assessment of diaphragm muscle strength during inspiratory crying efforts in infants.

Measurements. Accurate recordings of P_{es} and gastric pressure (P_{ga}) are essential.

Advantages. Transdiaphragmatic pressure is specific for diaphragmatic contraction.

Disadvantages. Disadvantages include (1) the fact that reliability of P_{di} requires accurate measurements of P_{es} ; and (2) similar limitations to crying $P_{I,max}$ with respect to variability in lung volume at which P_{di} is measured during crying efforts.

TABLE 1. NORMAL VALUES OF CHEST WALL COMPLIANCE WITH AGE

First Author	Reference No.	Age Range (yr)	Ccw		
			ml/cm H_2O	ml/cm H_2O /kg	Ccw/ C_L
Gerhardt	32	Preterm	5.7 ± 1.4	(3–10)	
Papastamelos	33	Infancy	17.4 ± 6.7	(2–5)	(3–6)
				2.8 ± 0.87	(1–2)
		1–3	20.1 ± 7.7	(1–3)	
				2.0 ± 0.51	(1–2)
Sharp	37	5–16			
		5	78	4	
		8	106	4	
		12	156	4	
		16	184	3	
Mittman	38	Adulthood			
		20–29	350	5	2
		30–39	250	3.5	1.2
		40–49	250	3.5	1
		50–59	250	3.5	0.8
		60–69	136	2	0.7
		70–79	210	3	0.7

Definition of abbreviations: Ccw = chest wall compliance; C_L = lung compliance. Values are means or means \pm SD. Values in parentheses are ranges.

TABLE 2. NORMAL VALUES OF MAXIMAL INSPIRATORY AND EXPIRATORY PRESSURES IN HEALTHY CHILDREN AND ADOLESCENTS

Reference	Age (yr)	P _{I,max} (cm H ₂ O)		P _{E,max} (cm H ₂ O)	
		At RV	At FRC	At TLC	At FRC
Males					
47	8			79	
13		77 ± 24	70 ± 24	99 ± 23	83 ± 16
47	10			90	
13		105 ± 27	97 ± 22	123 ± 27	100 ± 23
47	11–13			90–101 [‡]	
13		114 ± 27	105 ± 23	161 ± 37	132 ± 33
41*		130 ± 16		176 ± 24	
46	13–17	111 ± 34		131 ± 30	
47				107–129 [‡]	
42		107 ± 26		114 ± 35	
41 [†]		126 ± 22		166 ± 44	
Females					
47	8			62	
13		71 ± 29	59 ± 21	74 ± 25	65 ± 18
47	10			90	
13		71 ± 29	59 ± 21	74 ± 25	65 ± 18
47	11–13			77–86 [‡]	
13		108 ± 29	98 ± 25	126 ± 32	101 ± 26
41*		112 ± 20		138 ± 31	
46	13–17	85 ± 28		95 ± 29	
47				86–107	
42		76 ± 25		86 ± 22	
41 [†]		109 ± 21		135 ± 29	

Definition of abbreviations: FRC = functional residual capacity; P_{E,max} = maximum expiratory pressure; P_{I,max} = maximum inspiratory pressure; RV = residual volume; TLC = total lung capacity.

* Cylindric mouthpiece.

[†] Mean value ± SD.

[‡] Mean values for 11, 13, and 17 years.

Normal values. Transdiaphragmatic pressure during crying efforts has been measured in 18 healthy infants from 8 to 21 months postconceptional age, i.e., gestational age plus postnatal age (60). Crying P_{di} is ~ 60 cm H₂O at 1 month postnatal age, which is much lower than reported crying P_{I,max} (14). Crying P_{di} increases with postconceptional age (60).

Clinical application. Crying P_{di} may be useful in infants with abdominal wall defects or after repair of diaphragmatic hernia (60).

Occlusion Pressure

Rationale. Occlusion pressure (P_{mo,0.1s}) allows estimation of the respiratory drive (see Section 1 of this Statement).

Measurements. Measurements of P_{mo,0.1} can be performed in sleeping supine infants (61, 62) and in awake seated children as soon as the child is able to breathe quietly with a noseclip and a mouthpiece, i.e., after 3–4 years of age (15). Even light sedation is not recommended in young children because it will affect the level of consciousness. A period of at least 5 minutes of regular breathing is required before performing occlusions at intervals of at least 1 minute. A mean of five acceptable occlusions is used to determine P_{mo,0.1}.

Advantages. Occlusion pressure is easily measured.

Disadvantages. It may be argued that the duration of pressure measurement over 100 milliseconds, as established in adults, is not appropriate in infants and children because of a shorter inspiration time (T_i) than in adults. However, P_{mo,0.1} has been shown to be significantly related to the mean inspiratory flow (V_T/T_i) in children from 4 to 16 years of age (15). States of alertness influence respiratory drive and therefore accurate measurements in infants should include determina-

tion of sleep state. There is a relatively high CV, 11.7% in children (15); variability has not been determined in infants.

Normal values. Occlusion pressure was found to be 4.4 cm H₂O in full-term newborns (61, 62) and 3.6 cm H₂O in preterm infants (62). Occlusion pressures are available in awake children from 4–16 years of age during resting breathing of room air (Table 3) (15). P_{mo,0.1} decreases as a power function with age and reaches adult values at approximately 13 years of age.

Clinical application. Measurements of P_{mo,0.1} are useful to assess respiratory drive in infants and children with chronic intrinsic loaded breathing (bronchopulmonary dysplasia [62], interstitial lung disease [63], chronic obstructive lung disease [16, 51, 64]).

Inspiratory Pressure Reserve and Tension–Time Index

Rationale. Measurement of inspiratory pressure reserve, i.e., the ratio of the mean inspiratory pressure (P_i) during resting breathing over P_{I,max} at FRC, assesses the potential limitation of the inspiratory muscles to generate pressure at the end-expiratory level.

Measurements. Inspiratory pressure reserve can be assessed in children by noninvasive mouth pressure measurements. Inspiratory pressure is calculated as 0.5 × a × T_i (where a is P_{mo,0.1} × 10) (16). Inspiratory power for breathing at rest can be calculated as P_i × V_T/T_i × T_i/total inspiratory time (T_{tot}) (16). The critical inspiratory power (65), i.e., the inspiratory power above which fatigue occurs, can be calculated as P_{I,max} × V_T/T_i × T_i/T_{tot}. Critical P_{I,max} is assumed to be equal to 60% of P_{I,max} generated at FRC (65). A noninvasive pressure–time index for all the inspiratory muscles (PTImus) can be estimated as PTImus = P_i/P_{I,max} × T_i/T_{tot} (16, 55, 56).

Advantages. Assessment of inspiratory muscle function requires only noninvasive measurements. PTImus assesses all the inspiratory muscles.

Disadvantages. The validity of the estimation of P_i cannot be proved over the entire T_i. The rise in pressure during inspiration is approximated by a single power function of time assuming a linear applied pressure profile. If the inspiratory driving pressure increases as an exponential function of time, P_i is overestimated by extrapolating the P_{mo,0.1} over the entire T_i. Therefore, all derived parameters including P_i may be affected by an overestimation. However, in healthy adults and in adults with chronic obstructive pulmonary disease, P_i has been shown to be significantly correlated with P_{di}, and PTImus with the tension–time index of the diaphragm (TTIdi) (66). No comparison of PTImus and PTIdi is available in children.

Normal values. Table 3 shows that P_i/P_{I,max} at FRC decreases with age in children. TTImus decreases because of a decrease in P_i at rest and an increase in P_{I,max} at FRC, with no change in T_i/T_{tot} (15). However, no study has defined the critical PTImus above which fatigue occurs in children, as has been done in adults for PTIdi using electromyographic criteria (67).

Clinical application. Such measurements are helpful in children with increased load of breathing to estimate the degree of reduction of their inspiratory pressure reserve, the inspiratory power for breathing at rest, and the breathing strategy required to remain below the fatigue threshold of the respiratory muscles. It has been shown that the greater the P_i/P_{I,max} at FRC, the lower the T_i/T_{tot} in children with chronic obstructive pulmonary disease (16). The reduction in inspiratory pressure reserve limits the possibilities of adaptation of the pattern of breathing when an increase in the breathing load occurs, such as during exercise (68) or during sleep. The younger the child, the greater the risk (64). Such measurements should be performed in the follow-up of severe respiratory disorders, such as during the wait for lung transplant.

TABLE 3. NORMAL VALUES OF OCCLUSION PRESSURE, INSPIRATORY FORCE RESERVE, AND PRESSURE-TIME INDEX IN HEALTHY CHILDREN AND ADOLESCENTS

Age (yr)	Sex	P _{mo,0.1} * (cm H ₂ O)	P _i (cm H ₂ O)	P _{i,max,FRC} † (cm H ₂ O)	P _i /P _{i,max,FRC} (%)	PTImus‡
4	Male	3.60				
	Female	3.60				
6	Male	2.80				
	Female	2.80				
8	Male	2.34	15.2	70	21.7	0.10
						0.11
	Female	2.34	15.2	59	25.6	0.07
						0.09
10	Male	2.04	14.3	97	14.7	0.07
	Female	2.04	14.3	77	18.9	0.09
12	Male	1.82	13.7	105	13.0	0.06
	Female	1.82	13.7	98	13.9	0.06
14	Male	1.65				
	Female	1.65				
16	Male	1.52				
	Female	1.52				

Definition of abbreviations: P_{mo,0.1} = occlusion pressure; P_i = mean inspiratory pressure; P_{i,max,FRC} = maximal inspiratory pressure generated at functional residual capacity; PTImus = pressure-time index for all the inspiratory muscles.

* P_{mo,0.1} (occlusion pressure) from Gaultier and coworkers (15); P_{mo,0.1} is not significantly different between males and females.

† P_{i,max,FRC} (maximal inspiratory pressure generated at functional residual capacity) from Gaultier and Zinman (13).

‡ T_i/T_{tot} does not change with age in children (15), TTImus was calculated using a T_i/T_{tot} equal to 0.45, i.e., the mean value obtained in children between 4 and 16 years of age.

Electromyography of the Respiratory Muscles

Rationale. Electromyography can be used to assess the level and pattern of activation of the respiratory muscles.

Measurements. Surface electrodes have been used nearly exclusively for EMG recording of the respiratory muscles in infants and children. Surface electrodes are placed in the right sixth and seventh interspaces between the midaxillary and mid-clavicular lines for recording of diaphragmatic EMG (EMG_{di}) (69–71), in the second intercostal space parasternally for intercostal EMG recording, and at the midpoint between the umbilicus and iliac crest for abdominal muscle recording (71, 72). One study reported EMG_{di} using an esophageal electrode with specific equipment adapted for use in sleeping infants (73). No studies have been published using intramuscular electrodes for recording EMG of the respiratory muscles in infants or children.

Advantages. The recording of EMG of the respiratory muscles using surface electrodes is noninvasive.

Disadvantages. Surface electrode EMG_{di} tracings can be contaminated by other inspiratory or expiratory muscles (73). Therefore, when recording diaphragmatic EMG activity with surface electrodes, it is more appropriate to describe the values as chest wall EMG rather than EMG_{di}. Techniques to remove cardiac artifacts on the EMG_{di} have to take into account the high cardiac frequency in infants, especially in preterm infants (74) (see ARTIFACTS in Section 3 of this Statement).

Normal values. Quantitative measurements of chest wall EMG recorded with surface electrodes have been reported for EMG time and frequency domains (69, 70, 74, 75). Few studies have described the activation of the respiratory muscles during quiet breathing in infants without respiratory disorders. In infants nursed in the supine position, phasic and tonic activity of the intercostal muscles have been reported during NREM sleep (69). Contraction of the intercostal muscles stabilizes the highly compliant chest wall of the infant. The inter-

costal muscles are inhibited during REM sleep and chest wall distortion occurs during inspiration. No abdominal muscle activation has been reported in healthy infants nursed in the supine position during NREM sleep (71). Activation of abdominal muscles is observed during NREM sleep while breathing CO₂, but not during REM sleep (71).

Clinical application. The main utility of recording of EMG of the respiratory muscles is during sleep studies. Persistent phasic chest wall EMG activity helps to identify obstructive respiratory events, especially obstructive hypopneas during sleep, and therefore should limit the use of the invasive measurement of Pes (76). EMG recording of abdominal muscles assesses the degree of abdominal muscle contraction in children with loaded breathing related to partial upper airway obstruction during sleep (71, 72).

Integrated Pump Function: Thoracoabdominal Motion

Rationale. The respiratory muscles (diaphragm and intercostals) act on the rib cage to effect respiratory motion and ventilation. Rib cage motion can be taken as an index of intercostal muscle action, while AB motion can be taken as an index of diaphragmatic descent. Thus thoracoabdominal motion (TAM) provides a visual index of respiratory muscle function.

Methods. The most widely used method to assess TAM is respiratory inductive plethysmography, although strain gauges and magnetometers are also used. Respiratory inductive plethysmography uses thin cloth bands that are placed around the RC and AB. A wire is sewn into the bands, and when an oscillatory current is applied, changes in the cross-sectional area of the chest wall are reflected as changes in the electric inductance of the wires, displayed as a change in voltage output. Respiratory inductive plethysmography can be used to quantitate asynchrony by measuring a phase angle, ϕ ($\phi = 0^\circ$, synchronous breathing; $\phi = 180^\circ$, paradoxical breathing), between the RC and AB compartments. The calculation of ϕ does not require calibration for volume. Respiratory inductive plethysmography can also be used to quantitate the relative contribution of the RC and AB to V_T; this does require calibration for volume. Several techniques have been described for volumetric calibration. The isovolume, least mean squares, and quantitative diagnostic calibration techniques are described elsewhere (77–81) (see DEVICES USED TO MONITOR BREATHING in Section 6 of this Statement).

Advantages and disadvantages of respiratory inductive plethysmography. Respiratory inductive plethysmography is valuable as a direct, noninvasive measure of chest wall motion and an indirect measure of respiratory muscle function. Being an indirect measure, however, chest wall motion can reflect events other than respiratory muscle function. Chest wall motion is a final common pathway of integrated respiratory system output; it can be influenced by underlying lung mechanics and C_{cw}. Thus, asynchronous chest wall motion can represent neuromuscular weakness (82–84), fatigue (85), high C_{cw} (86), abnormally low C_L or high lung resistance (87, 88), upper airway obstruction (89), effects of anesthesia (90), or a combination of two or more of these. Its major weakness is thus that it is a nonspecific indicator, and abnormal chest wall motion must be interpreted in the context in which it occurs.

Calibration of respiratory inductive plethysmography for volume is difficult in infants, especially in preterm infants with highly compliant chest walls and paradoxical chest wall motion. The highly compliant infant chest wall probably invalidates the assumption of two degrees of freedom (RC and AB) that is the basis for most respiratory inductive plethysmography calibration equations. Furthermore, phase angles may be difficult to interpret if breathing does not approximate a sinusoidal pattern (91).

Normal values and alterations in disease. In infants, the high Ccw predisposes to asynchronous chest wall motion. Thus, normal preterm infants display asynchronous chest wall motion during NREM sleep (86). Normal full-term infants display synchronous RC-AB motion in NREM sleep ($\phi = 8 \pm 7^\circ$ [mean \pm SD]) (84), but may display asynchronous motion in REM sleep (21). The time spent with paradoxical inward RC movement during REM sleep decreases with advancing age; paradoxical, RC motion is present during nearly 100% of the REM time in the newborn, but only $\sim 10\%$ of the REM time by 3 years of age (21). For these reasons, it should be noted whether the infant is in the quiet awake state, or in clinically determined quiet or active sleep, when performing measurements of TAM.

Normal adults and children have synchronous breathing between the RC and AB compartments (92, 93).

As far as neuromuscular disease is concerned, assessment of TAM can pinpoint the site of weakness: paradoxical inward motion of the RC during inspiration indicates intercostal muscle weakness, whereas paradoxical inward motion of the AB during inspiration indicates diaphragmatic weakness (82, 83). Such chest wall asynchrony disappears during MV (94, 95), and may indicate respiratory muscle rest.

Turning to chronic airflow obstruction, in adults, abnormalities of diaphragmatic function accompany chronic hyperinflation (96). Similar problems occur in infancy and childhood. Preterm infants develop chest wall asynchrony and decreased minute ventilation when breathing through inspiratory resistive loads (8); it is not clear whether this represents respiratory muscle fatigue or simply high Ccw in the face of increasing negative intrathoracic pressure. Infants with bronchopulmonary dysplasia display asynchronous RC-AB motion. The degree of asynchrony is proportional to the degree of abnormality in lung compliance and resistance (88). This improves on administration of aerosolized bronchodilators (87). Upper airway obstruction can likewise cause thoracoabdominal asynchrony (89).

Clinical application. Measurements of TAM have been made in clinical research studies as described. By differentiating the summed RC and AB signals, tidal flow-volume curves have been analyzed (97). Measurements of TAM are also used in routine clinical practice, particularly for detecting upper airway obstruction during sleep studies. They are also used in infant monitoring devices to detect apnea.

The following two methods of analyzing integrated respiratory pump function have limited clinical applications at present and are primarily techniques under investigation.

1. Diaphragmatic movement (real-time ultrasonography): Diaphragmatic excursions have been measured in full-term infants by real-time ultrasonography (98). Only the right hemidiaphragm is accessible by this technique, through the ultrasonographic window provided by the liver; the left hemidiaphragm is obscured by stomach and bowel gas. The posterior aspect of the diaphragm moves to a greater extent than the anterior aspect, perhaps because of the effect of the larger posterior area of apposition to the inner chest wall. Diaphragmatic excursions are lessened, and the diaphragm moves more uniformly, in infants who are paralyzed and undergo MV. Similar observations (4) led to the conclusion that, unlike the piston-like motion of the adult diaphragm, the infant diaphragm has a bellows-like motion. Normal ultrasonographic values for diaphragmatic excursion in infants and adults have been presented (4, 99–101); there is a wide degree of variation between the infant studies, suggesting that, at least for now, clinical application is limited (Table 4).

2. Phrenic nerve stimulation (*see* STIMULATION TESTS in Section 3 of this Statement): Transcutaneous phrenic nerve stimulation has been applied to children in the clinical setting; to date phrenic nerve latency has been studied as a way of assessing phrenic nerve damage in, for example, patients recovering from cardiac surgery, but no studies of diaphragmatic fatigue have been performed. Normal phrenic nerve latency is on the order of 4.5–6.5 milliseconds. There is less than 10% day-to-day variability of this measurement (102). Phrenic nerve latency time diminishes slightly with age, by 0.5 to 1 millisecond between birth and 10 years (103). Delays of 2 milliseconds or longer may indicate phrenic nerve damage (102). Magnetic cervical stimulation may be an alternative, painless way to stimulate the phrenic nerves (104).

Anterior magnetic phrenic nerve stimulation is an established technique in adults (*see* Section 2 of this Statement). Experience with the technique in children is limited but the method can be used to assess diaphragm function in neonates in the intensive care unit (109).

Upper Airway Muscles

(*See* ELECTROMYOGRAPHY in Section 8 of this Statement.)

Rationale. Assessment of upper airway muscle activity and airway collapsibility is useful for assessing infants and children with increased upper airway resistance.

Measurements. Surface and fine wire EMGs have been used in research settings to evaluate the activity of upper airway muscles including the intrinsic laryngeal muscles (8), alae nasi (105), and the genioglossus (105). The function of upper airway muscles is normally assessed clinically by visualization of the size of the airway using fiberoptic endoscopy (106), fluoroscopy (107), or, more recently, fast magnetic resonance imaging techniques (108). Another useful indirect measurement, especially when assessing patients for obstructive sleep apnea, is to monitor airflow at the mouth/nose for evidence of reduced flow (109). Upper airway collapsibility can be assessed either by monitoring pharyngeal pressure during an airway occlusion or by applying positive and negative pressures at the airway opening and looking for evidence of airflow limitation during spontaneous breaths (24). The critical pressure (Pcrit) of the upper airway is defined from such measurements as the pressure at which flow equals zero as extrapolated from a maximum flow versus applied nasal pressure curve. Closing pressure of the upper airway has been measured in postmortem infants (110) and in normal sleeping infants (23).

Advantages. Measurement of upper airway muscle activity provides valuable information when assessing infants and children with suspected upper airway dysfunction. Visualization of the upper airway is a standard clinical procedure.

Disadvantages. Electromyographic measurements are not feasible for clinical assessment because of the technical difficulties, limited number of muscles that are accessible to surface measurements, and the inability to compare levels of EMG activity between patients. At the present time, measures of collapsibility are time-consuming and require special expertise.

Normal values. No normal values exist for the EMG of the upper airway muscles. In general, abductor muscles are active during inspiration with quiet breathing and some adductors are active during expiration. Measurements of Pcrit in a small number of children yielded values of -19.5 cm H₂O for children with primary snoring and $+1.0$ cm H₂O in children with obstructive sleep apnea (24). Closing pressures in postmortem infants averaged 0.8 cm H₂O (110) whereas those in sleeping infants averaged -3.8 cm H₂O (23). The more positive value in the postmortem measurements probably reflects the lack of upper airway muscle activation.

TABLE 4. AXIAL DIAPHRAGM DISPLACEMENT: NORMAL ULTRASONOGRAPHIC VALUES DURING TIDAL BREATHING

	Reference	Axial Diaphragm Displacement (mm)			
		Anterior	Middle	Posterior	Mean
Infancy	97	2.6	3.7	4.6	3.6
	4	7.4	—	12.1	9.7
Adulthood	98	—	—	—	15.2

Clinical application. Measurements of upper airway function are useful in assessing children with suspected obstructive sleep apnea due to abnormalities of either structure or upper airway muscle activation including those with craniofacial abnormalities, hypertrophied lymphoid tissue, and neuromuscular disease. They can also be useful in cases of vocal cord dysfunction.

CONCLUSION

The majority of techniques and tests described in this Section of the Statement are not presently in routine clinical use and many should be considered experimental. The tests can be put into one of three groups based on their feasibility in different settings.

1. Tests that are well established and validated for routine clinical use include $P_{i,max}$, $P_{E,max}$ and the direct visualization of upper airway structures.
2. Many tests are fairly well developed but still require validation and establishment of normal values. These tests are available for use in clinical investigations where there are specifically trained personnel and specialized equipment. They include measurements of $P_{mo,0.1}$, inspiratory pressure reserve and PTI, thoracoabdominal asynchrony, EMG of the respiratory and upper airway muscles, and critical and closing pressures of the upper airway.
3. Tests that are still under development and that are recommended for use only in research settings include measurement of C_{cw} , crying pressures, ultrasonography of the diaphragm, and phrenic nerve stimulation. These tests all require further investigation before their feasibility in clinical practice can be established.

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10. Assessment of Respiratory Muscle Function in the Intensive Care Unit

Few areas exist in clinical medicine where problems with the respiratory muscles play a greater role than in patients managed in an intensive care unit (ICU). The inability of the respiratory muscles to sustain spontaneous ventilation is the primary indication for the main therapeutic modality of an ICU, namely mechanical ventilation (1). Likewise, respiratory muscle performance is the major issue in deciding the timing and pace with which mechanical ventilation can be discontinued (2, 3). Many tests of respiratory muscle function require a high level of motivation and cooperation, making it much more difficult to obtain reliable measurements in critically ill patients than in an ambulatory-care setting. This section covers the tests of demonstrable, or potential, value that directly, or indirectly, relate to respiratory muscle function in the ICU setting. Consequently, the tests focus predominantly on a patient's need for mechanical ventilation and how this therapeutic modality can be best delivered.

BREATHING PATTERN

Abnormalities in respiratory frequency (f_R) and tidal volume (V_T) are extremely common in critically ill patients and, among other causes, can reflect respiratory muscle dysfunction. In several studies, an elevated f_R has been shown to predict an adverse outcome in general populations of critically ill patients. In a case-controlled study of patients discharged from an ICU, f_R ($p < 0.0002$) and hematocrit ($p = 0.01$) were the only continuous variables that predicted readmission to the ICU (4). Patients readmitted to the ICU had a much higher mortality than the control patients (42 and 7%, respectively). In a study of patients who had undergone a cardiopulmonary arrest, 53% had a documented deterioration in respiratory function in the 8 hours preceding the arrest (5). Respiratory frequency was elevated in the majority of these patients (mean \pm SE, 29 ± 1 breaths/minute), while other routine laboratory tests, including electrocardiograms, showed no consistent abnormalities. These and other studies (6, 7) demonstrate that tachypnea is an extremely sensitive marker of a worsening clinical status. However, it is also extremely nonspecific, and a physician needs to undertake additional diagnostic testing to elucidate the nature of the underlying disorder.

Tidal volume (V_T), breathing frequency (f_R), and minute ventilation are easy to measure in intubated patients, and the values are continuously displayed on virtually all modern mechanical ventilators. However, the accuracy and reliability of the instrumentation used for volume measurements have undergone remarkably little evaluation (8). To ensure reliability of volume measurements, a simple handheld spirometer is preferred. Tidal volume is rarely measured in the nonintubated patient, because these patients have a poor tolerance of mouthpieces. Moreover, such instrumentation usually causes a spurious increase in V_T and decrease in frequency (9, 10).

Systematic studies have not been undertaken in large populations of healthy subjects to define the normal range for breath components. Moreover, the values depend on whether recordings are made nonobtrusively or with instrumentation requiring the use of a mouthpiece (9, 10). The largest study using nonobtrusive methodology in healthy subjects ($n = 65$) revealed a mean \pm SD V_T of 383 ± 91 ml, f_R of 16 ± 2.8 breaths/minute, and minute ventilation of 6.01 ± 1.39 L/minute (11).

Additional data in smaller study populations are consistent with these values. Breath components display considerable breath-to-breath variability, and thus it is important to base the measurement on an adequate sampling period; unfortunately, investigations have not been conducted to define the optimal sampling duration. Calculations of breath components based on the mean of approximately 250 breaths revealed good reproducibility on a day-to-day basis in healthy subjects (coefficient of variation less than 9%) (12).

Rapid shallow breathing is particularly common in critically ill patients (Figure 1) (13), and some (14–16), but not all (17, 18), investigators have related its development to respiratory muscle fatigue. Even when rapid shallow breathing has been demonstrated following the induction of fatigue in healthy volunteers (16), it occurred when the subjects were employing only a small fraction of the pressure-generating capacity of the inspiratory muscles, making it unlikely that this alteration in breathing is a manifestation of fatigue per se. Critically ill patients are susceptible to many simultaneous challenges, and rapid shallow breathing in these patients may be the result of several mechanisms, including increased mechanical load, chemoreceptor stimulation, operating lung volume, reflexes originating in the lungs and respiratory muscles, altered respiratory motoneuron discharge patterns, sense of effort, and cortical influence. If rapid shallow breathing were an effective strategy for avoiding respiratory muscle fatigue in critically ill patients, one would expect a negative correlation between the degree of rapid shallow breathing and a measure of respiratory muscle fatigue. In 17 patients who failed a trial of weaning from mechanical ventilation, Jubran and Tobin (18) found no relationship ($r = 0.08$) between frequency-to-tidal volume ratio (f_R/V_T) and tension–time index. Vassilakopoulos and coworkers (19) have confirmed the lack of a relationship between f_R/V_T and tension–time index ($r = 0.16$) in 30 patients who failed a weaning trial. In the latter study (19), tension–time index decreased from a value of 0.162 ± 0.032 (SD) in patients who could not be weaned to 0.102 ± 0.023 at the time of weaning success. When a large number of variables reflecting respiratory muscle function, lung volumes, and mechanics were entered into a logistic regression model, f_R/V_T and tension–time were the only variables that were significantly related to weaning outcome.

While the pathophysiological mechanism(s) responsible for rapid shallow breathing is unknown, this does not detract from its use in clinical decision-making, especially with regard to the timing and pace of the weaning process (*see* subsequent text). Moreover, initial studies of computerized closed-loop adjustments of ventilator settings, based on V_T and f_R , with or without end-tidal PCO_2 and pulse oximetry, provide encouraging data suggesting that ventilator adjustments based on changes in breathing pattern might help in expediting the weaning process (20–22).

Asynchronous and paradoxical motion of the rib cage and abdomen is commonly detectable by inspection and palpation in critically ill patients. The magnitude of abnormal motion can be quantified with magnetometers or inductive plethysmography combined with the Konno–Mead method of analysis (23) (*see* ESTIMATION OF VENTILATION BASED ON CHEST WALL MOTION: KONNO–MEAD DIAGRAM in Section 6 of this Statement). Ashutosh, Gilbert, and coworkers (24, 25) showed that patients dis-

playing asynchronous rib cage–abdominal motion had an increased risk of ventilatory failure necessitating mechanical ventilation (24) and a poor prognosis (24). Subsequently, abdominal paradox and respiratory alternans, i.e., cyclic alteration in the relative contribution of the rib cage and diaphragmatic muscle groups, were thought to reflect respiratory muscle fatigue (14, 26, 27). Such an interpretation has major implications for the critically ill patient being weaned from mechanical ventilation. Because muscle rest with mechanical ventilation is the main means of reversing fatigue, the presence of paradox would prohibit the discontinuation of mechanical ventilation. Patients who fail a weaning trial, as a group, exhibit greater abdominal paradox than successfully weaned patients (28, 29), but there is considerable overlap among individual patients of the two groups. This lack of discrimination between the two groups of patients partly stems from the fact that the more seriously ill patients also switch between predominant use of the rib cage and diaphragmatic muscles (14, 28, 29). Moreover, in systematic experimental studies, respiratory muscle fatigue was shown to be neither necessary nor sufficient for the development of abnormal rib cage–abdominal motion (30, 31). Thus, quantification of abdominal paradox alone is not helpful in detecting respiratory muscle fatigue or predicting the development of respiratory failure. However, studies in small numbers of patients suggest that a global measure of overall asynchronous and paradoxical motion of both the rib cage and abdomen might be useful in predicting ventilatory failure (14, 24, 25, 28–30). Because quantification of abnormal rib cage–abdominal motion is relatively complex, such an index cannot be recommended for general clinical use without undertaking controlled prospective trials to determine if such a measurement is superior to simpler tests that are more easily performed (32).

LUNG VOLUMES

Few studies have been conducted in critically ill patients examining the usefulness of lung volume measurements. In a study of 10 patients with the Guillain–Barré syndrome, Chevrolet and Deleamont (33) found that monitoring vital capacity three times a day was helpful in predicting the need for ventilator support. Five patients required intubation approximately 12 days after the onset of neurological symptoms; vital capacity was 0.82 L (range, 0.65–1.00 L) immediately before intubation in these patients. In contrast, mean \pm SD vital capacity was 2.40 ± 0.57 L in another five patients who were managed without intubation. In general, when vital capacity fell by 50%

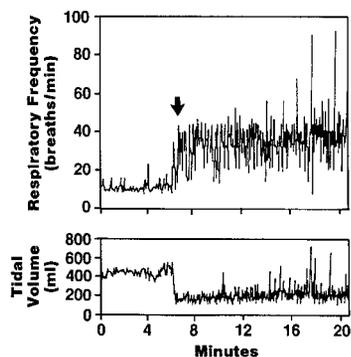


Figure 1. A breath-by-breath plot of respiratory frequency and tidal volume in a patient who failed a weaning trial. The arrow indicates the point of resuming spontaneous breathing following discontinuation of ventilator support. Rapid, shallow breathing developed almost immediately, suggesting the prompt establishment of a new steady state. Although it has been considered that rapid, shallow breathing may reflect the presence of respiratory muscle

fatigue, its almost instantaneous development without subsequent progression is difficult to reconcile with the development of respiratory muscle fatigue. Reprinted by permission from Reference 13.

from the first recorded value, ventilator support became necessary within the next 36 hours.

Rieder and coworkers (34) examined the accuracy of vital capacity in predicting the need for mechanical ventilation in patients with myasthenia gravis. The study consisted of a retrospective chart review of five patients who experienced 10 episodes of acute respiratory failure. Repeated measurements of vital capacity every 4 hours did not help in predicting the need for intubation and mechanical ventilation, which was instituted in four of the episodes. Indeed, the lowest values of vital capacity tended to be found in the patients who did not receive mechanical ventilation, mean \pm SD 11 ± 5 ml/kg, compared with 21 ± 9 ml/kg in the patients who received ventilator support. Although the study population is small, the results suggest that vital capacity is unlikely to be useful in this disease. The inability to predict deterioration may be due to the erratic course of this disease, which involves sudden deterioration (see STATIC LUNG VOLUMES in Section 1 and DEVICES USED TO MONITOR BREATHING in Section 6 of this Statement).

PRESSURE MEASUREMENTS

The respiratory system is an elastic structure that requires the generation of force (pressure) for its displacement (35). In many critically ill patients, positive pressure is delivered to the lungs through an endotracheal tube by a mechanical ventilator with the aim of improving arterial blood gases and unloading the respiratory muscles (36–38). The total respiratory system is composed of complex structures, namely the lungs, the upper and lower rib cage, and the diaphragm–abdominal compartments, each displaying different mechanical properties; in disease states, the situation is even more complicated due to time-constant inhomogeneity, expiratory flow limitation, etc. (see ASSESSMENT OF THE FUNCTION OF THE ACTIVE CHEST WALL in Section 6 of this Statement). Nevertheless, assessment of respiratory system mechanics is commonly based on a relatively simple equation of motion (Equation 1) (35):

$$P_{\text{appl}} = 1/C \dot{V} + R\dot{V} \quad (1)$$

where P_{appl} is the pressure applied to the system by either the ventilator or the combined action of the ventilator and the patient's inspiratory muscles, V and \dot{V} are the inflation volume and flow, respectively, C is the respiratory compliance, and R is the flow resistance. The endotracheal tubes and the ventilator circuits are rather stiff structures, such that a patient's compliance provides a good representation of the overall elastic properties of the patient–ventilator ensemble. In contrast, the endotracheal tube poses a substantial, highly flow-dependent resistance, which is important from the standpoint of a patient's respiratory muscle activity, because this resistance has to be overcome during lung inflation (39, 40) and it may retard expiratory flows, thus promoting dynamic hyperinflation (41, 42). Due to the flow characteristics of the endotracheal tubes, Equation 1 becomes Equation 2:

$$P_{\text{appl}} = 1/C \dot{V} + R_t + (k_1 \dot{V} + k_2 \dot{V}^2) \quad (2)$$

where R_t is the nonohmic component of total flow resistance, and k_1 and k_2 are constants related to laminar and turbulent flow, respectively. The additional work of breathing due to the endotracheal tube can be considerable at high levels of minute ventilation, and it may be negligible at low inspiratory flows.

Inspiratory effort is usually increased in critically ill patients because of abnormal respiratory mechanics, i.e., low compliance and high flow resistance (43–47). During mechanical ventilation, a variable portion of the ventilatory workload is decreased such that a patient's inspiratory muscles are un-

loaded by an amount that should be proportional to the degree of mechanical support (48–56). However, in some instances, a patient's inspiratory effort during ventilator-assisted breaths differs only slightly from that during unassisted breathing due to several factors: excessive ventilatory drive consequent to either metabolic factors (e.g., sepsis, fever, etc.) or psychologic (e.g., pain, anxiety, etc.) phenomena; substantial time lag between the onset of a patient's inspiratory effort and full machine support due to delayed opening of the ventilator circuit valves; ventilator-inspiratory flow that does not meet patient demands, especially at the onset of inspiration; intrinsic positive end-expiratory pressure (PEEP); and excessive V_T that requires a long expiratory time, during which ineffective patient's efforts may occur. If a patient's effort remains significant during mechanical ventilation, the respiratory muscles cannot recover from fatigue. Accordingly, progressive reduction and eventual discontinuation of mechanical ventilation can be very difficult (2, 3, 57).

Measurement of pressure at the airway opening is easy in ventilator-dependent patients because a stiff endotracheal tube bypasses the compliant upper airway, allowing the rapid transmission of changes in alveolar pressure to the airway opening even in presence of time-constant inhomogeneity (58, 59).

Airway Pressure Contour

Consistent with Equation 1, simple inspection of the airway pressure contour in a ventilator-dependent patient can provide useful information on the activity of a patient's respiratory muscles. With a given inspiratory flow waveform, any deviation from the relaxed configuration indicates active contraction of a patient's inspiratory muscles (Figure 2). The work performed by the patient can be quantified as the difference in area between the actual versus the relaxed airway pressure contour plotted against either time or volume (48, 49, 53). A patient actively contributes to the total work of breathing (WOB), either intentionally or unintentionally, whenever his or her ventilatory demands exceed the inspiratory flow rate setting on the ventilator—a phenomenon called flow deprivation. Some modern ventilators have the capability of detecting such an occurrence with their operational software and can compensate for it.

Maximum Inspiratory Pressure

Measurement of maximum inspiratory pressure ($P_{i,max}$) has long been used in the clinical setting to assess inspiratory mus-

cle strength (see Section 2 of this Statement). The maneuver consists of a maximum inspiratory effort against a closed airway and requires a considerable degree of patient cooperation and coordination (60). Although ventilator-dependent patients may display poor cooperation in the execution of voluntary maneuvers, even in these patients values of $P_{i,max}$ have been used to predict successful weaning (61). Marini and coworkers (62) suggested an approach for the standardization of the measurement of $P_{i,max}$ in such patients. They used a unidirectional valve to permit exhalation while inhalation was blocked, thereby allowing patients to perform the maximal inspiratory effort at a lung volume approaching residual volume, where $P_{i,max}$ is expected to be maximal; the highest $P_{i,max}$ values were generally reached after 15–20 efforts or after 15–20 seconds of airway occlusion (62). However, subsequent work has shown that even employing such a standardized approach, the reproducibility of $P_{i,max}$ values in ventilator-dependent patients is poor. "True" $P_{i,max}$ in ICU patients is often significantly underestimated, being both patient- and investigator-dependent; even highly reproducible $P_{i,max}$ measurements at any one sitting do not reliably reflect maximal efforts (63).

Although a high value of $P_{i,max}$, together with other measurements, may indicate that mechanical ventilation can be discontinued, a low $P_{i,max}$ value may reflect a submaximal effort due to poor patient coordination and cooperation. In addition, the problem of insufficient reproducibility may limit the clinical usefulness of this test, at least when used in isolation.

Pressure at the Airway Opening in the First 0.1 Second

The decrease in airway pressure at 0.1 second ($P_{0.1}$) after commencement of a tidal inspiratory effort against an occluded airway has commonly been used as an index of neuromuscular ventilatory drive (64–66). The value of $P_{0.1}$ depends not only on the inspiratory center output, but also on several other factors, including: (1) the intact neural pathway to the inspiratory muscles; (2) electro-mechanical coupling; and (3) the pressure-generating capacity of the inspiratory muscles and their velocity of shortening (see TESTS OF RESPIRATORY CONTROL in Section 1 of this Statement).

Although a high value of $P_{0.1}$ always indicates enhanced respiratory center activity, a low value may signify not only reduced center output, but also deterioration in the neural pathway, impaired electro-mechanical coupling, and impaired pres-

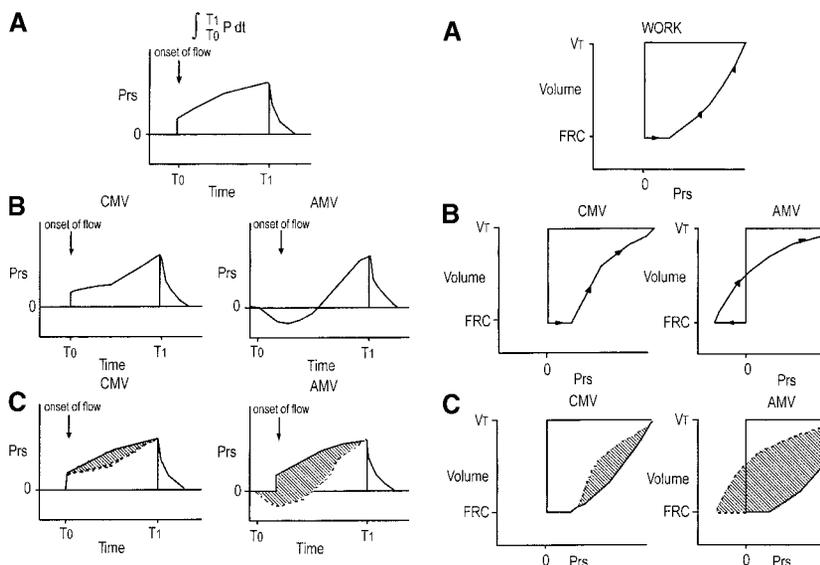


Figure 2. Subtraction of the area subtended by the inflation pressure (Prs)–volume (right) or -time (left) curve in the presence of inspiratory muscle activity (B) from that recorded during passive inflation (CMV, controlled mechanical ventilation; A) yields the work of inspiration performed by the patient (AMV, assisted mechanical ventilation; shaded area, C) and the pressure-time product ($\int P dt$) of the inspiratory muscles. Reprinted by permission from Reference 53.

sure-generating capacity due to respiratory muscle weakness and fatigue. Furthermore, in the presence of dynamic hyperinflation and PEEP_i, P0.1 measured as subatmospheric pressure 100 seconds after the apparent onset of effort, neglects the respiratory effort required to draw down PEEP_i. These factors must be kept in mind when evaluating P0.1 in the ventilator-dependent patient. In a patient with abnormal airway resistance breathing through an intact upper airway, the true value of P0.1 may be underestimated because of the long time constant, retarding the transmission of pressure changes from the alveoli to the mouth (67). In contrast, in a ventilator-dependent patient who has a rigid endotracheal tube bypassing the compliant region of the upper airway, P0.1 may more accurately reflect esophageal pressure changes and thus neuromuscular drive (68).

P0.1 is generally increased in patients with acute respiratory failure (69), although an authoritative study on the reproducibility of P0.1 measurement in the ICU setting has yet to be performed. In mechanically ventilated patients, P0.1 has been used to: (1) assess respiratory center output while changing the fraction of inspired oxygen (F_IO₂) (70); (2) predict weaning outcome values of P0.1 \geq 6 cm H₂O suggesting that discontinuation of mechanical ventilation is likely to be unsuccessful, while values \leq 4 cm H₂O suggest that weaning is likely to be successful (71, 72); and (3) set the appropriate level of assisted ventilation (73) and pressure support (56).

Measurement of P0.1 does not require sophisticated equipment, and a two-way valve and differential pressure transducer are sufficient. In ventilator-dependent patients, the procedure can become even simpler because the valves necessary for the measurement already exist in the ventilator. Indeed, to trigger a mechanical breath, the patient has to generate a small negative pressure at the airway opening, which opens the valves and allows the passage of inspiratory gas. In some ventilators, e.g., the Siemens Servo 900C, the time to open the valve exceeds 100 milliseconds, thus providing sufficient time to measure the P0.1. This modification has been used successfully by Fernandez and coworkers (69) and Conti and coworkers (74) to measure P0.1 in patients with intrinsic PEEP (see subsequent text). Kuhlén and coworkers (75) introduced an automated method to measure P0.1 in ventilator-dependent patients using a standard ventilator (i.e., the Dräger Evita). These authors correctly underscored the breath-by-breath variability of the measurement. In this connection, it has to be mentioned that expiratory muscle activity may increase the P0.1 variability and generate unreliable values.

In summary, P0.1 can be measured in ventilator-dependent patients and taken as an index of neuromuscular drive. High values of P0.1 are considered to predict weaning failure, whereas low values of P0.1 suggest that mechanical ventilation can be discontinued, provided that factors that can impair the pressure-generating capacity of the inspiratory muscles are excluded.

Pleural Pressure and Derived Variables

Recording of changes in pleural pressure (P_{pl}) represents a basic means of quantifying respiratory muscle activity. Recording the tidal swings in esophageal pressure (P_{es}) (as an estimate of P_{pl}) and a knowledge of the passive properties of the chest wall over lung volume allow the quantification of the pressure developed by the muscles, also referred to as “muscular pressure” (P_{mus}). This measurement has facilitated the gathering of important information in the field of mechanical ventilation, both in quantification of the effort performed by patients receiving ventilator assistance and for comparison of different modes of assisted ventilation (see ESOPHAGEAL, GASTRIC, AND TRANSDIAPHRAGMATIC PRESSURES in Section 2 of this Statement).

Two main variables can be derived: work of breathing (WOB) and pressure–time product (PTP) (see ASSESSMENT OF THE FUNCTION OF THE ACTIVE CHEST WALL: CAMPBELL DIAGRAM in Section 6 and PRESSURE–TIME PRODUCT in Section 4 of this Statement) (76). For both calculations, knowledge of the compliance curve of the chest wall is necessary; several methods have been used for this measurement in mechanically ventilated patients. Some investigators employ an assumed chest wall compliance value, amounting to 4% of the predicted vital capacity per cm H₂O (47, 77). Assuming that the chest wall compliance is linear over the range of lung volumes studied, a straight line can be traced over lung volume to delineate the pressure reference. This method has the major disadvantage of not measuring the true chest wall compliance, which has been shown to be substantially modified in some intubated patients with acute respiratory failure (43, 44, 78). A preferable approach is to measure the pressure–volume (PV) relationship, using P_{es} recordings over the range of lung volumes studied, during passive inflation under controlled mechanical ventilation. This makes it necessary to heavily sedate the patient and/or to abolish spontaneous activity by hyperventilating the patient. Again, for simplicity, this curve can be assumed to be linear, or it can also be superimposed graphically over each studied breath, assuming that the end-expiratory lung volume can be estimated (79). The latter approach allows quantification of active expiratory effort.

WOB is measured from pressure–volume loops using the Campbell diagram method (80) (see ASSESSMENT OF THE FUNCTION OF THE ACTIVE CHEST WALL: CAMPBELL DIAGRAM in Section 6 of this Statement). The measurement of the WOB in ICU patients raises no unique concerns, although recognition of some limitations of the measurement has led to the use of alternative methods of measuring respiratory energy expenditure. Measurement of WOB does not allow quantification of isometric efforts, such as an effort against a closed airway or inefficient or “wasted” inspiratory efforts that fail to trigger a ventilator (81–83); in addition, measurement of WOB is probably inadequate for the comparison of settings where part of the change in V_T is achieved by the ventilator. In such a case, an increase in WOB may be recorded in the absence of a true change in muscular effort. Such concerns about WOB have been recognized for a long time (76) and have prompted the use of other indices to quantify respiratory muscle effort in the ICU, especially PTP (51, 76).

Calculation of the PTP necessitates the integration of the area under the P_{pl} curve versus time. It also requires, however, a solution to the problem of determining the beginning of the inspiratory effort and of using PEEP_i to reference the true beginning of inspiration to the chest wall relaxation line (52). Different methods have been proposed to perform this calculation (which is applicable as well to the transdiaphragmatic pressure [P_{di}]), and the termination of inspiratory effort has been based on the inspiratory–expiratory flow transition point (52) or once the pressure has returned back to its baseline level (84). PTP can be expressed on a per-breath or a per-minute basis; today, it is probably one of the most useful tools for quantifying respiratory muscle effort in mechanically ventilated patients (18, 52, 80, 85–93) (see PRESSURE–TIME INDEX OF INSPIRATORY MUSCLES in Section 5 and PRESSURE–TIME PRODUCT in Section 4 of this Statement). PTP can be separated into a number of components: the effort made to counterbalance intrinsic PEEP; the effort to trigger the ventilator; and the effort to inflate the chest in the posttrigger phase (83, 87, 93) (Figure 3). However, the correct interpretation of this measurement when end-expiratory lung volume (FRC) undergoes concurrent change remains a question of controversy that has yet to be solved and deserves further investigation.

The presence of a phase lag between the onset of the decline in inspiratory pressure decay and the time at which the flow reaches zero indicates the presence of positive alveolar pressure at end-expiration. Because this positive pressure can result from either elastic recoil pressure generated by hyperinflation or from activity of abdominal and/or thoracic expiratory muscles, interpretation of this pressure is extremely difficult. Different methods have been proposed to solve this problem, using the Pdi (94) or the expiratory swings in gastric pressure (Pga) (95) to estimate the part related to expiratory muscle activity (*see subsequent text*). When Pga is not available, one can calculate a range of values between two extremes or bounds: at one extreme, it is assumed that all of the pressure drop before reaching zero flow is related to dynamic hyperinflation, and at the other extreme, it is assumed that all of this pressure drop is related to the relaxation of the expiratory muscles (79).

Measurements of Ppl and derived variables are very helpful in research. In the clinical setting, however, it has gained relatively little acceptance despite the availability of commercial systems. Some investigators have suggested that Ppl may help in understanding the reasons for the inability to tolerate discontinuation from mechanical ventilation (96–98). Although Ppl has potential implications for setting the ventilator, clear-cut data are not available on which to base individual targets for the employment of these measurements. In addition, a number of artifacts, including interference by cardiac contractions, make automatic calculations unreliable, especially regarding the detection of the end and the onset of both inspiratory and expiratory efforts.

Intrinsic PEEP

In ventilator-dependent patients, end-expiratory alveolar pressure may remain positive even in the absence of external PEEP whenever the time required to decompress the lungs to the elastic equilibrium volume is shorter than the expiratory time (t_E) available before the next inspiration (99, 100). This end-expiratory elastic recoil pressure ($P_{el,rs}$) has been termed occult PEEP, auto PEEP (101), and PEEPi (102). Both abnormalities in a patient's respiratory mechanics and inappropriate ventilator settings may cause PEEPi (100, 101). As in the case of set PEEP, PEEPi may decrease cardiac output (103, 104), and by thus impairing respiratory muscle perfusion, contribute to respiratory muscle dysfunction. Furthermore, PEEPi poses an inspiratory pressure threshold load during both spontaneous breathing and patient-triggered, assisted modes of mechanical ventilation. Indeed, PEEPi must be fully counterbalanced by the contraction of a patient's inspiratory muscles before the ventilator can be triggered (99), giving Equation 3:

$$P_{app} = PEEPi + V/C + Rt + (k_1 \dot{V} + k_2 \dot{V}^2) \quad (3)$$

Therefore, during assisted modes of mechanical ventilation, the total effort needed to trigger the ventilator does not correspond to the small negative pressure (i.e., -1 to -2 cm H₂O) usually set. Clearly, high levels of PEEPi, such as those in patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) (94, 105, 106) or asthma (107), can increase significantly the magnitude of a patient's effort to trigger the ventilator. In some instances, the achieved decrement in Ppl may be smaller than the level of PEEPi, resulting in failure to trigger the ventilator and the occurrence of ineffective or wasted efforts (81–83, 108–111). Application of a low level of PEEP and/or continuous positive airway pressure (CPAP) can improve patient-ventilator interaction and reduce significantly the magnitude of inspiratory effort during

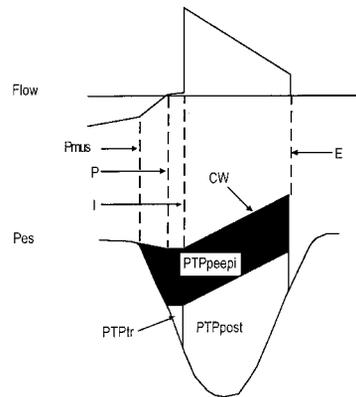


Figure 3. Illustration of method used to calculate the pressure-time product (PTP) for the esophageal pressure (Pes) and to partition it into its constituent components: efforts required to overcome PEEPi (PTPpEEPi), triggering effort (PTPptr), and posttriggering effort (PTPpost). PTPpEEPi constitutes a load imposed during the whole inspiration, whereas the triggering effort represents only a short delay before being transformed into volume. CW = chest wall; E = expiration; Pmus = muscular pressure; P = PEEPi; I = onset of inspiratory flow. Reprinted by permission from Reference 93.

assisted ventilation and weaning by counterbalancing PEEPi at least in part (91, 93, 111).

Intrinsic positive end-expiratory pressure can be measured in two ways: by the end-expiratory airway occlusion technique and by simultaneous recording of flow and Ppl.

End-expiratory airway occlusion technique. End-expiratory airway occlusion (EEO) for measurement of static PEEPi can be performed manually at the expiratory port of the ventilator during the last 0.5 seconds of the expiration (112). Alternatively, a pneumatic valve can be used for rapid occlusion at the airway opening (111, 113, 114). This second technique has the advantage of avoiding problems related to gas compression in the ventilator tubing, although some variability can occur due to timing of the occlusion. However, near the end of expiration, the volume expelled per unit of time is very small because of extreme airway compression, and therefore, small changes in t_E are not expected to affect substantially the magnitude of PEEPi, at least for a t_E of around 3 seconds (111). Measurement of PEEPi can be easily performed with ventilators that are already equipped with an end-expiratory occlusion hold option, either a manual operating button (e.g., the Siemens Servo 900C or 300) (115–118) or a hardware/software facility (e.g., the enhanced 7200 series of the Puritan-Bennett ventilator), for rapid occlusion of the expiratory port exactly at the end of a tidal expiration. With ventilators that do not include this option, airway occlusion can be performed using manually operated valves (119, 120).

Simultaneous recording of flow and Ppl. The accurate measurement of PEEPi can pose a problem in patients with spontaneous activity of the inspiratory muscles, although some authors have been able to relax patients and obtain an apparent end-expiratory plateau (91, 112). However, in actively breathing patients, measurement of PEEPi might require the insertion of an esophageal balloon to estimate changes in Ppl. Although the "occlusion test" has been suggested for validation of the esophageal balloon technique (121), its use in supine critically ill patients has been questioned and a legitimate study has never been really performed. As illustrated in Figure 4, PEEPi is measured as the decrease in Ppl preceding the onset of inspiratory flow. PEEPi measured in this way represents dynamic PEEPi (PEEPi,dyn), which is significantly less than static PEEPi (122). This method of measuring PEEPi,dyn is valid provided that the expiratory muscles are relaxed at the end of the expiration. Indeed, if the expiratory muscles are actively contracting during expiration, the decrease in Ppl at end-expiration could be due to expiratory muscle relaxation

rather than inspiratory muscle contraction (123). This may also occur in ventilator-dependent patients (94, 95).

To obtain the correct value of PEEPi, i.e., without positive end-expiratory alveolar pressure due to expiratory muscle activity, a number of approaches have been employed. Appendini and coworkers (94) suggested subtracting the corresponding change in Pga from the change in Ppl during the time interval from the onset of the inspiratory effort, as indicated by the swing in Pdi, to the start of inspiratory flow (Figure 4). Lessard and coworkers (95) proposed that the expiratory rise in gastric pressure should be subtracted, assuming a complete transmission of pressures generated by all or most of the expiratory muscle activities to the abdominal cavity. Recently, Yan and coworkers (124) used the Campbell diagram method to measure PEEPi,dyn in spontaneously breathing subjects and to correct for expiratory muscle activity without requiring the insertion of a gastric balloon. In this connection, it has to be mentioned that some nasogastric tubes used for nutrition include a balloon-catheter system for measurement of changes in Ppl, thus limiting the invasiveness of the maneuver (125). Yan and coworkers (124) urged caution when interpreting the measurement of PEEPi,dyn in actively breathing subjects, because of the confounding effects of the viscoelastic properties of the respiratory system, postinspiratory inspiratory muscle activity, and expiratory muscle activity. Moreover, it has to be considered that during the interval that PEEPi is being measured, contraction of the diaphragm can increase Pga while concomitant relaxation of the expiratory muscles can decrease Pga such that the relative magnitude of those two separate activities remains unpredictable. Furthermore, expiratory rib cage muscles can be active and also affect Pes. Therefore, even after using Pga to correct the recorded PEEPi,dyn, the corrected value may not truly quantify the magnitude of dynamic hyperinflation (124).

In summary, due to its important clinical implications, PEEPi should be measured in ventilator-dependent patients. The end-expiratory airway occlusion remains the reference maneuver, although interpretation is extremely difficult in the case of expiratory muscle recruitment (95).

Work of Breathing

Mechanical work (W) implies that an applied force or pressure (e.g., Papp in Equation 1) is producing some displacement in a system, e.g., change in volume (ΔV), according to Equation 4:

$$w = P_{app} \cdot V = \int P_{app} \cdot \Delta V \quad (4)$$

that represents the area subtended by the PV curve. WOB can be expressed in power (per unit of time) or per liter of ventilation (J/L). The relationship between work and minute volume, however, is usually nonlinear. Because the reduction of excessive patient WOB due to abnormal respiratory mechanics is a major goal of mechanical ventilation, measurement of WOB is of substantial interest in ventilator-dependent patients. However, the technique can be invasive and is not adequately standardized.

During controlled mechanical ventilation (CMV), the passive work is measured according to Equation 4. This measurement has been used not only to gather information on a patient's respiratory mechanics, but also to estimate a patient's WOB by mimicking a spontaneous breathing pattern (126). The use of such measurement to predict whether a ventilatory workload is compatible with unsupported breathing is too complex for routine use in weaning management (127–129). During assist-control ventilation, as suggested by Marini and

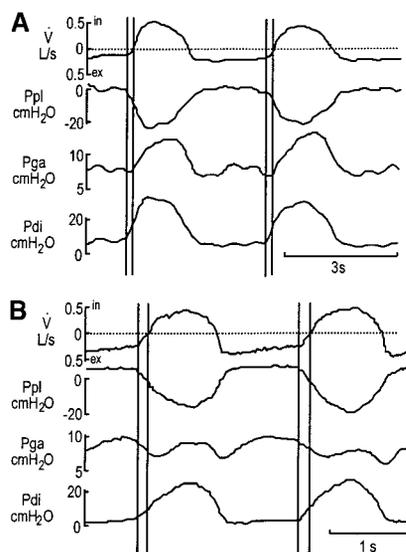


Figure 4. Experimental record illustrating the method used to determine the level of dynamic intrinsic PEEP (PEEPi,dyn) during spontaneous unoccluded breathing efforts in a representative patient with active expiratory muscles. From top to bottom, tracings represent flow (V), pleural pressure (Ppl), gastric pressure (Pga), and transdiaphragmatic pressure (Pdi). The first vertical line indicates the point corresponding to the onset of the inspiratory effort (Pdi swing). The second vertical line indicates the point corresponding to the start of the inspiratory flow. The

dotted horizontal line represents zero flow. in = inspiratory flow; ex = expiratory flow. (A) Tidal volume = 0.46 L. Note that expiratory flow ends abruptly before inspiration, whereas the Pdi and Ppl swings have already begun and Pga has remained constant during that interval. In this case PEEPi,dyn was measured as the negative deflection in Ppl between the point corresponding to the onset of the Pdi swing and the point of zero flow. (B) Tidal volume = 0.33 L. Note that Pga increases throughout most of the expiration. By contrast, Pga becomes less positive from the onset of the inspiratory effort indicated by the start of positive Pdi swing to the start of inspiratory flow. In this case PEEPi,dyn was measured as the negative Ppl deflection between the point corresponding to the onset of the Pdi swing and the point of zero flow subtracted by the amount of Pga negative deflection observed in that interval. Reprinted by permission from Reference 94.

coworkers (49, 50) and Ward and coworkers (53), the patient's WOB can be estimated noninvasively by comparing the pressure-volume (or pressure-time) relationship with that during CMV. Differences in WOB among patients, even in the same patient under different circumstances, may be used to compare the effects of the ventilatory settings, particularly volume and flow, the internal diameter of the endotracheal tube, the ventilator devices, or for evaluation of a patient's response to therapy, such as bronchodilators (93, 130–132). During assisted modes of ventilation, a patient's WOB can be measured with the esophageal balloon-catheter technique using the Campbell diagram (Figure 5), which also allows partitioning between elastic and resistive work, and the detection of expiratory muscle activity. The presence of a positive alveolar pressure at end-expiration (i.e., intrinsic PEEPi) can considerably increase the area enclosed in the loop and involve supplemental "elastic" work. Measurement of WOB may help in deciding an appropriate level or type of ventilator assistance and avoid both excessive and insufficient support. For instance, continuous flow systems seem to offer less resistance to breathing than demand flow (i.e., pressure-triggered) systems and can decrease a patient's WOB (86, 93, 133–135) (see ASSESSMENT OF THE FUNCTION OF THE ACTIVE CHEST WALL: CAMPBELL DIAGRAM in Section 6 of this Statement).

There is little doubt that measurement of WOB could be useful in many clinical conditions in ventilator-dependent patients. Automatic systems for its measurement are now available (99, 136–138). However, the superiority of the measurement of WOB, over more simple monitoring, for example over P0.1 (56, 74) or breathing pattern (13), has not been proved (76). The esophageal balloon technique is unlikely to

be used routinely for monitoring the magnitude of inspiratory effort and WOB. Whether measurements of Ppl could improve useful clinical-decision making and patient management in certain situations, such as the difficult-to-wean patient or the patient who unexpectedly “fights the ventilator (Figure 6),” remains to be determined.

Transdiaphragmatic Pressure

Transdiaphragmatic pressure can be measured in ICU patients for research or diagnostic purposes when diaphragmatic dysfunction is suspected. It requires simultaneous recordings of Pes and Pga; Pdi is obtained by measuring the differential pressure between these two signals. Because Pga usually rises, or is positive, during inspiration whereas the Pes signal is usually negative, subtraction of Pes from Pga is, in effect, the sum of the two tidal excursions. This measurement is described in more detail elsewhere. The potential applications of this measurement in ICU patients are summarized in subsequent text (see TECHNIQUES FOR PRESSURE MEASUREMENTS in Section 2 of this Statement).

Absolute values of the Pdi swings. Although this measurement has not been used for quantification of respiratory muscle dysfunction, its relation to the amplitude of V_T is a reflection of the degree of mechanical coupling between the respiratory muscles and the respiratory system. While a normal subject may require a Pdi swing of 5 cm H₂O to obtain a V_T of 500 ml, a severely diseased patient, as often seen in the ICU, may develop up to 30 cm H₂O to achieve only half of this volume (85). The same reasoning can be used for Pes swings. Minimizing tidal Pdi has also been proposed to be a target for titration of pressure support ventilation (139).

Maximum Pdi (Pdi,max) and mean Pdi over Pdi,max. This ratio has been proposed in the laboratory setting to predict the risk of respiratory muscle fatigue (140). Although it is of potential interest in the field of intensive care medicine, its use is limited by the extreme difficulty of obtaining reliable measurements of Pdi,max in this setting (141). It is necessary to motivate the patient and, in particular, to display the pressure traces while the patient performs the maneuver. The same

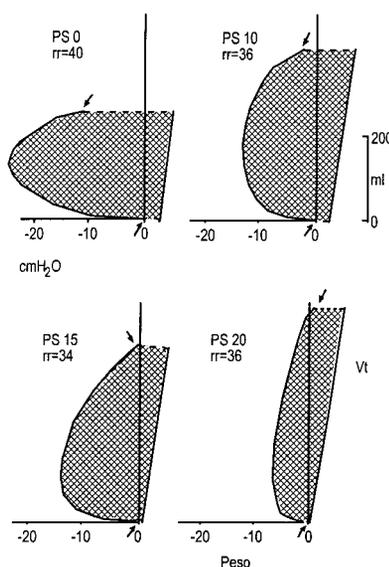


Figure 5. Loops of esophageal pressure against V_T used for computation of the work of breathing in a patient successively ventilated with pressure support (PS) of 0, 10, 15, and 20 cm H₂O. The work per breath is represented by the cross-hatched area subtended by the inspiratory part of the pressure-volume loop on the left and the relaxation curve of the chest wall on the right. Arrows indicate the beginning and end of inspiration. The relaxation curve of the chest wall is passed through the elastic recoil pressure of the chest at end exhalation, and the distance between the beginning of

the pressure-volume loop (arrow) and the relaxation curve represents intrinsic PEEP. The concomitant decrease in the work per breath and in the respiratory rate (rr) results in a large reduction in the work of breathing per minute (power). Reprinted by permission from Reference 55.

problem exists for the diaphragmatic tension time index ($Pdi/Pdi,max \times$ inspiratory time $[t_i]/$ total time of the respiratory cycle $[T_{TOT}]$), which incorporates the duty cycle (142). Also, calculation of mean Pdi and t_i/T_{TOT} is complicated by the difficulty in determining the baseline value of Pdi in such patients (84) (see MAXIMAL STATIC INSPIRATORY AND EXPIRATORY PRESSURES in Section 2 of this Statement).

The absolute values of Pdi,max can be used to estimate the strength of the diaphragm, but normal values have a wide range: varying between 60 and 240 cm H₂O. The Pdi value obtained during a sniff maneuver constitutes an attractive alternative because it is much simpler to perform. However, its reliability in intubated patients has not been rigorously tested.

The ratio of the inspiratory Pga swings to Pdi. The Pga/Pdi ratio has been proposed as a means of assessing the diaphragmatic contribution to the tidal effort (143). The higher this ratio, the greater is the diaphragmatic contribution to the tidal breathing and the smaller the contribution of other inspiratory muscles, which all contribute to the negative intrathoracic pressure swings. In ICU patients, this contribution is often small (frequently < 20%), indicating that recruitment of accessory muscles is a common occurrence (141–144). A precise quantification based on this index is made problematic by the fact that Pga is influenced by abdominal compliance, which can vary with abdominal muscle tone, position, and other factors related to abdominal contents. It is a crude yet useful index, nevertheless, for the detection of diaphragmatic dysfunction or paralysis, especially in the postoperative period (144–148). A negative Pga/Pdi ratio indicates severe diaphragmatic (or phrenic nerve) dysfunction and represents the equivalent of a paradoxical abdominal motion. Correct interpretation of this measurement requires careful avoidance of two pitfalls. First, the incorrect placement of the gastric balloon in the lower esophagus mimics exactly severe diaphragmatic dysfunction; this problem is not trivial, because the main criterion for checking the correct placement of the gastric balloon is often the shape of the signal (144). Second, recruitment of abdominal muscles during expiration is followed by a sudden relaxation at the beginning of the next inspiratory effort, which can also mimic diaphragmatic dysfunction (94, 95, 123, 149). Because this is a frequent occurrence in ICU patients, special attention should be paid to this problem (and ideally an abdominal wall relaxation curve should be obtained).

Examination of the Pga signal during expiration. This allows detection of phasic expiratory muscle activity, and it may help in the differentiation of dynamic hyperinflation from expiratory muscle recruitment as the mechanism that explains the presence of a phase lag between the beginning of the negative Pes swings and the onset of inspiratory flow, which is often referred to as “intrinsic PEEP” (94, 95, 123, 149). Ideally, measurement of pressures should be coupled with an estimate of thoracic and abdominal dimensions to correctly interpret the changes in pressure.

Maximum relaxation rate. The rate at which Pdi returns to baseline with each spontaneous breath, or after stimulation or after a sniff maneuver, can be used as a predictor of diaphragmatic fatigue (150, 151). Maximum relaxation rate has been used in the ICU to study patients being weaned from mechanical ventilation (152). Weaning failure was associated with a slowing of the maximum relaxation rate of the respiratory muscles (Pes) and of the diaphragm, indirectly suggesting that the applied load in these patients exceeded the capacity of the respiratory muscles (see RELAXATION RATE in Section 5 of this Statement).

Phrenic nerve stimulation. Performance of a full force-frequency curve for the detection of respiratory muscle fatigue is

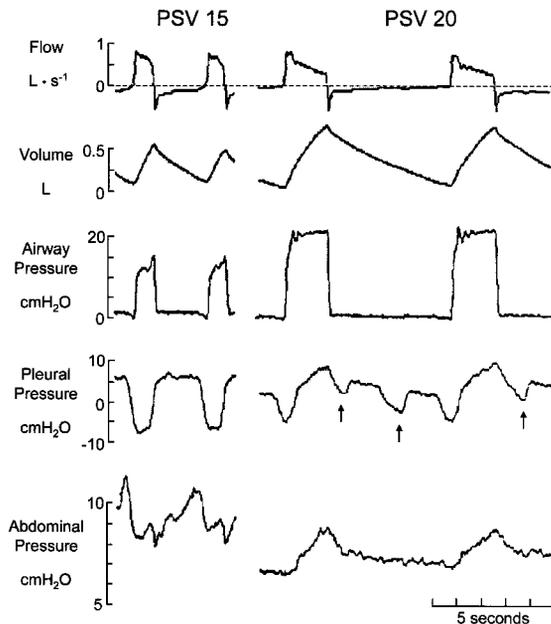


Figure 6. Recordings illustrating the method used to assess patient-ventilator interaction. From top to bottom: flow; volume; airway pressure; pleural pressure (Ppl); and abdominal (gastric) pressure. Ineffective inspiratory efforts are revealed by negative swings in Ppl during expiration (arrows) that are not matched with a ventilator-assisted breath. The concomitant declines in Ppl and abdominal pressure at the beginning of expiration suggest that Ppl was not dominated by abdominal muscle contraction. PSV 15 and PSV 20 indicate pressure support ventilation of 15 and 20 cm H₂O, respectively. Reprinted by permission from Reference 106.

impractical in critically ill patients (153). Measurement of the response to a single supramaximal stimulation of the phrenic nerve, i.e., twitch stimulation, is an appealing method of monitoring changes in diaphragmatic contractility (153). This approach has the considerable attraction of being independent of volitional influences (154). However, systematic investigations of twitch stimulation of the phrenic nerves in critically ill patients have yet to be published. The recent introduction of magnetic stimulation (155–157), which has several advantages over electrical stimulation of the phrenic nerves, should further increase the feasibility of twitch stimulation in the ICU setting (see PHRENIC NERVE STIMULATION in Section 2 of this Statement).

Diaphragmatic Electromyography

In mechanically ventilated patients, direct recording of the electrical activity of the crural diaphragm via an esophageal electrode has been used to quantify the activity of this muscle, and to examine the precise timing of activation (54, 55, 158–161) (see RECORDING ELECTRODES in Section 3 of this Statement).

PREDICTION OF WEANING

Management of the difficult-to-wean patient is one of the most challenging problems in critical care medicine (2, 3). Overall, approximately 40% of the time that a patient spends receiving mechanical ventilation is devoted to the weaning process, and in certain disease states, such as COPD, the weaning process accounts for approximately 60% of ventilator time (162). Deciding the best time to initiate weaning is especially important. If weaning onset is postponed, the patient is placed at an increased risk of life-threatening, ventilator-induced complications. If weaning is commenced prematurely, the patient may

suffer severe cardiopulmonary or psychological decompensation, which sets the patient back in his or her clinical course. Although careful clinical assessment is necessary in deciding when to discontinue mechanical ventilation, this alone is not sufficient, as demonstrated by Stroetz and Hubmayr (163). They studied 31 patients being weaned by gradual reductions in the level of pressure support. The physician in charge of each patient was asked to predict a patient's ability to sustain unassisted breathing without distress for 1 hour. Of 22 patients whom the physicians thought likely to fail a weaning trial, 11 were successfully weaned; of nine patients thought likely to be successfully weaned, three failed the trial. This study provides clear evidence of the need to employ objective tests, i.e., predictive indices, when deciding if a patient can tolerate the discontinuation of mechanical ventilation.

Several tests have been described to guide the timing and pace of the weaning process. Because an imbalance between respiratory mechanical load and respiratory muscle capability appears to be the major cause of weaning failure (18, 19), many of the weaning indices directly or indirectly relate to respiratory muscle function. Before assessing respiratory muscle function in a ventilator-supported patient, it is imperative to show that the patient is not likely to develop hazardous hypoxemia. Weaning should not be contemplated in a patient with a PaO₂ of less than 55 mm Hg at an inspired oxygen fraction (F_IO₂) of 0.40 or higher, because weaning failure is very likely in such patients. However, many patients with satisfactory oxygenation fail weaning attempts, and, except in the patient with marked hypoxemia, indices of oxygenation, such as the PaO₂/F_IO₂ ratio, are unreliable predictors of weaning outcome (164, 165).

Maximum inspiratory pressure, a measurement of inspiratory muscle strength (see VOLITIONAL TESTS OF RESPIRATORY MUSCLE STRENGTH in Section 2 of this Statement), is a standard weaning index. In an early study, Sahn and Lakshminarayan (61) found that all patients with a P_{I,max} value more negative than –30 cm H₂O were successfully weaned while all patients with a P_{I,max} less negative than –20 cm H₂O failed a weaning trial. Subsequent investigators have not found P_{I,max} to provide such clear separation between weaning success and weaning failure patients (13, 18, 106, 164–169). Studies with accessible data on the accuracy of P_{I,max} are summarized in Table 1. Because the studies differ in design (prospective, retrospective), method of performing P_{I,max} (best of three attempts, sustained occlusion for 20 seconds), method of weaning (trials of spontaneous breathing, intermittent mandatory ventilation, pressure support), and definitions of weaning success and failure, it is not surprising that accuracy of P_{I,max} varied considerably among the studies. Nevertheless, it is possible to arrive at some general conclusions. Sensitivity was approximately 0.80, meaning that approximately 80% of patients who succeeded in a weaning trial had a P_{I,max} value that predicted success (i.e., more negative than –30 cm H₂O). However, specificity was approximately 0.25, meaning that only a minority (25%) of patients who failed a weaning trial had a P_{I,max} that predicted weaning failure (i.e., less negative than –30 cm H₂O). Moreover, the ability to predict outcome was not improved by employing a standardized method of measuring P_{I,max} (18, 106, 165). Based on these data, P_{I,max} measurements appear to be more helpful in understanding the reason why a particular patient failed a weaning trial rather than in deciding whether to attempt a weaning trial (see additional discussion of P_{I,max} in this section).

A minute ventilation of less than 10 L/minute, indicating acceptable ventilatory requirements, is another standard weaning index (61). However, in most studies, minute ventilation

has been shown to be little better than chance in predicting outcome (165, 166). More helpful is the partitioning of minute ventilation into its V_T and f_R components, so as to formulate the ratio of f_R to V_T , which can be used to quantitate the extent of rapid shallow breathing. The f_R/V_T ratio, measured with a simple handheld spirometer attached to the endotracheal tube while the patient spontaneously breathes room air for 1 minute, has been proposed as a reliable method of predicting weaning outcome (165). In an initial "training data set" in 36 patients, an f_R/V_T ratio of 105 breaths/minute/L provided the best separation between patients who were successfully weaned and those in whom weaning failed. This threshold value was then prospectively evaluated in 64 patients who constituted the "validation data set." The positive and negative predictive values were 0.78 and 0.95, respectively (165). Analyzing the data with receiver-operating-characteristic (ROC) curves, the area under the curve for the f_R/V_T ratio (0.89) was the highest of 10 weaning indices evaluated in the study. Of note, the area under the ROC curves of conventional weaning indices such as minute ventilation (0.40), the $P_{aO_2}/P_{A_{O_2}}$ ratio (0.48), and $P_{I,max}$ (0.61) were not significantly greater than that of an arbitrary test that is expected *a priori* to have no discriminating value (Figure 7). Jaechke and coworkers (170) reanalyzed the data of Yang and Tobin (165) in terms of likelihood ratios (171). The likelihood ratio for an f_R/V_T ratio of less than 80 breaths/minute/L is 7.53 (Table 2). In other words, an f_R/V_T of less than 80 is 7.53 times more likely to occur in a patient who is subsequently successfully weaned than to occur in a patient who will fail a weaning trial; a likelihood ratio of 5–10 is considered to generate moderate and usually useful shifts in pretest to posttest probability (171). Conversely, an f_R/V_T ratio greater than 100 is only 0.04 as likely to occur in a patient who will be successfully weaned as in a patient who subsequently fails a weaning trial; a likelihood ratio of < 0.10 is considered to generate large and often conclusive changes in the probability of a given diagnosis (in this case weaning failure).

In patients being weaned from mechanical ventilation, Sassoon and Mahutte (168) found that the f_R/V_T ratio had a sensitivity of 0.97 and a specificity of 0.40. The product of f_R/V_T and airway occlusion pressure ($P_{0.1}$) had the same sensitivity, but specificity increased to 0.60. Disappointingly, the combination of f_R/V_T and $P_{0.1}$ did not have a higher area under the ROC curve than that achieved by f_R/V_T alone.

Epstein (172) studied 84 patients with an f_R/V_T ratio < 100 breaths/minute/L and observed a positive-predictive value of 0.83. Fourteen patients required reintubation, and all but one of these had developed a new problem such as upper airway obstruction or congestive heart failure. Ten patients with an $f_R/V_T > 100$ were extubated, and four required reintubation (negative predictive value 0.4).

Chatila and coworkers (169) measured f_R/V_T with a hand-held spirometer in 100 medical-cardiac patients being weaned from mechanical ventilation. The f_R/V_T ratio was measured during the first minute of spontaneous breathing, and the patients were then weaned using T-tube trials, CPAP, or pressure-support ventilation. After 30–60 minutes, the f_R/V_T ratio was again measured. The area under the ROC curve was higher for the f_R/V_T ratio measured at 30–60 minutes than during the first minute of spontaneous breathing, 0.92 ± 0.03 and 0.74 ± 0.05 , respectively. Interestingly, the area under the ROC curve for 30–60 minutes is similar to that reported by Yang and Tobin (0.89) (165). This study by Chatila and coworkers (169) emphasizes the importance of not measuring the f_R/V_T ratio during the first minute of spontaneous breathing, when respiratory drive may still be suppressed. It does not necessarily mean that one needs to wait 30–60 minutes to reach a steady-state value that truly represents the patient's clinical status.

In a study of 218 extubated patients in a medical ICU, Epstein and Ciubotaru (173) showed that women have a higher f_R/V_T ratio than men, which could not be explained by body size, and that f_R/V_T was further increased in women with a narrow endotracheal tube. Consequently, the false-negative rate for f_R/V_T in women with a narrow endotracheal tube (≤ 7 mm internal diameter) was especially high. When comparing data from different studies of weaning indices, the pretest probability of a successful outcome becomes very important. Epstein and Ciubotaru (173) deliberately selected patients with a very high pretest probability of successful outcome (0.84), because every patient tolerated a weaning trial and was extubated; in contrast, outcome was in considerable doubt (pretest probability 0.56) in the patients studied by Yang and Tobin (165), who were trying to identify the earliest point in time that a patient could resume spontaneous ventilation. For identical false-negative (0.03) and true-negative rates (0.64) (166), the posttest probability of a successful outcome for $f_R/V_T > 100$ breaths/minute/L, calculated on the basis of Bayes' theorem, is 20% for the patients of Epstein and Ciubotaru (173) versus 5% for the patients of Yang and Tobin (165). In other words, f_R/V_T is less helpful in cases when the physician strongly suspects that the patient can tolerate weaning and extubation than when the physician is very doubtful about a patient's outcome.

Recently, Ely and coworkers (129) investigated whether the combination of predictive indices followed by a trial of spontaneous breathing would hasten the pace of weaning. Over a 9-month period, ventilator-supported patients in their medical ICU and coronary care units were screened each morning for five factors: $P_{aO_2}/F_{I_{O_2}}$ ratio > 200 ; PEEP ≤ 5 cm H_2O ; $f_R/V_T \leq 105$ breaths/minute/L; intact cough on suctioning; and absence of infusions of sedative or vasopressor agents.

TABLE 1. ACCURACY OF MAXIMAL INSPIRATORY PRESSURE AS A PREDICTOR OF WEANING OUTCOME

$P_{I,max}$ Threshold (cm H_2O)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Reference Number
≤ -30	0.68	0	0.56	0	166
≤ -30	1.00	0	0.67	0	167
≤ -20	NA	NA	0.91	0.22	164
≤ -30	NA	NA	0.92	0.21	164
≤ -15	1.00	0.11	0.59	1.00	165
≤ -20	1.00	0.14	0.60	1.00	165
≤ -30	0.86	0.21	0.58	0.55	165
≤ -20	0.91	0.30	0.82	0.55	168
≤ -20	0.90	0.26	0.67	0.60	169
≤ -30	0.67	0.69	0.78	0.55	169

Definition of abbreviations: NA = not available; $P_{I,max}$ = maximum inspiratory pressure.

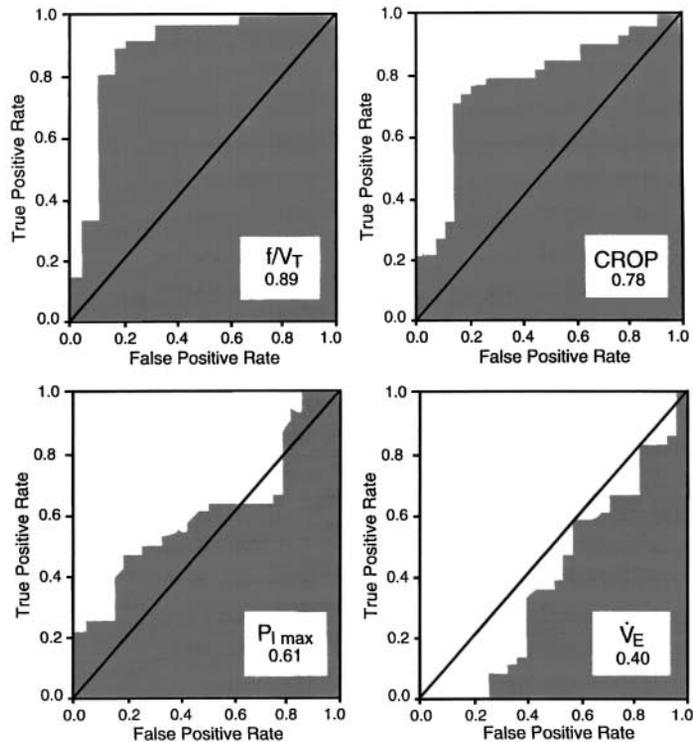


Figure 7. Receiver operating characteristic (ROC) curves for frequency/tidal volume (f/V_T) ratio, CROP index (an index that integrates measurements of dynamic compliance, respiratory rate, arterial oxygenation, and maximal inspiratory pressure), maximal inspiratory pressure ($P_{I,max}$), and minute ventilation (\dot{V}_E) in 36 patients who were successfully weaned and 28 patients who failed a weaning trial. The ROC curve is generated by plotting the proportion of true positive results against the proportion of false positive results for each value of a test. The curve for an arbitrary test that is expected *a priori* to have no discriminatory value appears as a *diagonal line*, whereas a useful test has an ROC curve that rises rapidly and reaches a plateau. The area under the curve (*shaded*) is expressed (*boxed*) as a proportion of the total area. Reprinted by permission from Reference 165.

Patients in the intervention group ($n = 149$) who met all five criteria underwent a 2-hour trial of spontaneous breathing that same morning. If the patient did not develop clinical signs of distress, employing objective criteria developed in earlier studies of weaning techniques (127, 128), the trial was considered successful, and the patient's physician was notified of this result. The control group ($n = 151$) had daily screening but did not undergo the spontaneous breathing trial. Although patients in the intervention group had more severe disease, with higher APACHE II and acute-lung-injury scores, their median duration of mechanical ventilation was 1.5 days less than the control group ($p = 0.003$), and they had lower rates of complications ($p = 0.001$) and reintubation ($p = 0.04$) and lower ICU charges ($p = 0.03$). This study demonstrates that the systematic use of weaning indices results in better patient outcomes than reliance on the clinical judgment of the attending physician.

In the original description of the f_r/V_T ratio, the measurement was obtained with a hand-held spirometer while the patient was disconnected from the ventilator and breathed room air for 1 minute (165). Some investigators have measured f_r/V_T during partial ventilator assistance, such as pressure support. For example, Lee and coworkers (174) reported that eight of nine patients who failed a weaning trial had an $f_r/V_T < 105$ breaths/minute/L, and they concluded that f_r/V_T was unhelpful. Because pressure support is well known to decrease f_r and increase V_T , it is not surprising that the f_r/V_T threshold value developed during unassisted breathing would not apply during pressure support ventilation.

Finally, the definition of the outcome event is very important in assessing the accuracy of a diagnostic test. Accumulating data suggest that the f_r/V_T ratio is more helpful in predicting the earliest point in time that a patient can breathe spontaneously without assistance from a ventilator than in predicting the need for reintubation after the patient has been extubated (129, 172, 173, 175). That is, f_r/V_T appears to be more helpful in deciding when to initiate the weaning process,

rather than deciding when to terminate it and extubate the patient.

CONCLUSION

This Section of the Statement has reviewed the tests of respiratory muscle function, direct and indirect, that are relevant to the particular environment of the ICU. The scientific basis and methodology of many of these tests are discussed in earlier Sections of the Statement. This article also focuses on the crucial issue of weaning from mechanical ventilation.

Abnormalities of the pattern of breathing are common in ICU patients, especially in those with respiratory muscle dysfunction. Tachypnea is a sensitive marker of deteriorating clinical status, but is not specific. Paradoxical motion of the rib cage and abdomen occurs with elevated respiratory load, but is not diagnostic of respiratory muscle fatigue. Measurements of maximum inspiratory pressure have poor reproducibility in critically ill patients and are of limited use for decision making in the ICU. Airway occlusion pressure ($P_{0.1}$) is easy to measure in patients receiving assisted ventilation, and high values signal increased respiratory motor output. The most direct measures of patient effort are work of breathing and PTP, but these measurements require considerable attention to detail and their use is confined to research settings. A scooped contour of the airway pressure tracing during volume and flow preset assisted ventilation indicates patient effort. The relative

TABLE 2. LIKELIHOOD OF SUCCESSFUL WEANING RELATED TO f_r/V_T RATIO*

f_r/V_T Ratio	Likelihood Ratio
< 80	7.53
80–100	0.77
> 100	0.04

Definition of abbreviations: f_r = respiratory frequency; V_T = tidal volume.
* Based on data of Yang and Tobin (171).

swings in esophageal and gastric pressures provides insight into the recruitment of different respiratory muscle groups. Respiratory muscle contractility can be assessed by recording transdiaphragmatic pressure provides in response to phrenic nerve stimulation, a complex and invasive technique. Intrinsic PEEPi, common in critically ill patients, can be measured using the EEO pressure in ventilated patients and by an esophageal balloon catheter in patients breathing spontaneously; with both techniques, however, the value can be falsely elevated because of expiratory muscle activity.

The ICU setting where tests of respiratory muscle function have greatest application is in the prediction of weaning outcome. Traditional predictors, such as maximum inspiratory pressure, vital capacity, and minute ventilation, are frequently falsely positive and negative. Although patients failing a weaning trial may have an elevated tension-time index and airway occlusion pressure, these tests have not gained popularity in everyday ICU practice. The ratio of respiratory frequency to tidal volume is the most reliable simple predictor of weaning outcome.

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