Medical Intelligence

New Tests of Pulmonary Function:
Physiologic Basis and Interpretation

Norman A. Bergman, M.D.*

It has become apparent that in many patients significant early chronic pulmonary disease develops in the absence of signs and symptoms. When these appear the disease process may already be moderately advanced. Early diagnosis is important, since there is evidence that pulmonary disease may be reversible if identifiable etiologic factors, such as cigarette smoking, environmental irritant exposure, and chronic infection, are eliminated early. Certain spirometric measurements are now widely used to evaluate mechanical performance of the respiratory system. These include such familiar tests as vital capacity, fraction of vital capacity expired in one second (FEV1), other timed vital capacities, estimation of peak flow rate, and maximum voluntary ventilation. It is now recognized that these spirometric tests frequently fail to detect chronic pulmonary disease until it is relatively advanced.

Recently, new tests of mechanical pulmonary function have been introduced into clinical practice. Three such tests are evaluation of maximum expiratory flow-volume curves, measurement of lung closing volume, and determination of frequency dependence of compliance. These tests appear to have the capability for recognition of chronic pulmonary disease at stages at which signs and symptoms may be absent or equivocal, where currently popular tests are nondiscriminatory, and when the pathologic process might be reversible. It is likely that these tests will be encountered with increasing frequency, and the anesthesiologist should be familiar with them. In order to understand these tests, it is necessary to consider the concept of small airways as the “silent zone” of the lung.

The “Silent Zone” of the Lung

Eighty per cent or more of tracheobronchial resistance resides in large central airways. In this context large central airways are designated as those belonging to the first five or six generations of the bronchial tree. Their diameter is greater than 2 mm. Included are subsegmental, segmental, lobar and main bronchi, and the trachea. The remaining 17 or 18 generations of small peripheral bronchi, therefore, contribute less than 20 per cent of total resistance to flow. These conclusions are based on calculations relating gas flow to observed structure and dimensions of the bronchial tree, as well as experimental evidence.

The cross-sectional area of the trachea is about 2.5 cm². At the bronchiolar level (generation 13–14, diameter 0.7–0.8 mm, quantity about 22,000), the cross-sectional area is about 40–70 cm². Respiratory bronchioles (generation 18–19, diameter 0.5 mm, quantity about 750,000) have a total cross-sectional area of 500–900 cm². During respiratory maneuvers identical volumes of gas must traverse each successive bronchial generation in any given time. Because of the progressive increase in total cross-sectional area from large central to small peripheral airways, there is a corresponding decrease in linear flow velocity. Decreases in pressure across different parts of the bronchial tree have been related to observed cross-sectional areas and flow velocities.

* Professor and Chairman, Department of Anesthesiology, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201. Accepted for publication November 14, 1975. Address reprint requests to Dr. Bergman.
Calculations confirm that the greatest fraction of total resistance resides in large airways, where total cross-sectional area is small and linear flow velocity is high. Small peripheral airways, with large total cross-sectional area and slow flow velocity, contribute only a small fraction of total resistance.5

Reductions of pressure along the airway from alveolus to airway opening have been partitioned experimentally with a “retrograde catheter.” This device is capable of measuring lateral pressure in 2-4-mm bronchi in animals and excised human lungs with minimal interference with gas flow through the bronchus in which it is placed. The catheter is introduced over a fine wire and positioned so that the flared tip is almost flush with the bronchial wall while the other end is brought out through the lung surface. It is then possible to partition airway resistance by relating flow to simultaneously measured difference in pressure between alveolus and airway opening (total airway resistance); between alveolus and retrograde catheter lodged in a small bronchus (peripheral airway resistance) and between retrograde catheter and airway opening (central airway resistance). Again, in healthy lungs the greatest fraction of total airway resistance was shown to originate in large central airways.2-8

Pathologic changes in certain forms of pulmonary disease occur initially in small airways. The most prominent example is the pathologic state called “chronic obstructive pulmonary disease.”9 Because peripheral airways contribute such a small fraction of total airway resistance it is possible to have in small airways appreciable disease involvement that is not detectable by measurement of airway resistance. A numerical example can illustrate this situation. Airway resistance in healthy subjects is small. Values of 1.0–2.0 cm H2O/l/sec are frequently reported.10 In a patient with a total resistance of 1.0 cm H2O/l/sec, only 0.2 cm H2O/l/sec might originate in small peripheral airways. A fivefold increase in resistance in small airways would raise total measured resistance to only 1.8 cm H2O/l/sec. This value is still within the normal range and is unlikely to cause symptoms or arouse suspicion. When symptoms and a significant increase in measured airway resistance occur, disease is usually moderately advanced. Currently popular spirometric tests such as FEV1 frequently fail to detect early disease in small airways, for reasons discussed below. Small peripheral airways have been characterized as the “silent zone” of the lung because they may be the site of significant disease that in the past has defied detection.11

Maximum Expiratory Flow–Volume (MEFV) Curves

ISOVOLUMIC PRESSURE–FLOW CURVES

Study of isovolumic pressure–flow curves has been of great importance for interpreting events that occur during a forced expiratory maneuver. To obtain these curves, a subject performs a series of expirations, each one at constant flow rate, over the whole range of his vital capacity. Actual flow rate is progressively increased from breath to breath (e.g., 0.5, 1.0, 1.5, 2.0 . . . l/sec). During these maneuvers transpulmonary (pleural) pressure, flow rates and lung volume are simultaneously recorded. Since the entire lung volume from total lung capacity (TLC) to residual volume (RV) has been traversed at several flow rates and the associated pressures measured, it is possible to select any desired lung volume in the vital capacity and to determine applied pressures necessary to produce the selected flows at this volume. A plot of such data is an isovolumic pressure–flow curve. A family of
The manner in which expiratory flow rate varies with lung volume during a maximum-effort vital capacity maneuver is illustrated in figure 2. This is a MEFV curve. As exhalation begins from TLC, peak flow is rapidly attained. Peak flow occurs in the effort-dependent region of lung volume so that its magnitude is determined by willingness and ability to exert expiratory muscles. As exhalation continues through the effort-independent regions of the vital capacity, flow rate continuously and progressively decreases even though maximum expiratory effort is sustained. At each lung volume during this maneuver measured flow is the maximum attainable flow for the identical lung volume as determined from isovolumic pressure-flow curves (fig. 3). During inspiration, flow is effort-dependent at all lung volumes.

The mechanism responsible for effort independence of flow as described above is dynamic compression of airways (fig. 4). During a forced expiration, all intrathoracic structures, including bronchi and lung, are subjected to positive pleural pressure. Intra-alveolar pressure is the sum of pleural pressure plus elastic recoil pressure of the lung. Pressure within bronchi decreases progressively down the airway due to frictional losses and acceleration of gas. Intraluminal pressure in small peripheral bronchi is only slightly less than that in alveoli and greater than pleural pressure. These airways are passively distended by positive transmural pressure. They are also actively distended by their tethering attachment to lung tissue at large lung volumes. Intraluminal pressure in large central bronchi toward the airway open-

![Diagram showing expiratory flow-volume curve](image1)

**FIG. 2.** A maximum expiratory flow-volume (MEFV) curve from a healthy patient.

![Diagram showing isovolumic pressure-flow curves](image2)

**FIG. 3.** Isovolumic pressure-flow (IVPF) curves and a maximum expiratory flow-volume curve from the same individual. If maximum effort is sustained throughout exhalation, flows at any volume during the MEFV maneuver are identical to maximum attainable flows for the corresponding lung volumes as determined with IVPF curves.
ing is close to ambient (zero) pressure and less than surrounding pleural pressure. These airways are compressed owing to their negative transmural pressure during most of a forced expiratory maneuver. There is a point in the airway where intraluminal pressure is equal to pleural pressure. This point where transmural bronchial pressure is zero has been called the “equal-pressure point.” Downstream (toward the airway opening) from the equal-pressure point airways undergo dynamic compression during forced exhalation and act as a fixed resistor. Upstream (toward alveoli) from the equal-pressure point resistance is variable and changes with lung volume. Resistance in upstream airways is low at large lung volumes and increases as residual volume is approached.15,18

An important feature of a forced vital capacity maneuver is that once sufficient pressure is generated to initiate the above-described flow-limiting mechanisms, expiratory flow at any lung volume becomes essentially independent of any subsequent increase in applied pressure (fig. 5). Pressure increases are transmitted equally to the pleural space, alveoli, and bronchi. Absolute pressure at all points within the thorax may be altered with changes in pleural pressure, but the pressure difference between alveoli and the downstream flow-limiting segment remains constant. Therefore, although alveolar pressure is the sum of pleural and lung elastic recoil pressures, the pressure difference effective in producing gas flow between alveoli and the flow-limiting segment at any volume is simply lung elastic recoil pressure at that volume. Similarly, properties of the flow-limiting segment should be essentially constant since bronchial transmural pressure changes little with increases in pleural pressure.

In summary, during forced exhalation the phenomena of flow limitation and effort-independence of flow are caused by development of a dynamically compressed segment of the bronchial tree with fixed resistance downstream from the equal pressure point. The magnitude of flows attained and the characteristic configuration of the maximum expiratory flow-volume (MEFV) curve (fig. 2I), however, are determined by the properties and behavior of small peripheral airways upstream from the equal-pressure point, as well as lung elastic recoil. MEFV curves are determined by establishment of flow conditions that become independent of applied (pleural) pressure once flow limitation has occurred.

Conventional spirometric measurements, such as FEV₁, which frequently fail to detect
early disease involvement in small airways, focus on events occurring in the initial effort-dependent portion of forced exhalation. Small but significant deviations from normal flow patterns may be overlooked. Conventional spirometric tests that might be more useful for early detection of lung disease are those that emphasize events occurring lower in the vital capacity after peak flow has been attained. These include measurement of maximum mid-expiratory flow (MMF) or forced expiratory flow rate between exhalation of 75 and 85 per cent of VC (FEE75–85).19

**NATURE OF THE MEFV TEST**

Evaluation of MEFV curves is currently proposed as a technique particularly useful for early diagnosis of airway disease. To obtain such a curve the subject inspires to total lung capacity and performs a rapid, forceful vital capacity maneuver. During the maneuver flow rate is recorded as a function of lung volume. This requires a recording device with which one variable can be displayed as a function of a second variable. Both X-Y recorders and oscilloscopes have been used. (With conventional spirometry, volumes are recorded as a function of time.) Representative MEFV curves are shown in figures 2 and 6. Peak expiratory flow is attained very early in expiration and can be read directly from the record. Peak flow, however, is markedly effort-dependent and is not regarded as particularly informative for early diagnosis of airway disease. Throughout the remainder of the forced exhalation, flow rate progressively diminishes as lung volume decreases toward residual volume. Flow rates at any lung volume can be read directly from the record. If appropriate effort is sustained throughout exhalation, each flow rate represents the maximum attainable in the respective lung volume due to the flow-limiting mechanisms described above. Magnitude of flow at any volume depends on resistance of small, peripheral upstream airways and upon lung elastic recoil. MEFV curves thus provide much of the information obtainable from isovolumic pressure–flow curves without necessity for measuring pleural pressure.

**INTERPRETATION OF MEFV CURVES**

Flow rates that should be attained at any given lung volume during performance of a forced vital capacity maneuver have been published. These flow rates are greater in males, increase with body height, and decrease with age. For example, a healthy 40-year-old 6-foot man should attain an expiratory flow rate of 5–6 l/sec at 50 per cent VC and a flow rate of 2.0–2.5 l/sec at 25 per cent VC.20,21 A flow rate significantly below predicted at one or more specified lung volumes (e.g., 50 or 60 per cent VC to TLC, 1 liter above RV, etc.) indicates abnormal pulmonary function. The reciprocal of the slope of the descending limb of the MEFV curve is related to the time constant (product of resistance times compliance) of the respiratory system. Decreases in slope of this segment of the curve, therefore, also signify altered pulmonary function. In healthy subjects, most of the descending limb of the MEFV curve approximates a straight line. An additional change associated with the presence of abnormal pulmonary function is “scallopilng,” where the curve becomes convex to the volume axis. Although this phenomenon has been attributed to asynchronous sequential emptying of parallel lung units having different time constants, other mechanisms are also likely to be involved.22,23 If time markers are used while recording MEFV curves, other spirometric measurements, such
as FEV\textsubscript{1.06} can be determined directly from the record.

Use of MEFV curves in pulmonary function testing is a fairly recent development. Much remains to be done in standardization of technique, establishment of normal values, and establishment of criteria for analysis and interpretation of data.\textsuperscript{24-26} Since the MEFV curve is influenced by both lung elasticity and resistance in small peripheral airways, an abnormal MEFV curve can signify disease of pulmonary parenchyma, pathologic processes involving small air passages, or both. Further tests suggested for more precise diagnosis of pulmonary disease in patients with abnormal MEFV curves include measurements of diffusing capacity, static transpulmonary pressure, and alveolar-arterial oxygen tension difference.\textsuperscript{26-27}

**Measurement of Closing Volume**

**CONSEQUENCES OF THE VERTICAL GRADIENT OF INTRAPLEURAL PRESSURE**

Pressure within the pleural space is not uniform. It is least in nondependent areas and progressively increases to become maximum in the most dependent regions.\textsuperscript{28} In the healthy erect adult, pleural pressure surrounding apices of the lung may be about \(-10\) cm H\textsubscript{2}O. Pressure increases about \(0.25\) cm H\textsubscript{2}O per cm distance down the lung to become about \(-2\) cm H\textsubscript{2}O at the bases.\textsuperscript{29} In the supine subject, the vertical gradient of pressure increases from anterior to posterior regions of the lung and is less than in the erect position because of the smaller A-P diameter of the thoracic cavity. There are probably several causes for this gradient of pressure, such as variations in hydrostatic and structural properties in different lung and thoracic regions.\textsuperscript{30} Innate elasticity of tissue is uniform throughout the lung.\textsuperscript{31} Therefore, lung units in nondependent areas where transpulmonary pressure is greatest are already well expanded at the resting end-expiratory position but have limited capability for further volume expansion. Lung units in dependent areas, where transpulmonary pressure is least, are less well expanded at rest but have greater capability for further expansion.\textsuperscript{28} At total lung capacity, expansion of pulmonary units is uniform throughout the lung.

If a young, healthy erect subject does a forced expiration down to residual volume, pleural pressure over his entire lung increases. Pleural pressure around the apices becomes greater (less negative) than at rest, and apical volume decreases. At the base, where pleural pressure was initially higher, the increase in pressure with forced expiration may cause compression and volume reduction to the extent that some lung units close. If inspiration now starts from residual volume, gas is distributed initially to lung units at the apex, which are open. Inspired gas will not enter closed basilar lung units until pleural pressure surrounding this area has decreased sufficiently to relieve compression. Once these previously closed basilar units open, however, inspired gas is subsequently preferentially distributed to them throughout the remainder of inspiration.\textsuperscript{32}

There are two causes for this pattern of gas distribution. As stated above, basilar regions which are initially relatively incompletely expanded have a larger capacity for further expansion than apical areas. In addition, basilar regions operate along the steep portion of the pressure-volume curve of the lung. In this region of the curve, a small change in pressure causes a large change in volume. More fully expanded apical regions operate along the flatter portion of the curve, where comparable pressure changes cause less volume change. The volume at which lung units begin to close on reduction of lung volume has been called "closing volume."

With advancing age, bronchi become more susceptible to closure by compression because of gradual loss of the structural integrity of their walls. In addition, loss of lung elastic recoil diminishes the magnitude of tethering radial traction that normally acts on bronchial walls to assist in maintaining patency. Pleural pressure becomes more positive in the elderly.\textsuperscript{33,34} With aging, the lung volume at which closure of basilar units begins to occur gradually increases and approaches the resting end-expiratory level. At about 65 years of age, closing volume is at FRC in the seated subject, so that any reduction of lung volume...
below the resting level is associated with closure of dependent lung units. After 65 years of age, some lung units may close above FRC during normal tidal ventilation. Closing volume also varies with body posture. In the supine position, closing volume coincides with FRC at about 45 years of age. Supine elderly subjects may have extensive closure during normal ventilation.35,36

Pathologic changes in small airways render them more susceptible to closure. This occurs relatively early in various types of pulmonary disease. Therefore, measurement of closing volume is proposed as another method for the early detection of lung disease at a stage when symptoms may be minimal or absent and conventional spirometric tests may be nondiscriminatory.37-38 Closure of lung units associated with reduction of FRC has been proposed as a physiologic basis for the pulmonary dysfunction known to occur in anesthetized patients.39

**NATURE OF THE CLOSING VOLUME (CV) TEST**

Closing volume may be determined using a modification of the single-breath test for measurement of uniformity of distribution of inspired gas. Nitrogen is the most convenient test gas, since most pulmonary function laboratories have nitrogen analyzers. The subject, who has been breathing air, takes several deep inspirations and the exhales completely down to residual volume (RV). At RV the inspired gas is changed to 100 per cent oxygen. He then inspires oxygen slowly to total lung capacity (TLC). Finally, a slow, even exhalation back down to RV is delivered. During this final exhalation expired volume and nitrogen concentration are measured. Expired nitrogen concentration is displayed as a function of exhaled volume so that, again, some type of X-Y recording apparatus is necessary. A representative closing volume curve is shown in figure 7. Four phases can be distinguished in the curve. During phase I, nitrogen concentration is zero. This represents exhalation of 100 per cent oxygen that filled the respiratory deadspace at the end of the preceding inspiration. The rapidly increasing nitrogen concentration of phase II represents exhalation of mixed deadspace and alveolar gas. Phase III has been called the “alveolar plateau” and represents exhalation of alveolar gas. Nitrogen concentration progressively increases, but the change is small in normal subjects. During phase IV the exhaled nitrogen concentration continues to increase, but the slope of the curve is appreciably greater than in phase III. The volume at which the junction of phase III and phase IV occurs is the closing volume.37

The configuration of phases III and IV of the closing volume curve can be explained by consideration of the pattern and sequence of filling and emptying of the lung. During inspiration of oxygen from RV the gas is initially distributed to open, nondependent areas. These regions are relatively well expanded at RV and undergo only moderate further expansion during inspiration to TLC. Dilution of alveolar nitrogen with inspired oxygen will not be extensive in these areas. Dependent lung regions are closed at RV. Inspired oxygen will not enter these areas until they open at some volume above RV. Once they are open, however, subsequent volume expansion is large and dilution of alveolar nitrogen is more extensive. At the end of the maximum inspiration of oxygen to TLC, there is a vertical gradient of nitrogen concentration in alveoli down the lung. The highest concentration is
at the apex and the lowest concentration is at the base. The increasing slope of nitrogen concentration during phases III and IV of the curve is attributable to asynchronous emptying of the lung. Preferential emptying of regions that had the greatest volume expansion and nitrogen dilution (basilar regions) occurs early in expiration. As exhalation proceeds, these regions gradually empty, and the contribution to expired gas from units in which nitrogen was less diluted progressively increases (phase III). At closing volume the contribution of basilar units, with a low nitrogen concentration, abruptly diminishes. The remainder of exhalation consists primarily of gas from apical units having a higher nitrogen concentration (phase IV). Thus, the junction between phases III and IV can be used to identify the volume during exhalation when basilar lung units start to close. The rate of increase of the expired nitrogen concentration during phase III (alveolar plateau) is the basis for the single-breath test of uniformity of distribution of inspired gas. In a normal non-smoking man, the increase of nitrogen concentration should not exceed about 1–2 per cent per liter exhaled during phase III.\(^\text{40,41}\)

**INTERPRETATION OF CLOSING VOLUME MEASUREMENTS**

Vital capacity can be determined directly from the closing volume curve. It is the total distance from start to end of exhalation along the volume axis. Closing volume, the junction of phases III and IV of the exhaled nitrogen recording, can also be determined directly from the curve. Closing volume (CV) is most frequently reported as percentage of vital capacity. It is, therefore, expressed as the ratio of the distance from RV to CV to the distance from RV to TLC. CV in healthy subjects is influenced primarily by age and posture. Values for healthy subjects, both seated and supine, have been published. For example, CV in healthy seated subjects is 13 per cent at 30, 16 per cent at 40, and 20 per cent at 50 years of age, with an SD of about 3 per cent VC. A closing volume significantly above these predicted values suggests the presence of pulmonary disease. Closing volume may not be clearly identifiable in some patients with pulmonary disease. However, these individuals usually have abnormalities of phase III of the closing volume curve, as well as derangements of other pulmonary function tests. "Closing capacity" has also been suggested for clinical use. Closing capacity is the sum of residual volume plus closing volume. It is reported as percentage of total lung capacity and requires determination of RV as well as CV. Measurement of closing capacity is useful in patients who have large residual volumes and high RV/TLC ratios. In such individuals, CV (expressed as per cent VC) may be normal even though closure of lung units occurs high in TLC because of the enlarged RV.\(^\text{42,43}\) When gases other than nitrogen (e.g., argon; radioactive gases) are used for CV measurement, the procedure and equipment are different but the type of recording obtained and interpretation of results are similar.

**Frequency Dependence of Compliance**

In subjects with healthy lungs, dynamic pulmonary compliance does not vary with respiratory frequencies as high as 60–80/min and is not appreciably different from static compliance. In patients with early airway disease (e.g., bronchitis, asthma) compliance may be frequency dependent. In these individuals, dynamic compliance measured at 60 breaths/min may be less than 50 per cent of that measured at 10/min. Presumably, during early disease, involvement of small airways occurs in a random and irregular fashion so that marked differences in time constants develop among different units. In this situation, as time available for inspiration decreases at rapid frequencies, affected units cannot fill completely and may still be inspiring while other units with shorter time constants are exhaling.\(^\text{44}\) Increasing non-uniformity of distribution of inspired gas may be associated with reduced dynamic compliance at rapid frequency.\(^\text{44}\)

Comparison of dynamic lung compliances at slow and rapid breathing frequencies may be the most sensitive test for early detection of disease involving small peripheral airways. However, this procedure requires insertion of an esophageal balloon for transpulmonary pressure measurement. The invasive nature of this maneuver makes it unlikely that determination of frequency dependence of compli-
ance will attain wide popularity as a simple screening test of pulmonary function. However, it might be useful when other tests yield equivocal results.

Relevance to Anesthetic Practice

The new tests described in this presentation are highly sensitive and can frequently distinguish between asymptomatic smokers and non-smokers. The importance of such sensitive tests for early recognition of chronic pulmonary disease in general medical practice has been discussed. Their specific role in preanesthetic evaluation of pulmonary function remains to be determined. Patients with signs and symptoms referable to the respiratory system will have marked abnormalities in MEFV curves and closing volume measurement and should be easily identifiable using currently popular procedures. Perhaps the most important benefit from recent investigations as applied to these individuals is the realization that even mild symptoms and arrangements of spirometric tests represent moderately advanced pulmonary disease.

What should be the approach to the candidate for anesthesia who lacks respiratory signs and symptoms but has an abnormal MEFV or CV test? At present it seems wise to obtain additional pulmonary function studies, which might include routine spirometry, measurement of arterial blood gases, determination of pulmonary diffusing capacity, and radiographic procedures. Probably a number of unsuspected cases of established pulmonary disease will be discovered by these methods. It is anticipated, however, that there will be a number of patients with abnormal MEFV or CV tests as an isolated finding. Is this extent of pulmonary abnormality of significance to the anesthesiologist? Do these patients represent increased anesthetic risks? Should they have any special considerations in preoperative management or postoperative care? Will these new tests of pulmonary function provide any information more useful to the anesthesiologist than that obtainable by careful history and physical examination? Answers to these questions will be awaited with interest. Of equal interest, however, is the physiologic basis for these tests. The concepts of flow-limiting mechanisms and closure of lung units discussed in this presentation may explain certain aspects of pulmonary dysfunction known to occur during anesthe

sis. The tests described provide methods for examining aspects of pulmonary function previously inaccessible to investigation in clinical circumstances. Both closing volume and MEFV measurements can be made in anesthetized patients. It is anticipated that information obtained under these circumstances will contribute to a better understanding of pulmonary function during anesthesia.

References