American Thoracic Society/European Respiratory Society

Respiratory Mechanics in Infants: Physiologic Evaluation in Health and Disease

CONTENTS

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE EUROPEAN RESPIRATORY SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS (JUNE 1992) AND THE ERS EXECUTIVE COMMITTEE (SEPTEMBER 1992).

Respiratory disease is now the number one cause of morbidity and mortality in infants worldwide. Advances in neonatal care are continuing to increase the rates of survival of prematurely born infants with respiratory disease. Rapid progress in the basic sciences is providing new diagnostic and therapeutic approaches for the management of respiratory disease. In the first 18 months of life the respiratory system undergoes extraordinary functional developmental changes. Until recently, however, our knowledge of the normal mechanical properties of the developing human lungs and airways during this period of rapid growth has been extremely limited. Similarly, it has been difficult to assess the effects of disease and the responses to therapeutic interventions in infants.

In the last decade many new and innovative methods for assessing pulmonary function in infants have been developed, while older, classic techniques have continued to evolve. Studies using these methods have already provided valuable insights into the normal process of growth and development of infant lungs and airways. The effects of various prenatal and postnatal biologic, mechanical, and environmental insults that disrupt this normal process and result in dysfunction are also now being characterized quantitatively using these measures.

Tests of pulmonary function in infants are now being used worldwide. Although our understanding of the physiologic basis for many of these measurements remains incomplete, they are yielding important new information about the respiratory problems of infancy. The marketing of commercial devices has made the technology for these measurements widely available. However, procedural guidelines and equipment standards for these tests have not yet been developed. Given the worldwide importance of respiratory disease in early life and the new therapeutic approaches originating from advances in the basic sciences, there has been a growing need for a coordinated effort to understand, develop, and standardize methods for assessing pulmonary function in infants. This process was initiated in 1989 with the report of European Society for Clinical Respiratory Physiology on the standardization of lung function tests in pediatrics (1). This review encompassed many aspects of infant lung function testing, including the measurement of lung volumes, respiratory mechanics, and FEF in infancy.

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Am Rev Respir Dis Vol 147. pp 474–496, 1993

In order to further this process, a group of experts in the field of infant respiratory mechanics convened under the auspices of the American Thoracic Society and the European Respiratory Society in January 1991. Their aim was to (*1*) determine what was known about currently available tests and (*2*) define what further information needed to be learned before the process of standardization could begin. The purpose of this Statement is thus to summarize what is known and agreed upon by investigators in this field, and thereby provide the scientific basis for the future standardization of infant pulmonary function tests.

Tests of pulmonary function in infants are summarized in four sections: MEASURES OF FORCED EXPIRATORY FLOW, MEASURES OF COMPLIANCE AND RESISTANCE, MEASURES OF LUNG VOLUME, and OTHER TESTS (including measures of tidal volume and respiratory pattern, chest wall motion, and gas mixing). Each section is organized under the general subheadings of INTRODUCTION, METHODS (what is known), CURRENT CONTROVERSIES (what is not known, uncertain, or controversial), and FUTURE DIRECTIONS (what needs to be known). A critique of the available reference values is presented for each category of measures.

MEASURES OF FORCED EXPIRATORY FLOW

Introduction

The maximal expiratory flow volume (MEFV) relationship was first described by Hyatt and coworkers in 1958 (2). In the years since, research has established that maximum expiratory flow (MEF) on the descending portion of the MEFV curve is independent of effort (flow limitation) and reflects airway caliber upstream (peripheral) from the airway segment subjected to flow limitation (3, 4). The measurement of MEF has been standardized and has come to play a central role in the clinical evaluation of lung function as a sensitive test of abnormalities in the intrathoracic airways. The ability to measure MEF reproducibly has expanded our knowledge of normal and abnormal human lungs, thus contributing greatly to the diagnosis and treatment of lung disease in adults and older children.

In the last decade, two methods have evolved to allow the forced expiratory flow-volume relationship to be examined in infants. The first, the forced deflation technique, was initially described in 1977 (5). In this technique the lungs are inflated to a pressure of 40 cm H_2O and then deflated rapidly to residual volume (RV) by a sudden exposure to negative pressure. The advantage of the forced deflation method is that it generates increased flows over the entire range of the vital capacity (VC). The disadvantage of this technique is that it requires endotracheal intubation as well as deep sedation and muscle relaxation. These requirements limit its use to intensive care or surgical settings. The second technique, rapid thoracoabdominal compression (RTC), was described in 1978 (6) and later modified (7). In this technique, forced expiratory flows are produced by the sudden application of a compressive pressure to the thorax and abdomen at end-tidal inspiration. The advantage of the RTC method is that it is relatively noninvasive and can be performed in the clinical setting with neither intubation nor deep sedation (8). This technique has the disadvantage of producing only a partial expiratory flow-volume (PEFV) maneuver. Also, it is unclear at present whether or not flow limitation is achieved using this method.

Much controversy remains regarding the comparability of the forced flows produced by these two methods in infants with the flows measured in adults and older children during voluntary forced expiratory maneuvers. Nonetheless, the results of studies using these techniques document their value as research tools. The use of forced expiratory flow measurements to assess lung function in infants has extended our understanding of the normal growth and development of the lungs during infancy (9–11) and helped to describe the pulmonary abnormalities seen in acute and chronic infantile lung diseases (12–18). Both methods have also helped to define the onset of and recovery from bronchopulmonary dysplasia (BPD) in prematurely born infants. Much remains to be learned, however, about the treatment and management of both the acute and the chronic aspects of the pulmonary sequelae of premature birth. Measurements of forced expiration are central to the management of lung disease in older children and adults with cystic fibrosis (CF). RTC measurements have been used in infants with CF (19, 20) to define the severity of disease at diagnosis and to measure the short-term effects of antibiotic and bronchodilator therapy.

Studies using various bronchodilator and bronchoconstrictor stimuli have shown that normal infants and infants with wheezy bronchitis, CF, or neonatal lung disease have significant airway reactivity (14–27). Bronchoconstrictors, however, have produced substantial decreases in flow in a large percentage of otherwise healthy infants (21, 22), and bronchodilators have produced paradoxic decreases in forced flows in some wheezy infants (25). Although the significance of these changes in forced expiratory flow after bronchial challenges are not yet fully understood, further application and development of forced expiratory methods should help to define the origins of infantile and childhood asthma.

Forced expiratory flow measurements have revealed not only levels of dysfunction and responses to therapy in infants with respiratory disease, but also characteristics of normal infants who are at increased risk for later respiratory problems. Epidemiologic population studies have suggested that altered airway function precedes and predicts recurrent wheezing and an increased incidence of lower respiratory illness in infancy (11, 28). Studies in normal infants have further suggested a significant negative effect of maternal smoking during pregnancy on infant lung function (24, 29).

Although the current methods of measuring forced expiratory flows in infants have provided much information, many concerns still exist regarding the techniques and the interpretation of the measurements obtained (30–33). Further research to develop and standardize these tools, however, should improve their utility.

Methods

Forced deflation technique. This technique is limited to infants and children who already have an endotracheal tube or a tracheostomy. The subject must be deeply sedated or under general anesthesia with or without muscle relaxation. For the test procedure (5, 14), the lungs are inflated manually with a breathing bag to +40 cm H_2O of airway pressure, defined as total lung capacity (TLC), and held for 2 to 3 s. Manual inflation is performed four times to recruit lung volume from previously closed or atelectatic segments and to establish a consistent volume history. On the fourth inflation, after TLC has been reached and maintained for a few seconds, an air-tight slide valve is pushed open, suddenly exposing the endotracheal tube via a pneumotachograph to a 100-L capacity, constant negative pressure source (−40 cm H_2O). The valve is held open until the expiratory flow ceases at RV or for a maximum of 3 s (FEV_3). In healthy infants RV is reached (i.e., FVC is produced) within 1 to 2 s.

Immediately, the slide valve is pushed closed, reconnecting the endotracheal tube to the breathing bag. The lungs are reinflated to TLC with an oxygen-enriched gas mixture several times to ensure full reexpansion before tidal ventilation is resumed. Throughout the forced deflation procedure, the subject is con-

tinuously monitored with a pulse oximeter to assure adequate oxygenation.

The flow signals and integrated volume signals are plotted instantaneously on a storage oscilloscope to produce an MEFV curve. The maneuver is repeated until three virtually identical MEFV curves are superimposed on the oscilloscope screen. Alternatively, flow signals may be A/D converted, and the MEFV curves produced by a computer.

With this technique, MEFV curves and FVC are highly reproducible unless previously collapsed airway segments are successively recruited by lung inflation. MEF is measured at 25% and 10% of FVC from RV (MEF_{25} and MEF_{10}, respectively) and the ratios of MEF_{25}/FVC and MEF_{10}/FVC are calculated as indices of the rate constant of the upstream airway segment (34). Flows are measured low in the VC (MEF_{25}, MEF_{10}) to help ensure that flow limitation has been achieved. Flows > 30% of VC appear not to be at flow limitation. Further, artifact introduced by the endotracheal tube acting as a critical orifice may also occur at lung volumes > mid-VC.

In eight healthy infants undergoing elective surgical procedures under general endotracheal anesthesia, the deflation negative pressure applied at TLC was decreased successively from −40 cm H_2O to −10 cm H_2O to determine the pressure necessary to produce flow limitation (Motoyama EK, unpublished observations, 1990). At 25% FVC from RV, which is near FRC, the negative pressure necessary to produce flow limitation ranged from −25 to −30 cm H_2O. In contrast, infants with lower airway obstruction (15) required much less pressure to produce flow limitation at FRC. Accordingly, a deflation negative pressure of −40 cm H_2O has been used routinely to ensure flow limitation at and below 25% of VC in all infants studied as well as to determine TLC in the forced deflation technique.

Rapid Thoracoabdominal Compression Technique

For an RTC maneuver, infants are usually sedated with 50 to 100 mg/kg of chloral hydrate given orally. The RTC technique produces forced expiratory flows by applying a sudden pressure to the thorax and abdomen at end-tidal inspiration using an inflatable thoracoabdominal jacket connected to a positive-pressure reservoir (8, 32). Compression is usually maintained for 1 s, but a longer time may be required in some infants with severe obstruction. Flow is measured at the mouth using an appropriately sized pneumotachograph with a face mask. To reduce potential leaks, either petroleum jelly or a silicone putty sealant is applied to the face mask before placement. Flow signals are integrated to obtain volume signals, and the flow-volume plot is displayed in real time on an oscilloscope screen or computer monitor. Before the RTC maneuver, a reproducible end-expiratory point, or FRC, is established on the volume axis by at least three tidal breaths. RTC at end-inspiration then produces a PEFV curve with exhalation continuing to a point below FRC. FRC has been the most commonly used reference point (8) for the measurement of forced expiratory flow by this technique. The jacket compression pressure is steadily increased until no further increase in flow at this FRC point is observed.

The compression jacket should have a noncompliant outer surface and an inflatable inner surface, and it should cover the entire thorax and abdomen. The jacket should be wrapped snugly around the infant, with the arms outside (35), but not so tightly that it decreases FRC. The jacket should be inflated rapidly, so that peak jacket pressure is reached in 50 to 100 ms. In normal infants the PEFV maneuver may be completed within 200 ms. For this reason, the frequency response of flow and pressure measuring devices should be linear through at least 10 Hz. The true frequency content of PEFV maneuvers, however, remains to be studied in depth, and the value of 10 Hz is probably an underestimate. Nonlinearity in the frequency response can result in overestimation or underestimation of rapidly changing flows. Furthermore, in computer-based systems the digital sampling rate needs to be at least 64 Hz with 12-bit resolution, to allow adequate frequency response and accurate digital integration.

The jacket pressures used to produce forced expiratory flows in infants have ranged from 40 to > 80 cm H_2O. In many infants with significant airway obstruction, reproducible PEFV curves can be generated using a jacket pressure of 40 cm H_2O or less. Additional increases in jacket pressure in such infants have been shown to decrease flow (9, 36). In normal infants, jacket pressures of 80 cm H_2O or more may not produce flow limitation. Pressures of up to 100 cm H_2O have produced steadily increasing flows in some infants. Most investigators have placed a limit on the maximal jacket pressure to be used. As the pressure actually transmitted to the pleural space is probably influenced by such factors as the construction of the jacket and how tightly the infant is wrapped in the jacket, it is impossible currently to specify a maximum compression pressure that will guarantee flow limitation in all infants. Thus, the jacket compression pressures used to produce forced expiratory flows should always be reported. Furthermore, some authors have suggested that the efficiency of jacket pressure transmission is variable and should be measured and reported as well (36).

Because it is uncertain whether this technique produces flow limitation at wave speed, most investigators have judged the quality of the resultant PEFV curves in terms of their shape. An "acceptable" PEFV curve is generally triangular, with the flow-volume relationship rising sharply to a peak and then falling smoothly to a point below the initial end-expiratory volume. Irregular or jagged curves are usually considered to have been distorted by pharyngeal or glottic closure. This problem can often be remedied by gently extending the infant's neck. Infants frequently inspire before the completion of chest compression. Curves that end near, at, or above the resting end-expiratory volume are generally considered to have been distorted by inspiratory effort and are unacceptable.

How best to compute the values of flow measured at FRC is unclear. In most studies the intrasubject coefficients of variation (CV = SD/mean × 100) for technically acceptable flows measured at FRC have been approximately 10 to 15% within a single test session (9). It seems reasonable to attempt to obtain three maximal measurements varying by no more than 10% and to report the final result as the mean of those three values. Some have argued on a physiologic basis that only the highest flow achieved should be reported, as this flow must represent the flow nearest to maximal flow. To the degree that the flows produced by the RTC technique exceed those during tidal breathing, they may provide a useful forcing function to evaluate the respiratory system even if flow limitation is not reached.

Current Controversies

Forced deflation technique. The use of the forced deflation method in obtaining MEFV curves has been limited to a small number of institutions and essentially the same technique as originally described (5, 14). As a result, controversies in terms of procedural standards have not emerged. The potential controversies include the following: Various sedatives, anesthetics, muscle relaxants, and adjuvant medications may affect bronchomotor tone, compliance, and lung volume. Inhaled anesthetics, such as halothane

and isoflurane, and anticholinergic drugs, such as atropine, are potent bronchodilators, affecting different segments of the airway system, whereas morphine and the muscle relaxant d-tubocurarine are potential bronchoconstrictors by causing histamine release. Although clinically significant alterations in vital signs with the forced deflation method have not been reported, repeated maneuvers may result in hypocapnia, affecting vascular and bronchomotor tone. Further, the positive pressure used to inflate the lungs may impede venous return to the right side of the heart, especially in hypovolemic subjects. Continual monitoring of vital signs with pulse oximetry and other means is indicated.

The use of an endotracheal tube may influence the site of flow limitation and prevent movement of the choke point upstream during deflation. The effect of the endotracheal tube needs to be studied; however, measuring flow at a low lung volume (MEF_{25}, MEF_{10}), may avoid this problem in infants. In older children and adolescents care needs to be taken to ensure that the tube is not acting as a critical orifice preventing flow limitation in the tracheobronchial lumen. In patients in the intensive care unit, the fraction of inspired oxygen (FI_{O_2}) should be increased during a forced deflation maneuver, to ensure optimal hemoglobin saturation and tissue oxygen delivery. When different gas mixtures (increased FI_{O_2}, nitrous oxide, helium) are used, the calibration of the pneumotachograph should be adjusted for the alteration in gas physical properties. Finally, the impact of altered volume history on lung function in infancy needs to be delineated. Measurements of MEF after repeated recruitment of airspaces may not represent airway function at steady state. Further, the impact of altered volume history on airway and parenchymal characteristics needs to be defined in infants with and without lung disease.

Rapid thoracoabdominal compression technique. Controversy surrounds almost all aspects of the RTC method. The most critical question, however, is whether or not physiologically determined flow limitation is reliably produced by RTC. Flow limitation is usually documented using isovolume pressure-flow curves in adults (2). These have not been successfully obtained in normal infants, however. Although flow-limited isovolume pressure curves have been demonstrated during RTC maneuvers in infants with severe airway obstruction, flow limitation in normal infants has not been clearly or consistently documented using this standard method. In infants with BPD, most of whom were near flow limitation during tidal breathing, a clear plateau in the pressure-flow curve relationship was observed with a minimal increase in the pressures applied to and transmitted across the chest wall (37, 38). In infants with less severe airway obstruction or normal airway function, higher intrathoracic pressures are required to produce flow limitation at FRC and a plateau in the isovolume pressure-flow relationship. Using the forced deflation technique, airway pressures of -25 to -30 cm H_2O are required to produce consistent flow limitation at low lung volumes near FRC (25% FVC) in intubated, anesthetized, paralyzed infants with normal lung function (see METHODS: FORCED DEFLATION TECHNIQUE). Measurements of intrathoracic pressure during a dynamic RTC maneuver suggest that only approximately 25% of the applied jacket compression pressure is transmitted to the pleural space at FRC (7, 37, 39). This means that even with jacket pressures of 80 cm H_2O only about 20 cm H_2O is transmitted across the chest wall to produce the flows observed. Thus, it is not surprising that most investigators are uncertain of the ability of RTC to produce flow limitation in normal infants. When infants undergo RTC under assumed static, relaxed conditions (obstruction at the mouth), from 60 to 80% of jacket pressure appears to be transmitted through the thorax (36). It has been suggested (30, 33) that this difference in transmission between dynamic and static conditions may be explained by reflex inspiratory activity induced by sudden thoracoabdominal compression. Diaphragmatic contraction or an increase in chest and abdominal wall resistance may account in part for the inefficient transmission of pressure during a dynamic RTC maneuver.

As an alternative method of assessing flow limitation during RTC, the superimposition of an oscillatory pressure wave obtained at the chest wall has been studied (40). The disappearance of flow oscillations measured at the mouth is proposed to signal the onset of physiologic flow limitation in the airways. Although this technique looks promising, additional measurements of intrathoracic pressure and simultaneous corroboration of flow limitation using isovolume pressure-flow curves will be necessary to document its validity. To date, flow limitation as evidenced by a maximal flow plateau in the isovolume pressure-flow curve has not been consistently demonstrated during RTC in normal infants (41). Although flow limitation is not produced in all infants, the results of studies in both normal infants and those with airway obstruction document the utility of the RTC technique. Without true flow limitation, however, comparisons between and within individuals are problematic.

A potential source of error in PEFV measurement that has not been investigated in infants is the use of integrated flow at the mouth to describe volume. Because of intrathoracic gas compression in subjects with obstructive lung disease, the flow-volume relationship may be systematically altered unless volume is measured by plethysmography (42, 43).

Increased upper airway resistance may represent another source of interference in the measurement of intrathoracically determined flows. Care must be taken to prevent nasal compression, and the head and neck must be positioned to minimize pharyngeal narrowing. Reflex glottic closure may cause problems in some infants. Compression of the chest wall in lambs elicits glottic closure, and most investigators have observed rapid decreases in flow during RTC maneuvers that are compatible with glottic closure (32, 33, 44). Although glottic closure at FRC makes it impossible to determine flow at FRC, the effect of earlier or partial glottic closure remains poorly defined (45).

Levels of end-expiratory lung volume are actively controlled in infants and consequently may be variable. Variations in end-expiratory level of lung volume or FRC may affect measurements of flow at FRC. Measured flows are likely to increase if end-expiratory level increases and to decrease if end-expiratory level decreases. This problem is particularly acute when the response to bronchodilator or bronchoconstrictor agents is being evaluated. Measuring lung volume by gas dilution or plethysmography may help to limit the variability, but is only a partial solution to the problem because of the additional errors inherent in volume measurements.

The flow-volume relationship produced by the RTC method, even if flow is limited, represents only a small, low-lung-volume segment of the full MEFV curve. This segment is highly variable and extremely sensitive to even minor changes in airway function. Many of the problems encountered in the RTC method might be solved if techniques were developed to measure the flow-volume relationship in infants over a larger portion of the VC range, as in the forced deflation method. Preliminary efforts using the expiratory volume clamping technique and positive-pressure inflation through a face mask in sedated infants appear to offer promise (46).

Standardization of the RTC techniques presents many problems, and much remains to be learned about the effects of seemingly minor procedural changes on the flow-volume curves produced. In all reported studies, the methods used should be

specified in detail, as such variations in procedure may explain the sometimes large discrepancies in results from different laboratories.

Reference Values and Interpretation

Because of the difficulty of recruiting normal subjects and the lack of standardized procedures, adequate reference values for these techniques are lacking.

Forced deflation technique. Although no reference values are available for the forced deflation technique, limited data have been published (5, 14–17). In six otherwise healthy newborn infants under general anesthesia for elective surgery (16), the mean (± SD) MEF_{25} was 49 ± 16.2 ml/kg/s, and the mean MEF_{25}/FVC was 1.12 ± 0.27/s. In four sedated and intubated preterm newborn infants with a mean gestational age of 27.7 wk and no apparent lung disease (14), the mean MEF_{25} was 95 ± 27.7 ml/kg/s, and the mean MEF_{25}/FVC was 1.67 ± 0.38/s. When adjusted for weight and lung volume, the values in the preterm infants were much higher than those in full-term newborns (16, 17).

Rapid thoracic compression technique. Limited reference values are available for the RTC method. Only two studies have reported flow measurements generated by RTC in large numbers of normal infants. In 1986, forced expiratory flow measurements taken in 120 normal infants from Tucson, Arizona, were reported (9), and in 1990, a report of 148 measurements in 72 normal infants from Boston, Massachusetts, was published (10). In the Tucson series, flow measured at FRC was related to body length by the equation: flow at FRC (ml/s) = 4.5 × length (cm) − 123. In the Boston series the relationship was: flow at FRC (ml/s) = 9.67 × length (cm) − 399.8. The results from these two studies appear to differ, as the second equation reflects a more rapid increase in flow measured at FRC with increasing body length than does the first. The measured flows in infants less than 3 months of age were similar in both studies. In the Tucson study, most infants measured were less than 3 months of age (< 60 cm in length). The Tucson study also reported flow measurements from five normal full-term and six normal premature newborns, which were higher than those in normal infants 1 to 3 months of age, a finding that remains unexplained. The increased flows in newborns, coupled with the relative paucity of measurements from infants longer than 65 cm (older than 6 months), in the Tucson study appear to account for the slower increase in measured flow at FRC with increasing length by comparison with the results from Boston. Although most infants tested in the Boston study were also younger than 6 months of age, this study included more measurements taken in the second 6 months of life. Very few measurements were taken in the second year of life in either study. Thus, the data from both studies appear to serve as predictors of normal RTC-generated flows at FRC in young infants, but the Boston study, which predicts significantly higher flows in infants 6 months of age and older, probably provides more reasonable predicted values in older infants.

That flows measured at FRC in older infants are higher than predicted by the Tucson study is confirmed by an independent set of measurements taken in normal infants in Indianapolis, Indiana. These 22 infants, whose average age was 13 months and length was 72 cm, had average flows at FRC of 273 ml/s (20). This value is close to the 296 ml/s prediction for 72-cm infants from the Boston data, but is significantly higher than the 201 ml/s prediction from the Tucson data. Jacket compression pressures averaged 45 cm H_2O in the Tucson study and were approximately 80 cm H_2O in the Boston study. The reasons for these differences are unclear, as the same criteria for increasing jacket pressures until flow at FRC reached an apparent maximum were used in both studies.

At present, the Tucson and the Boston data provide preliminary reference values for forced expiratory flow by RTC in infants less than 6 months of age. From 6 months of age onward, the Boston data are probably the better reference. Limited data are available on forced flows produced by the RTC method in infants in the second year of life. Predicted values in this age range are based primarily on extrapolation.

Future Directions

Three primary concerns remain in the understanding of the physiology of forced expiratory flow. First, methods to determine or achieve flow limitation in healthy infants need to be developed. Second, these methods need to be standardized and applied in population studies to define the normal development and growth of the lungs and to provide useful reference values. Third, potential sources of variation in the measurements need to be characterized and limited. This effort will entail studies of transmission pressure, isovolume pressure-flow relationships, the impact of chest wall tone, and upper airway resistance. A critical comparison of MEF values obtained by the RTC technique during sedation with values obtained by the forced deflation technique during anesthesia and paralysis in the same infants (41) would help to solve a number of these questions.

The effect of variations in lung volume on the flows measured in both the RTC and the forced deflation techniques needs to be addressed. Functional residual capacity may be dynamically determined, and hence be variable, in infants, thus altering the flow measurements obtained. End-expiratory lung volume (relaxation volume) under anesthesia or muscle relaxation is much lower than dynamic FRC. Thus, MEF at relaxation volume during forced deflation cannot be equated with MEF at FRC during RTC. Studies involving the use of bronchodilators or bronchoconstrictors may systematically alter lung volume, thus altering volume-based flow measurements. An accurate, noninvasive method of rapidly tracking this volume change is needed.

Methods designed to increase the volume at which flow is initiated should be further developed. Two promising techniques are the use of volume clamping to raise lung volume progressively, breath by breath, and the rapid inflation technique, in which the lungs are inflated before the PEFV maneuver by positive pressure applied through a face mask. By generating a larger segment of the MEFV curve, these methods might better characterize the kinetics of volume elimination.

Two goals must be achieved before MEF measurements can be recommended for general use. First, the procedures for both the RTC and the forced deflation techniques need to be standardized. Until this is accomplished, investigators must supply detailed descriptions of their methods, including not only flow production techniques but also curve selection criteria. Second, a longitudinal study using standardized methods in a large number of normal infants needs to be undertaken to generate normal prediction equations over the first 18 months of life. The population studied also needs to include sufficient proportions of infants of differing race and gender to develop specific equations for different population groups. Further, the upper age at which useful MEFV measurements can be performed needs to be determined.

MEASURES OF COMPLIANCE AND RESISTANCE

Introduction

In adults, compliance and resistance are rarely measured directly, and pulmonary function is assessed using standardized, indirect

tests from which abnormalities of these mechanical characteristics are inferred. In infants and young children, however, these standardized tests are difficult to perform because they require the subject's cooperation and coordination. Therefore, a number of innovative approaches have been devised to measure compliance and resistance directly in infants.

Using these techniques, valuable clinical and physiologic information has been obtained in many laboratories. For example, the normal development of the lungs and the chest wall have been assessed by measuring compliance and resistance during maturation. Compliance measurements have been used to investigate the efficacy of surfactant replacement therapy in neonates and of steroid therapy in interstitial lung disease in young children, and to differentiate the severity of disease in infants with CF. Resistance measurements have been used to assess the severity of infant respiratory diseases and the efficacy of bronchodilator therapy. The studies with bronchodilators have revealed that, contrary to established beliefs, significant bronchoconstriction can occur even in preterm infants studied during the first weeks of life.

At present, instruments to perform some of the measurements of compliance and resistance are commercially available. Nevertheless, there remains considerable controversy over the optimal methods to be used and the interpretation of the data obtained. Thus, although the techniques to be described have great potential for providing sound clinical data on pulmonary function in infants, a number of problems must be resolved before they can be confidently recommended for wide clinical use.

Methods

General Considerations

Techniques for measuring compliance and resistance can be classified as passive or quasistatic and dynamic. All require measurements of airflow, volume, and pressure. Dynamic mechanics are measured during either spontaneous or, less frequently, mechanically assisted ventilation, and passive mechanics are measured during maneuvers that silence the respiratory muscles.

In most techniques, the description of the mechanical properties is derived from the general equation of motion of the lung: $Pdr = (1/C \times V) + (R \times \dot{V}) + (I \times d^2V/dt^2)$, where Pdr is the driving pressure for the system, C is compliance, R is resistance, I is inertance, V is volume, $\dot{V}$ is flow, and d^2V/dt^2 is acceleration. The principal assumption is that the system follows a linear function such that unique values exist to describe it. Although this assumption may be tenable in the V_T range for normal infants, the function of the respiratory system during disease is less well described by a linear pattern. A further basic assumption for all methods is that the inertance is negligible, thus simplifying the equation to the compliance and the resistance terms. This assumption has not been tested in infants at high respiratory rates, when inertance may make a larger contribution. The measurement of pressure at the airway opening (Pao) relative to barometric pressure (P_B) represents the driving pressure across the total respiratory system (airways, lungs, and chest wall) and in relation to volume and flow yields respiratory system compliance (Crs) and resistance (Rrs). Rrs and Crs can both be partitioned into lung and chest wall components by measuring the relevant driving pressure for each component. The measurement of lung compliance (C_L) and resistance (R_L) requires the measurement of transpulmonary pressure (Ptp, the difference between pleural pressure [Ppl] and Pao), with Ppl usually approximated as esophageal pressure (Pes). Esophageal pressure is measured with either a water-filled catheter or an air-filled esophageal balloon on a catheter. The catheter is placed either through the nose (in intubated infants) or through the mouth. Nasal insertion substantially increases the contribution of nasal resistance to the total measured resistance in nonintubated infants.

The physical characteristics of esophageal balloons for infants have been extensively investigated (47). Balloons with a diameter of 5.5 to 7.7 mm and a length of 3.5 to 5.0 cm are recommended for use, after their pressure-volume characteristics have been established and the optimal operating volume has been determined from the passive compliance curve. Balloon thickness also affects the pressure-volume characteristics. Water-filled esophageal catheter systems are easier to pass into the esophagus than are balloon-tipped catheters, and, in certain cases, an existing nasogastric catheter can be withdrawn into the esophagus and used to measure changes in esophageal pressure. The existence of a hydrostatic pressure gradient between the transducer and the catheter tip makes it impossible to measure absolute pressures, but the difference can be minimized by positioning the transducer in the supine infant at the mid-axillary line. Because of the possibility of partial obstruction, multiple orifices are needed in the catheter. The fluid column must be kept free of bubbles ("degassed"), as the quality of the measurement depends upon minimizing the compliance of the measuring device. Using 8-French catheters, the system has been shown to have an adequate frequency response and to provide useful clinical information (48–50).

During an inspiratory effort against an occluded airway, when there is no airflow ($\dot{V} = 0$), the change in alveolar pressure (ΔPalv) is approximated by the change in Pao (ΔPao). Pleural pressure differs from Palv by the static elastic recoil pressure, but during occlusion, when $\dot{V} = 0$, the change in Ppl (ΔPpl) should equal ΔPalv and, hence, ΔPao. Therefore, if the change in Pes (ΔPes) = ΔPao, Pes is the equivalent of Ppl. The "occlusion test" (51) has been used to demonstrate that this relationship is valid under inspiratory occlusion conditions in normal adults and in normal infants (48). Esophageal pressure measurements are unreliable in a subject with esophagospasm or previous surgical trauma to the esophagus. A satisfactory occlusion test requires < 5% difference between ΔPao and ΔPes (52).

The functional properties of the chest wall (Cw, Rw) can be determined from the pressure across the chest wall ($P_W = P_{ES} - P_B$). Under normal functional conditions, Pw is the combination of the static elastic properties and the effect of the pressure generated by the activity of the muscles in the chest wall. Accordingly, the passive mechanical properties of the chest wall can be derived only when the muscle pressure is inhibited (passive conditions).

A pneumotachograph is normally used to measure airflow, which is integrated to obtain volume. The flow range of the pneumotachograph should encompass the maximal flow of the infant. Because any attachments to the pneumotachograph contribute to its characteristics, linearity and frequency should be ascertained in the entire system through which the infant respires. In intubated patients, the endotracheal tube itself offers a significant resistance to $\dot{V}$ (53) and increases the difficulty of obtaining a leakproof seal (54). Nasal adapters have been used (55), but they significantly augment the large component of resistance contributed by the nasal airway (56, 57). As an alternative method a face mask may be used, but it introduces sources of error including small unapparent leaks (54) and stimulation of the trigeminal nerve distribution (58). Evidence of a competent mask includes no change in flow or volume with airway occlusion and a return to the preocclusion end-expiratory volume baseline after release of the occlusion (52, 59).

Three important concerns related to the use of the pneu-

motachograph are (1) that the increase in dead space can increase P_{aCO_2} and change both VT and respiratory rate; (2) that the pneumotachograph increases resistance; and (3) that failure to calibrate with the gas composition being breathed by the subject can cause error in the flow measurements. A low-dead-space system has recently been described (60).

The transducers used to measure the relevant pressures should have appropriate frequency response characteristics to 10 Hz, and the phase response characteristics should be the same for all signals (61–63).

Infants should be tested in quiet sleep when respiration is regular, and rapid eye movement (REM) and gross body motion are absent (64). Sleep state is an important but rarely monitored variable that may profoundly alter the measurements. For instance, FRC has been suggested to decrease with active sleep (65) in full-term but not in premature infants (66). Although the absolute changes in lung volume in full-term infants have not been confirmed in subsequent studies (67), variations in lung volume during active sleep are apparent. Diaphragmatic muscle tone is inhibited and postural (intercostal and abdominal) muscle recruitment and laryngeal braking of expiratory airflow are greatly reduced in active sleep (68–70). Posture may also influence respiratory mechanics. The supine posture has been suggested as a standard for the measurement of Pes (68). The absolute Pes, by balloon measurement, is affected by posture, although changes in pressure are unaffected (71, 72) except in anesthetized patients or those with unilateral lung disease (72). Sedation with chloral hydrate (25 to 100 mg/kg) is popular and appears not to interfere with the measurements (73, 74), although both this technique and the alternative, sleep deprivation, may alter upper airway tone (75–77), thus increasing upper airway resistance and the risk of obstruction.

Because infants almost always breathe through the nose during testing, upper respiratory tract infections, allergic rhinitis, and other factors may influence the results obtained. If baseline measurements are desired, testing should be delayed until several weeks after resolution of upper respiratory tract pathology.

Dynamic Techniques

The Mead-Whittenberger technique (78) was used in many of the original studies of respiratory mechanics in infants. In this technique, Pes is measured to obtain measurements of CL, Cw, RL, and Rw. The original analysis was performed by deriving compliance at the points of zero flow at the end of inspiration and expiration as Cdyn = $\Delta V/\Delta P$, assuming that compliance is linear over the VT range. Using points of equal volume in the midvolume range, one during inspiration and the corresponding volume during expiration, the assumption is that the elastic forces are equal but opposing (78), and therefore Rdyn = $\Delta P/\Delta \dot{V}$.

The major assumption for these measurements is that the CLdyn and RL are constant throughout both phases of respiration: an assertion that may be true over the normal VT range in newborns but becomes more suspect with progressive lung hyperinflation (79). With hyperinflation, CLdyn may be constant within the VT range but may differ from the values at lower lung volumes. Studies in infants with lung disease have demonstrated the nonlinearity of RL (80, 81). The limitation of assuming a single value for RL becomes apparent when the variability of pressure-flow curve shapes in infants is examined (82). Furthermore, the larynx actively modulates the expiratory flow and resistance (83) in nonintubated patients. Nevertheless, given the limitations of the model, the technique has been used for the repeated assessment of newborns.

Another approach to analyzing the same data is the method of multiple simultaneous equations, in which all values of flow, volume, and pressure are fit to a linear model. Although this is the most popular computerized method, it requires considerable data filtering (84) as well as an arbitrary selection of breaths for analysis and an arbitrary end point. Despite these limitations, the technique has proved effective for clinical use and trend monitoring.

Another analysis variation is least-squares regression, in which the plot of Pdr versus $\dot{V}$ (the Pdr/$\dot{V}$ loop) is fit with a linear regression of the data points, such that the slope of the line is the resistance (85). Before the regression line is determined, pressure is corrected for tissue elastance such that the plotted pressure = Pdr − (C × V), to eliminate the viscoelastic component of the driving pressure. This method also assumes a linear relationship of the data.

A variation on this technique has been described in infants (85, 86) in which the relationship is plotted as P/V versus $\dot{V}$/V, where the intercept of the regression line is P/V (the reciprocal of compliance, elastance = 1/C) and the slope is the resistance. Again a linear relationship is assumed, although there is deviation from linearity at the extremes of the equation. An advantage of the regression techniques is the separate description of inspiratory and expiratory resistances. In ventilated infants or children, however, the expiratory values are influenced by the characteristics of the ventilator. Furthermore, valves in the breathing circuit introduce high-frequency noise in the flow and pressure signals.

Measurements of Pao and analysis of the data by a regression technique are frequently used in acute clinical situations in intensive care units to describe the respiratory system in infants receiving mechanical ventilation during a disease process. The measurements are relatively simple to make, but the calculation of results is more difficult because of the interference pattern induced by the mechanical action of the valves in the ventilator.

Dynamic lung resistance values derived in the same infants using each of the various linear methods of analysis have recently been compared (87). The Mead-Whittenberger technique consistently yielded higher values than the regression techniques, presumably because inspiratory and expiratory resistances both contribute to, and expiratory resistance normally exceeds the inspiratory value.

In addition to methods that use the equation of motion for the respiratory system, several other techniques are available for measuring dynamic mechanics.

(1) Body plethysmography. This technique to measure airways resistance (Raw) was first described by DuBois and coworkers (88). In adults and older children, the technique is applied during shallow panting to alleviate confounding variables such as changes in lung volume and temperature differentials between inspiration and expiration. As this is impractical in infants, the most commonly used technique involves rebreathing from a bag containing heated, humidified, oxygen-enriched gas at BTPS (55, 89). This is a sophisticated technique requiring substantial training. This method has the advantage of providing both simultaneous measurements of lung volume and resistance and pressure-flow curves. Inspection of the latter can give valuable information regarding changes in resistance throughout the respiratory cycle (90). The limitations of plethysmographic measurements are detailed in MEASURES OF LUNG VOLUME.

(2) Forced oscillation. This technique has been well reviewed in published reports (91). It has been applied in infants by several investigators (92, 93). The approach is to impose oscillatory changes in pressure and therefore flow at the airway and to mea-

sure resistance from the oscillatory relationship. Recently this technique has been improved through the use of multiple frequencies of oscillations. However, the predominance and variability of the contribution of upper airway compliance and resistance when pressure is applied at the mouth have limited its clinical use.

(3) Interrupter technique. Airways resistance in ventilated infants can be approximated by the quotient of the initial decrease in pressure during rapid occlusion of the airway in ventilated infants divided by the flow just preceding occlusion (94). In this technique, the calculation of compliance can be made using essentially the multiple occlusion approach (see PASSIVE AND QUASISTATIC TECHNIQUES). The technique allows for the calculation of both airflow and viscous tissue resistance and is being developed for use in infants. It is considered to be in the developmental stage and is of use only in intubated infants.

Passive and Quasistatic Techniques

All the techniques to be described in this section provide measurements of Crs and, in some cases, Rrs but do not permit partitioning of these values into chest wall, lung, and airway components. However, Cw is so high (4- to 5-fold greater than CL [49]) in infants that Crs is nearly equivalent to CL. For all these techniques, it is assumed that the respiratory muscles are totally relaxed at the point of measurement.

The most widely used passive or quasistatic approaches are the multiple occlusion technique for compliance and the flow-volume technique for compliance, resistance, and time constant. Both techniques rely on the assumption that the Hering-Breuer inflation reflex, producing complete relaxation of both inspiratory and expiratory pump muscles, can be elicited during airway occlusion and that Pao comes into equilibrium with Palv during the occlusion.

(1) Multiple occlusion. In the multiple occlusion technique (59, 95), pressure is measured at the mouth or outlet of an endotracheal tube during brief airway occlusions on multiple spontaneous breaths. The occlusions are performed at different volumes above end-expiratory level, and the individual measurements are plotted as volume versus pressure. The slope of the least-squares linear regression fit to these data is the measured Crs.

This technique has been extended to include measurements outside of the VT range by "volume clamping" (96), in which the expiratory side of the breathing circuit is kept occluded during several successive breaths. This procedure allows lung volume to increase progressively above the normal VT, thereby progressively activating the Hering Breuer reflex. Pressure and volume are measured during the expiratory pause following each successive inspiration, and compliance is calculated from curve fitting of the pressure-volume relationship.

(2) Passive flow-volume. The passive flow-volume technique, as originally described for infants (85) and later extended (97), involves measuring the pressure measurement during occlusion of the airway at end-inspiration and fitting a straight line relationship to the flow-volume curve obtained during the subsequent passive expiration. Thus, both compliance and resistance can be obtained from a single breath, and multiple measurements are made to confirm the result. This technique is particularly well suited to intubated, acutely ill patients because it is relatively noninvasive and easy to use. However, it is applicable only if the flow-volume curve is truly linear over the expired volume range.

(3) Weighted spirometer. Another technique that has received some attention is the weighted spirometer approach for measuring compliance (98). The infant or child breathes through a face mask into a closed-system spirometer. After control measurements are obtained, a weight is placed on the spirometer. By imposing a force upon the spirometer bell, the weight increases end-expiratory pressure, thus increasing FRC. Compliance is calculated as the quotient of the change in volume divided by the applied pressure. Several considerations are important in the use of this technique. The compliance of the spirometer system must be a reasonably small percentage of the total compliance or, alternatively, must be measured and subtracted from the abovementioned quotient. The cheeks and the upper airway should be positioned so that their compliance does not change when the weight is applied. To the extent that lung compliance is increased with increasing lung volume, the size of the weight may correlate with compliance. Finally, the weight imposes a load on the respiratory system that may elicit compensatory mechanisms, altering respiratory volumes and timing.

When the passive and quasistatic techniques are used, any muscle activity, either inspiratory or expiratory, can alter the results. Furthermore, clinically undetectable laryngeal narrowing during expiration ("grunting") may modulate the flow signal (82, 99) and alter the measurement of resistance. Because of this problem, the passive flow-volume technique should be used with caution to measure resistance in nonintubated infants. One way to check for laryngeal influences is to compare the value obtained with the value measured by some other technique, such as multiple occlusion. Laryngeal modulation of airflow usually results in extrapolation of a falsely elevated end-expiratory volume from the passive flow-volume curve and, therefore, calculation of a falsely elevated compliance value.

Current Controversies

The measurements obtained by the various techniques described are difficult to interpret, and further work is required to define their validity in normal infants and in those with lung disease. Compliance is interpreted differently in acute versus chronic lung disease. In an infant with acute lung disease, assessed in the short term, the intrinsic elastic properties of the tissue are assumed to be a constant, and therefore compliance is proportional to changes in lung volume. This assumption is only partially true. If compliance is increasing because volume is being recruited, a situation likely to occur in the immediate postnatal period, elastic recoil will probably decrease simultaneously because of a decrease in surface tension. Despite this, compliance does appear to reflect the gas exchange surface and correlates closely with the course of acute lung disease. In infants with chronic lung disease it is hoped, but not yet proved, that compliance can be used to identify changes in elastic recoil. However, if specific compliance (compliance corrected for FRC) is not measured, the measured Crs may still reflect changes in lung volume. Both RL and CL are volume dependent, but the degree to which changes in lung volume affect compliance and resistance measurements using the techniques described above requires investigation.

Respiratory system resistance is dominated by the upper airways and hence measured values may not reflect modest changes in lower airway resistance. The situation is further complicated in infants by high nasal resistance, active expiratory glottic adduction, or the presence of an endotracheal tube. Although it has been proposed based on morphometric and *in vitro* physiologic evidence (100) that the peripheral airway resistance in infants is proportionately higher than that in adults, this view has not been substantiated by subsequent evidence (5–7, 34). It thus seems likely that the upper airway still accounts for a large proportion of the resistance in infants. Therefore measurements of resistance in infants are considered to be of greatest value to examine spe-

cific upper airway pathology, tracheal stenosis, tracheomalacia, or the response to bronchodilator therapy. Because Rrs measurements are dominated by the upper airways, only relatively large changes in Raw due to bronchodilators are accurately detected.

A major point of discussion (101) has been the validity of Pes measurements in infants with chest wall distortion (102) due to respiratory disease or prematurity and in intubated infants (103, 104). Some investigators have found that Ptp can be determined, even in the presence of severe lung disease (49, 50), to measure the dynamic lung mechanics. The conditions under which measurements of Pes (and thus of Ptp) can be used in newborns remain to be clarified.

All the measurements described may be significantly altered by spontaneous variability in the subject and by the measurement conditions. There are insufficient data for any of the techniques to define the intrasubject or intersubject variability. Many criteria have been suggested for judging the acceptability of data, but no standardized criteria have been developed. For example, what constitutes a sufficiently good straight-line fit to flow-volume and pressure-volume curves? Can methods be developed to quantify more accurately the curvilinear flow-volume and pressure-flow relationships often seen in passive and dynamic measurements made in infants with severe lung disease? Although several nonlinear models have been described (105) they have not achieved popularity. A nonlinear expression may describe the relationship of compliance and resistance better but could be difficult to transform into useful clinical information. A linear slope does not necessarily indicate relaxation of the respiratory muscles. An even, descending slope could represent balanced respiratory muscle contraction.

Those techniques that involve the measurement of a relaxed pressure during occlusion require sufficient time for relaxation of inspiratory muscles and equilibration of pressure throughout the lung, the time constant of which increases with increased airway resistance. However, the longer the occlusion is held, the more likely is the recruitment of expiratory or inspiratory muscle activity. Further, the degree to which expiratory laryngeal narrowing and diaphragmatic braking influence resistance and compliance values measured by the passive flow-volume technique in nonintubated infants needs to be investigated.

Reference Values and Interpretation

Although correction for size is often based on body weight or length, the best basis for comparison of measurements from different subjects is the lung volume at which they were obtained. While this approach appears to be valid in older infants, it must be viewed with caution in neonates (89). Given normal intrauterine growth, expression per unit body weight is reasonably precise in the immediate postnatal period (50). However, because elastance decreases and conductance increases linearly with lung volume, which itself is a power function of somatic growth in normal infants, the range of reference values needs to be expressed per unit lung volume. The reference values to be reported here are not definitive, because none is based on a large population of subjects studied either cross-sectionally or longitudinally during infancy and childhood. Furthermore, few reports are available of values obtained using different techniques in the same subjects (99, 106, 107), providing insufficient data to allow for comparison of all techniques over all age ranges.

Dynamic lung compliance values for infants and newborns (both full-term and preterm) range from 1.1 to 2.0 ml/kg/cm H_2O, and specific dynamic compliance ranges from 0.04 to 0.08 ml/cm H_2O/ml FRC or volume of thoracic gas (Vtg) (95, 108–115). The larger range of specific compliance may be explained by the consistently lower values of FRC measured by helium dilution relative to Vtg measured by plethysmography (see MEASURES OF LUNG VOLUME). The reported values of passive compliance in infants and newborns range from 1.0 to 1.6 ml/kg/cm H_2O (85, 95–98, 116, 117), and the specific passive compliance reported in one study of healthy preterm infants was 0.06 ml/cm H_2O/ml FRC (95). In a longitudinal study of five full-term infants studied four times each between 4 and 55 wk of age using the passive flow volume-technique, Crs = 0.87 + 26.3 × height^3 (118), and in another study over the age range of 3 to 54 months using the multiple occlusion technique the relationship was Crs = 0.88 × weight(kg)$^{1.09}$ (119). Coefficients of variation of 10 to 13% for Crs (107, 120, 121) and 28% for CLdyn (122) have been reported.

Although few studies of Cw have been done in infants, values measured in preterm infants exceed those in full-term infants (6.4 versus 4.2 ml/cm H_2O/kg under quastistatic conditions in paralyzed, ventilated infants [123]). During relaxed expiration after end-expiratory occlusion in nonparalyzed preterm infants, Cw ranged from 2.4 to 3.8 ml/cm H_2O/kg (49). Dynamic Cw has been assessed in one study of preterm infants (124). Mean Cw was 7.8 ml/cm H_2O during tidal breathing in infants weighing 890 to 1,700 g. During airway occlusion in the same infants, Cw decreased to 0.89 ml/cm H_2O, probably because of chest wall muscle activity.

Values for Raw are high at birth but decrease rapidly during the first year of life (89). Because of this rapid change, specific airway conductance (SGaw = 1/[Raw × Vtg]), where Vtg is the volume of thoracic gas) is recommended as a more constant parameter during development. Specific airway conductance is approximately 0.3/cm H_2O·s at birth in full-term infants, then decreases to 0.2/cm H_2O·s, the normal value used in older children and adults. Values as high as 0.6 have been reported for preterm infants (112). The initial investigations (55, 89) reported values of inspiratory airway resistance at two-thirds of the tidal flow range. More recent studies (82, 90) have used computerized techniques describing Raw throughout the respiratory cycle, but there are insufficient reference values for use outside the two-thirds flow range. Resistance values using passive and quasistatic techniques in infants have been reported as Rrs = 0.047 − 0.036 × height^3 (118) or Rrs = 5.36 × weight(kg)$^{-0.75}$ (125). Reported coefficients of variation are 11 to 15% for Rrs (107, 120, 121) and 56% for RL in one study (122).

Future Directions

As discussed earlier, a number of techniques have been developed and successfully applied in infants to measure the resistance and static and dynamic compliances of the lungs and the respiratory system. Each technique has inherent strengths and limitations, and none has clearly predominated in efficacy under all circumstances of study: subject size and age, ease of technique application, presence of an endotracheal tube, and so on. Thus, an important need exists to further evaluate these methods with respect to standardizing the procedures on the basis of studies designed to determine optimal methods to circumvent the technical problems and interpretation controversies described; assessing the reproducibility of the measurements obtained; determining the influence of such factors as sedation, sleep state, and anesthesia; and obtaining values for normal infants and young children over a wide age range. The validity of assumptions regarding respiratory muscle activity following airway occlusion needs to be tested in healthy and sick infants. The influence of possible active respiratory muscle responses during passive and quasistatic measurements needs to be defined.

For the techniques used to measure compliance proposed fu-

ture directions for research include: assessment of the relationship between C_L and Crs and of the age-related changes in the contribution of Cw; evaluation of age-related changes in the relationship between passive or quasistatic compliance and dynamic compliance; determination of the shape and position of the inflation and deflation limbs of the pressure-volume curves of the lungs, chest wall, and respiratory system outside the V_T range; and incorporation of measurements of absolute lung volume (e.g., Vtg or FRC) as a means of obtaining volume-specific indices of compliance.

The methods used to measure flow resistance in infants are as diverse as the compliance techniques. In this regard, some proposed future directions for research include: assessment of the relationships between R_L, Raw, and other measures of Rrs in healthy infants and those with pulmonary disorders; partitioning of the contribution of nasal resistance from that of the lungs and chest wall; partitioning of the airway resistance from that contributed by the viscoelastic properties of the lungs and chest wall; evaluation of the utility and limitations of derived measurements of resistance based on analysis of the flow-volume relationships during "passive" lung deflation in healthy infants and infants with obstructive or restrictive lung disease; and incorporation of measurements of absolute lung volume as a means of correcting flow resistance per unit of lung volume.

MEASURES OF LUNG VOLUME

Knowledge of lung volume can play an important role in the respiratory care of infants and young children and assist in interpreting measurements of resistance, compliance, and forced expiratory flow.

Functional residual capacity, that is, the volume of air in the lungs and airways at end-expiration, is mechanically determined by the balance between the outward recoil of the chest wall and the inward recoil of the lungs. It corresponds approximately with 40% of TLC and 25% of VC in older subjects. Some evidence suggests that FRC is closer to RV in infants, such that airway closure may occur during tidal breathing. During early infancy, FRC may be dynamically increased above the passive level determined by the characteristics of the lungs and the chest wall (126–128). The mechanisms underlying this phenomenon include laryngeal braking and postinspiratory diaphragmatic activity, which prolong the expiratory time constant, combined with a relatively short expiratory time (i.e., rapid respiratory rate). Infants with airway disease may exhibit a similar but more marked phenomenon in which increased Raw prolongs the expiratory time constants, contributing to hyperinflation of the lungs.

FRC is the only lung volume that can be measured accurately, repeatedly, and reliably in infants. Other lung volumes such as TLC and RV have been estimated from measurements of VC during crying (129–132), but these estimates have an unacceptable degree of reproducibility for routine use. Similarly, although TLC and RV have been estimated from forced inflation and deflation maneuvers (5, 15, 18), such techniques require the presence of an endotracheal tube and are used mainly for research. Consequently, this section concentrates on the measurement of FRC in infants.

The assessment of FRC in infants has contributed important information about the growth and development of the lungs in health (9, 10, 89, 131, 133) and disease. FRC may be reduced by abnormal alveolar development (134–136), by atelectasis, or by decreased lung or increased chest wall compliance (137–141). Increased FRC may be caused by abnormal alveolar development (142) but more commonly occurs in relation to gas trapping associated with airway obstruction (143). From a clinical point of view, measurement of FRC in infants may be valuable in the management of controlled ventilation (143, 145), and in the evaluation of potential hyperinflation and treatment efficacy in airway disease (143, 146–148).

The two physical principles that are routinely applied to the measurement of FRC in infants are whole body plethysmography and gas dilution. Whole body plethysmography is based on Boyle's law, as originally described by DuBois and associates (149), and measures thoracic gas volume, Vtg. The helium dilution and the nitrogen washout techniques are based on the conservation of mass principle. All three techniques have been used in infants since the early 1960s, and substantial information has accumulated to define the normal range of lung volumes over the first year of life (150) as well as the changes observed with disease.

Despite increasing interest in the assessment of lung volume by a variety of imaging techniques (151–154), these methods have yet to be fully validated. Consequently, this discussion focuses on the three most widely used techniques for assessing FRC in infants: whole body plethysmography, helium dilution, and nitrogen washout.

Methods

Whole Body Plethysmography

In 1956, DuBois and colleagues (149) described a technique of measuring Vtg by determining the change in volume when a gas undergoes isothermal compression, as assessed by Boyle's law: $P_1V_1 = P_2V_2$. In practice, a subject is placed in a rigid, closed container (a plethysmograph) and makes respiratory efforts against an occlusion at the airway opening, which rarefy and compress the thoracic gas. The resultant changes in the subject's body volume can then be measured either directly, by a spirometer (the volume displacement plethysmograph [155]), or indirectly, by measuring the small pressure changes occurring within the container (the pressure plethysmograph). If the changes in Pao (which in the absence of airflow are equivalent to the changes in Palv) are related to the changes in volume, the initial Vtg can be calculated by applying Boyle's law as follows: $(P_B - P_{H_2O}) \times Vtg = (P_B - P_{H_2O} + \Delta P) \times (Vtg - \Delta V)$, where P_B is the barometric pressure in kPa (mm Hg), P_{H_2O} is the saturated water vapor pressure at 37° C (6.27 kPa [47 mm Hg]), ΔP is the change in Pao during the occluded respiratory maneuver, and ΔV is the resulting change in Pao during the occluded respiratory maneuver, and ΔV is the resulting change in volume of the thorax. Water vapor pressure is subtracted from all pressures because it relates only to temperature (going in and out of the vapor state as temperature changes) and thus, under saturated conditions, does not behave as a compressible gas. Ignoring the negligibly small product of $\Delta P \times \Delta V$ and solving the equation for Vtg gives: $Vtg = (P_B - 6.27) \times \Delta V/\Delta P$. This method was rapidly adapted for use in infants (156–158) and continues to be used in research centers throughout the world. Although most published results have been based on the pressure plethysmograph (89, 158, 159), the successful use of an integrated flow plethysmograph was recently reported in infants (160).

The major advantage of plethysmography is that it measures all the gas in the thorax, including gas that is not in direct communication with the airway, thus allowing the assessment of gas trapping in obstructive lung diseases (146, 161). Furthermore, this technique can produce rapid, reproducible, and accurate measurements of FRC in infants (89). However, the equipment required is expensive and cumbersome, requires considerable operator training, and is not applicable in the intensive care unit. Conse-

quently, its application has been largely restricted to research establishments. In recent years, computerized techniques have been used increasingly to facilitate data collection and analysis (80, 90, 162), and several user-friendly systems now exist.

The plethysmographic technique is based on four assumptions: *(1) There is no gas flow, and hence no flow-resistive loss in pressure, during respiratory efforts against the occluded airway; consequently, Pao equals Palv.* This assumption has been challenged in some studies in adults. These studies have suggested that the upper airway acts as a shunt capacitor during airway occlusion, allowing gas to flow back and forth in the airway, so that changes in Ppl exceed changes in Pao, leading to an overestimate of Vtg (163–165). Although, theoretically, this phenomenon could occur in all subjects, only those with significant airway obstruction have been shown to have sufficient airway resistance to cause losses in pressure. Panting at slower frequencies (i.e., around 60/min^{-1}) reduces the error (166) but may not completely eliminate it (163). Infants do not "pant" during airway occlusion and indeed tend to make fewer respiratory efforts (rarely more than 30/min^{-1}) than when breathing spontaneously.

(2) The pulmonary parenchyma is sufficiently elastic that changes in pressure are transmitted across the parenchyma to all gas-containing spaces, with no pressure gradient across the tissue. Although this assumption is probably reasonable in most adults, it has been challenged in infants. Values of Vtg that were much lower than expected from clinical findings have been observed in infants recovering from bronchiolitis (167, 168). These studies suggested that the lungs of these infants have regions of such high resistance and low compliance that they act as rigid spheres, so that the gas contained escapes rarefaction and compression during occlusion. Other potential problems in estimation of Vtg in sick infants have also been reported (169, 170). These reports suggested that a better approximation of swings in Palv during occlusion may be obtained by esophageal manometry, but this remains controversial (170–172).

(3) The changes in pressure and volume are isothermal. The proximity of the tissue to the gas in the respiratory system is such that heat generated during occluded respiratory maneuvers is rapidly lost to the body, and changes in volume within the subject are isothermal (173). Moreover, during rarefaction and compression of the gas inside the plethysmograph, heat may or may not be lost to the walls of the container, and therefore plethysmographic pressure changes may be either adiabatic or polytropic. The plethysmograph must be calibrated at the approximate frequency of respiratory efforts during occlusion to compensate for any error introduced by polytropic conditions (162, 174).

(4) Only gas in the thorax undergoes rarefaction and compression. The volume of gas in the gastrointestinal tract is assumed to be either insignificant, uncompressed, or both. This assumption was confirmed in adults (163) and in sick infants (168, 170) and appears to be valid in healthy infants (168, 170), because the changes in intraabdominal pressure are small relative to the changes in Pao during respiratory efforts against airway occlusion.

Detailed descriptions of plethysmographic measurements of Vtg in infants have been reported (89, 160, 168, 175, 176). In the first month of life measurements can be made during natural sleep, but in older infants sedation is usually required. Although in adults Vtg is conventionally calculated from the slope of box pressure (or displacement volume) versus Pao ($\Delta V/\Delta P$), for calculations in infants the additional use of time-based traces is strongly recommended. The latter approach makes it possible to assess any variations in end-expiratory level more accurately, to correct for thermal or metabolic drifts during airway occlusion, and to occlude the airway at any phase of the tidal breath (e.g., at end-inspiration) and subsequently correct to the end-expiratory level.

The sleeping infant is placed inside the plethysmograph, and a face mask attached to a pneumotachograph and shutter is sealed around the nose and mouth. The seal can be tested by recording at least five tidal breaths before occlusion to establish a stable end-expiratory level, then briefly closing the shutter at end-inspiration. Any increase in the volume baseline after release of the occlusion or decay of the Pao signal during occlusion suggests a leak (59, 175). Ideally, the mask should be held in place with strapping to support the cheeks and hence reduce the risk of shunting to the upper airways during the occlusion. After leaks have been eliminated, the plethysmograph is closed.

If a pressure plethysmograph is used, it is allowed to reach thermal equilibrium (as indicated by minimal drift of the box pressure signal). At least five tidal breaths (more if end-expiratory level is unstable) should then be recorded before the airway is occluded. Thoracic gas volume is conventionally measured by closing a shutter at end-expiration and allowing the infant to make two to four respiratory efforts against the occlusion, from which the relationship of box volume to changes in Pao (ΔPao) is established. In practice, occlusion is frequently performed at end-inspiration, with subsequent subtraction of the volume above end-expiratory level at the moment of occlusion. This procedure improves the signal-to-noise ratio, is better tolerated by most infants, and reduces the incidence of glottic closure, which can invalidate results. The appropriate volume at which to occlude is still under debate (see CURRENT CONTROVERSIES) (170, 177). In healthy infants, measurements made at end-expiration and end-inspiration (corrected to end-expiratory level) usually agree within 5%, thereby providing a simple *in vivo* method of validating the accuracy of the measurements.

During the occlusion, the changes in box volume and Pao should be strictly in phase. A loop appearing on the *x-y* display usually indicates a leak in the system or glottic closure. Three to five separate occlusions should be made in each infant. All measurements should be obtained during quiet sleep (64).

The thermal characteristics of the box must be accounted for during calibration (see above, Assumption *3*). This can be achieved by replacing the volume of the infant with bags of saline and dynamically calibrating the instrument at the frequency observed during respiratory efforts against the occlusion (174). Alternatively, a computerized correction factor can be used (162).

Although no standardized approach to reporting Vtg values in infants has been established, it seems reasonable to report the mean value of at least three separate, technically satisfactory measurements. In healthy infants, Vtg measurements tend to be very reproducible, with a coefficient of variation of $< 5\%$ (176). The variability may be greater in infants with respiratory disease (178), those who are not in quiet sleep (179), or those without a stable end-expiratory level before occlusion.

Helium Dilution Technique

The helium dilution technique is the most widely used method for determining FRC in infants (9, 10, 130, 131, 133, 180–183). This technique is based on the principle of gas equilibration between an unknown lung volume (VL) and a known volume (Vgas) containing helium as an indicator gas. Gas mixing is brought about by ventilatory movements. Assuming mass balance, the unknown lung volume can be derived from the change in helium concentration. That is, if C_1 is the helium concentration at the start of the experiment and C_2 is the concentration when gas mixing is complete, then $Vgas \times C_1 = (Vgas + VL) \times C_2$ and $VL = [Vgas \times$

$(C_i - C_2)]/C_2$. Detailed descriptions of the helium dilution technique for the measurement of FRC in infants have been reported (9, 10, 130). The equipment needed to perform the test is simple, reliable, relatively cheap (compared with plethysmography), and suitable for bedside measurements, but still requires considerable operator training to achieve reliable results consistently.

After a stable end-expiratory level has been established, the infant is switched into a spirometer breathing circuit that contains a known volume of gas with a known concentration of helium, and this mixture is rebreathed until equilibration is complete (concentration of helium is stable). The system must include a rapid and accurate helium analyzer, a CO_2 scrubber, a water absorption system, and an efficient circulating pump for fast response and prevention of rebreathing. The spirometer is normally attached via a face mask. Although measurements can be made in intubated infants, a leak-free connection is difficult to achieve because cuffed endotracheal tubes are rarely used in this age group (184). The calculated volume at FRC must be corrected for any inspired volume above end-expiratory level at the moment the infant is switched into the spirometer circuit and for the dead space of the apparatus, and must be converted to BTPS conditions. To improve the resolution of the measurement, the volume of the spirometric system should be as small and as close to the infant's lung volume as possible. Commercially available 1-L spirometric bells should suffice for older infants and toddlers, but a smaller size is recommended for neonates. The circuit must contain sufficient air to accommodate large sighs (two to three times normal VT). The system should be calibrated by adding several known increments of volume over the range of lung volumes being measured.

The helium analyzer should be operating within its linear range and be accurate within 1% of full-scale deflection. It must be calibrated specifically for each F_{IO_2} used. Spirometer temperature should be monitored internally and kept constant, as the helium analyzer is sensitive to changes in temperature. When connected to the enclosed system, the spirometer should be carefully balanced with the fan on, so that the system pressure remains as close as possible to atmospheric pressure. A useful method of checking for leaks in the system is to weight the spirometer bell temporarily and note any downward drift in the volume trace. During the measurements, oxygen must be added to keep the volume of the circuit constant. A fluctuating volume in the circuit may result in substantial errors in calculated FRC.

The time to equilibration is usually 20 to 60 s in healthy infants and young children (131), but may be considerably longer (3 to 5 min) in those with airway disease. Thus, rebreathing should be continued until helium concentration has been stable for at least 30 s. All helium should be cleared from the lungs before measurements are repeated. The interval required depends upon the mixing time for the particular subject. A leak in the system will cause a continuous decrease in helium concentration, and a small decrease may be difficult to distinguish from that due to poor mixing or inappropriate oxygen supplementation. Common practice is to average at least two FRC values within 10% of each other. As prolonged rebreathing is necessary in some infants with airway disease, this technique can require a lengthy testing period.

Helium dilution measurements of FRC have been reported to be reproducible in healthy infants (mean CV ± SD = 4 ± 2.8%) (131). Gas dilution techniques assume full equilibration of all lung units with the airway opening, and hence may underestimate true resting lung volume in subjects with gas trapping due to airway obstruction. Resting lung volume may also be underestimated if the F_{IO_2} is high, possibly as a result of increased alveolar oxygen transfer with subsequent reduction in alveolar volume (182).

Nitrogen washout technique. A third method of estimating FRC is to measure the volume of nitrogen washed out of the lungs when the infant rebreathes from a reservoir of nitrogen-free gas. In the original studies the equipment used was fairly simple, but the more recent techniques rely on mass spectrometers, which are technically demanding to maintain. As with the helium dilution technique, the apparatus needs to be sized appropriately for the subject. If the amount of washed out nitrogen is measured and the initial concentration of alveolar nitrogen is known, then the lung volume at which the washout started can be derived. If washout starts at FRC, then FRC equals the volume of nitrogen washed out divided by the initial nitrogen concentration in the lungs.

The difficult aspect of this technique is the accurate measurement of the volume of nitrogen washed out. In the two most commonly used methods, the volume of nitrogen is either measured from the expired gas in a collection bag or obtained by continuous integration of nitrogen concentration in the expired gas (185–187). A closed-circuit technique has also been described in which the infant rebreathes from a bag for a short time (188), but this method is limited and assumes conditions that are difficult to verify. At end of washout the nitrogen concentration and volume of the bag are measured.

In the expired gas collection method, the expired nitrogen volume is calculated as the product of the nitrogen concentration and the bag volume. Any inaccuracy in the measurement of the bag volume or, more commonly, the final nitrogen washout concentration, will cause significant errors. Because the final nitrogen concentration is very low, having been diluted with large amounts of oxygen, an error of < 1% in its measurement will cause substantial error. The resolution, and thus the accuracy, of the method depends on the initial alveolar nitrogen concentration. Thus, when an infant is breathing gas with a relatively high F_{IO_2} (i.e., low F_{IN_2}), the volume of nitrogen to be washed out will be very small, which may adversely affect results. At $F_{IO_2} > 0.7$ to 0.8, virtually no nitrogen is washed out of the lungs, and the technique cannot be used.

Using rapidly responding gas analyzers (or mass spectrometers) to obtain instantaneous nitrogen concentration and a computer to integrate flow signals, an open-circuit system can be created without a collection reservoir (185, 187). This system is potentially suitable for measurements in the neonate because its dead space is very low. Recent adaptations of the open-circuit technique have used a constant background flow of oxygen, to eliminate changes in instantaneous flow rate, and incorporated a mixing chamber in the exhalation circuit prior to the sampling port for nitrogen analysis (to minimize the effect of respiratory phase on estimation of nitrogen concentration) (191). In this method, the volume of nitrogen is proportional to flow rate through the system, and extreme care is needed to ascertain that flow rates remain truly constant. It is also important to ensure that the background flow remains higher than peak inspiratory flow of the subject.

Other potential problems with the nitrogen washout technique include those associated with analyzer response time, lag time between flow rate and gas concentration, and sampling rate. Corrections must be made for the nitrogen flushed from the tissues and blood. The latter usually causes < 5% error within a typical washout period of 2 to 3 min (187, 190) but may be larger if washout is prolonged in infants with lung disease. In the usual adult methods, end-tidal nitrogen concentration is measured continuously and required to decrease to < 2%, because concentrations higher than 2% tend to overlook the effects of extremely slow spaces. Final nitrogen concentrations of < 1% tend to exaggerate the effect of normal nitrogen diffusion from pulmonary blood

to the alveolar space. In some methods the final concentration is derived from exponential analysis of only a few breaths, but this has been used in only one study in infants (191).

The nitrogen washout has recently been adapted for use in ventilated infants (144). A second ventilator, with settings identical to those being used for the infant, is set up to deliver pure oxygen. At FRC, the patient is switched to the second ventilator and washout starts. The technique is accurate and reproducible but has the same disadvantages of the other nitrogen washout methods just described. As with all gas dilution techniques, results may be invalidated by leaks and accurate measurements may be feasible only if a cuffed endotracheal tube is in place.

Current Controversies

Measures of lung volume in infants remain controversial with respect to the conditions and techniques of measurement, the characteristics of the equipment, and apparent physiologic artifacts. In addition, the relative limitations and advantages of plethysmography versus the gas dilution techniques, and recommendations regarding the best test to use in specific clinical or research situations have yet to be clearly defined. Controversies about the presentation of results and the use of reference values are discussed in REFERENCE VALUES AND INTERPRETATION.

Measurement conditions. Measurements of FRC are usually made in sleeping, supine infants who, if more than 1 month of postnatal age, have been sedated with chloral hydrate. Alternative sedatives such as phenobarbital suppositories have been used, but infrequently. Anesthesia with a volatile gas such as halothane has been reported to reduce lung volume markedly (137, 138) in all age groups, although ketamine does not (192). Sedatives in the doses usually given for lung function tests appear to have little effect on respiratory pattern, resting lung volume, or the amount of time spent in quiet sleep (193–196), but caution is required in patients with upper airway obstruction because chloral hydrate may decrease upper airway muscle tone. The use of sleep deprivation to achieve such measurements is not recommended because it may disturb the breathing pattern (76).

Sleep state may affect lung volume measurements. In one report, Vtg measured by plethysmography was approximately 30% lower during active sleep than during quiet sleep (197). Only six infants in the first week of life were studied, however, and subsequent studies using both gas dilution and plethysmography have failed to demonstrate any significant change in lung volume with sleep state (66, 67, 179, 183). Nevertheless, the increased variability of end-expiratory level and the difficulty of obtaining reliable estimates of FRC during active sleep are such that measurements should ideally be confined to quiet sleep. Since the proportion of active sleep in relation to the total sleep time is at least 50% in full-term infants, and even greater in preterm infants, the time available for lung function studies is limited. Failure to monitor sleep state may contribute to the discrepancies between various published studies. Further research is required to define the influence of phasic versus tonic active sleep on lung volume.

In the absence of unilateral lung disease, measurements of FRC appear similar in the lateral and supine positions (72). In adults, significantly lower values of FRC are observed in the supine compared with the upright or sitting position, but this relationship has not been established in infants. For practical reasons, infants are always studied lying down, and this needs to be kept in mind when FRC measurements are compared between infants and older subjects.

Equipment and technical procedures. A great difficulty in comparing and interpreting results from different centers is the lack of standards for equipment, methods, and calculation procedures. Most equipment for measuring lung volumes in infants is homemade, and the necessary specifications for comparative conclusions are rarely presented in published reports. Substantial differences currently exist with respect to the thermal and frequency characteristics of the equipment, the response time of gas analyzers, and the dead space and resistance of the apparatus. The frequency response of measuring equipment should be adequate to at least five times the basic frequency of the respiratory maneuvers being measured (i.e., at least 10 Hz for measurements in infants). However, a standardized approach to simple, accurate methods of assessing the frequency response of infant lung function equipment has yet to be defined (172).

In the past few years, efforts have been made to introduce some degree of standardization into measurement techniques (130, 175, 198), but criteria for technically satisfactory data have not been established clearly enough for recommendations to gain widespread acceptance. With respect to the helium dilution technique, the primary areas of controversy include the optimal ratio of spirometer size to lung volume, the recommended duration of rebreathing (i.e., how "equilibration" is defined in health and disease), and whether extrapolation of helium concentration should be used in the presence of a relatively small but constant decline in helium concentration (175). With respect to the nitrogen washout technique, methods of overcoming the potential practical and theoretical difficulties have only recently been described (144, 189), and numerous methodologic variations still exist between different centers using this technique. Further work is required before a standardized approach can be adopted.

With all the techniques there is controversy regarding how many measurements should be made in each infant and how the results should be expressed. Obtaining three to five repeat measurements is relatively simple and quick with plethysmography. This is less feasible with the gas dilution techniques because of the duration of rebreathing or washout required and the necessary interval between tests. An acceptable result should be based on the mean of at least two measurements within 10% of each other.

Apparent physiologic artifacts. Once body size has been accounted for, plethysmographically determined values of FRC (Vtg) appear similar throughout life, and are comparable to measurements made in other mammalian species. By contrast, the gas dilution techniques, especially nitrogen washout, yield consistently lower values of FRC. This discrepancy between lung volumes measured using plethysmographic versus gas dilution techniques appears to be greater in healthy infants than in older children and adults. Further carefully designed comparative studies are required to elucidate the true magnitude of this difference and the reasons underlying it.

Particularly puzzling and controversial is the apparent underestimation of Vtg by plethysmography in infants with chronic wheezing after bronchiolitis (168). By contrast, the plethysmograph appears to measure Vtg accurately in infants with other types of obstructive lung disease including CF and acute bronchiolitis (136, 143, 147, 199). Further studies are required to resolve this specific controversy.

A further controversial aspect of plethysmography is the observation that different Vtg values may result from occlusions at end-inspiration and end-expiration. Whereas several groups have found this to be the case in infants with airway obstruction, others do not believe the problem exists (167, 170, 177, 200). Whether the differences are real, and if so, which occlusion volume should be used, remains to be determined.

Reference Values and Interpretation

Although numerous reports of reference values for lung volume in infancy have been published and recently summarized (150), discrepancies remain between different studies and techniques. Problems in the appropriate use of reference values arise because few of the published studies are based on more than 50 healthy infants and the data are generally cross-sectional. Furthermore, the characteristics of the reference population may differ from those of the study group with respect to the age, body size, gender, or ethnic origin, as well as the equipment and techniques used.

In healthy newborn infants, body weight and length may be equally good predictors of lung size. At this age, normalization based on body weight may be preferable because length may be more difficult to measure accurately, especially in sick preterm infants. Beyond the neonatal period, body length appears to be a better predictor of lung volume, being less influenced by differences in body fat in healthy infants and less dependent on the relative undernourishment that may accompany disease states such as CF. Lung volumes must be expressed in relation to prediction equations based on length, not as a simple ratio, because expression of lung volume as milliliters per centimeter of length results in "false ratios" and gross misinterpretation of results (198, 201). Although lung volumes are commonly expressed as "percent predicted" (202, 203), this approach necessitates the use of some arbitrary cut-off point for normality, which precludes the interpretation of a subject's result with respect to the range of values found in the reference population. The relative advantages of alternative approaches such as the use of percentiles and standardized residuals (146, 204, 205) need to be addressed. It is essential that statistically correct methods of prediction be used, whatever method of normalization is chosen.

Numerous studies have reported values for FRC in healthy infants using both gas dilution and plethysmography. Many of these studies have confined measurements to the neonatal period, thereby precluding calculation of prediction equations based on body weight or length. However, lung volume has frequently been expressed per kilogram of body weight. Using this approach, the mean values of FRC measured by gas dilution techniques have ranged from 20 to 24 ml/kg in infants as old as 18 months of age (9, 10, 131, 133, 181, 187, 190); the lowest values were obtained using the nitrogen washout technique. In contrast, mean values of Vtg have ranged from 29 to 34 ml/kg in infants as old as 1 yr (55, 89, 113, 159, 206, 210). The results of many of these studies have had wide scatter.

Most studies of FRC in infants have reported similar values in boys and girls (9, 10, 131, 133), but one of these suggested a small difference due to gender in younger infants, FRC being larger in boys than in girls (133). Insufficient data have been collected to ascertain whether race is an important determinant of lung volume during the first year of life, although clear evidence supports this in older children (208, 209).

Future Directions

International collaborative efforts are urgently needed to standardize equipment and techniques for the assessment of lung volumes in infants, with special emphasis on the areas outlined in CURRENT CONTROVERSIES. With the increasing commercial availability of equipment for infant lung function testing, it is particularly important to establish firm guidelines that can be adopted by manufacturers. These guidelines should address suitable equipment characteristics, such as frequency response, thermal characteristics, size, dead space and resistance of apparatus, sampling speed, and response time of gas analyzers. In the meantime, manufacturers should provide complete details of their equipment, including evidence of performance tests or the means by which the user can perform such tests.

Future work is required to assess the reproducibility of each technique in both healthy and sick infants and to assess the relative limitations and advantages of the various methods of assessing lung volume in specific research and clinical situations. Methods of assessing the *in vivo* accuracy of the three techniques need to be developed, together with a consensus on what constitutes technically acceptable data. Once standards have been established there is a need to obtain valid reference values during the first 2 yr of life. The development of training programs in infant lung function testing, by means of postgraduate courses or within designated laboratories, could greatly facilitate the process of standardization and establishment of common criteria for quality control.

In healthy infants, measurements of FRC by gas dilution are consistently lower than those obtained by plethysmography. The physiologic basis of this phenomenon must be clarified by carefully designed comparative studies.

Further studies are required to clarify how factors such as the chest wall, the respiratory muscles, and the central control of breathing influence breathing strategy in infants, how such factors evolve during the first year of life, and the extent to which they may influence lung volume measurements. To achieve this, simpler, noninvasive methods are needed to assess sleep state and respiratory muscle function, including that of the upper airways.

Improved methods and equipment for bedside investigations of lung volume in sick, intubated, or ventilated infants are required. Although the use of radiographic assessments of lung volume may be limited by the undesirable X-ray exposure, techniques such as echoplanar imaging and computed tomography hold considerable potential for future clinical use because they are less labor intensive, are easily repeatable, carry minimal risk other than the high dose of radiation, and require no sedation (151–154). However, considerable further development and validation will be required before such techniques can be applied routinely.

OTHER TESTS

Introduction

This section covers three categories of pulmonary function tests performed during tidal breathing: (*1*) measures of VT, respiratory rate, and tidal breathing patterns, (*2*) measures taken at the chest wall surface, and (*3*) measures of gas mixing. These tests are included because they represent standard or promising new measures of pulmonary mechanical function in infants that deserve further investigation. Not covered in this section are measures of gas exchange (lung diffusion, arterial-alveolar gradients, respiratory quotient, oxygen consumption, and carbon dioxide production), measures of respiratory drive (oxygen and carbon dioxide response, $P_{0.1}$), and lung scintigraphy (ventilation and perfusion scans).

Measures of VT, Respiratory Rate, and Breathing Pattern

Introduction. Although respiratory rate and clinical estimates of VT have been used for decades to assess infants with lung disease, few physiologic studies of these indices of minute ventilation have been done to define their determinants and normal values in infants. A major determinant of minute ventilation in infants appears to be the increase in metabolic demand related to growth and increasing activity. After birth in normal infants, VT

increases with weight while respiratory rate steadily declines through infancy. This change in pattern may be due to a decrease in Cw with growth (34), allowing for a more mechanically efficient increase in VT. It is unlikely to be due to alterations in CL, because specific compliance changes little during infancy (210). As will be discussed, these variables are apparently simple to measure but difficult to interpret, because the act of measurement can alter the infant's breathing pattern.

Although VT and respiratory rate offer information about how the ventilatory requirement is met in a given infant, the pattern of tidal breathing may serve as an indirect reflection of respiratory mechanics. Two recent studies suggest that tidal breathing pattern analysis in infants may be a sensitive indicator of lung disease (11, 211).

Methods. Tidal volume (VT) is most commonly measured with a pneumotachograph of the appropriate size attached to a face mask. The use of a face mask alters breathing pattern, however (212). The 2.2 ml/kg dead space of the commonly used apparatus and even slight apparatus resistances can also increase VT (213). Nasal prongs and nasal masks have been used in an effort to reduce dead space, but even newborn infants are not necessarily obligate nasal breathers (214). Other methods created to eliminate the problems of dead space and resistance include reverse plethysmography (215) and measurement of the expiratory gas dilution of a collateral flow stream (216).

Respiratory rate is often used as a nonspecific indicator of respiratory distress in infants. It is best measured during quiet sleep, usually by observing or feeling chest movements. The instrumentation techniques mentioned previously as well as capnography, nasal thermal changes, and respiratory inductance plethysmography have also been used to measure respiratory rate.

Two methods of breathing pattern analysis have been proposed. In the first, ventilation is partitioned into its "neuromechanical drive" and "duty cycle" determinants, given by the mean expiratory flow (VT/TI) or inspiratory time divided by total cycle duration (TI/Ttot), respectively (217–219). In the second method the form of tidal expiration is analyzed. For both methods, flow is measured by a pneumotachograph attached to the subject by means of a face mask. Care must be taken to obtain a leak-free seal and to avoid obstructing the nares. Flow signals are integrated to obtain volume, and a tidal flow-volume loop is displayed on an oscilloscope or a computer monitor. In one study, after a regular pattern of tidal breathing was observed as the superimposition of at least five sequential flow-volume loops, 10 breaths were sampled for analysis (11). The tidal expiratory flow pattern may then be quantitated as the ratio of the time to peak tidal expiratory flow (TME) divided by the expiratory time (TE), TME/TE.

Current controversies. The main controversy surrounding measurements of VT and respiratory rate in infants relates to their sources of variability. Studies have identified various sources but not their relative effects or the strength of their interactions. They include differences in state of arousal or sleep, gestational age or weight, and testing conditions. Subjects are often sedated with chloral hydrate, but this has been shown to have inconsistent effects on respiratory frequency (9, 71) and possibly on minute ventilation.

Little is known about the determinants of TME/TE in infancy. The relationship of TME/TE to lung function may exist because TME/TE quantitates the degree of active tidal slowing that occurs in response to respiratory system mechanics. In other words, TME/TE may reflect the neuromuscular response to the passive respiratory system rate constant and the resting lung volume (220–222). Slowing of expiration by postinspiratory diaphragmatic tone or laryngeal adduction seems to control TE and VT, thus adjusting the respiratory pattern to respond efficiently to demands for increased minute ventilation while maintaining a stable end-expiratory lung volume. In a patient with obstructive lung disease and a slow passive exhalation, the need for active braking might be expected to diminish, resulting in an early increase to peak expiratory flow (decreasing TME). Further, because exhalation is slow, TE must be relatively increased to allow exhalation to be completed. Thus, TME/TE would be abnormally low. This effect could be further augmented in severe obstruction with active exhalation with no active braking. However, this explanation for the observed relationship between low TME/TE values and obstructive airway disease is purely speculative. Indeed, studies in adults with chronic obstructive pulmonary disease (COPD) (223) show increased laryngeal adduction, which may further prolong TE. Much work remains to be done to reveal the meaning and the limitations of this technique.

TABLE 1

PREDICTED VALUES OF RESPIRATORY RATE (BREATHS/MIN) FROM SELECTED STUDIES OF INFANTS

		Age (*months*)				
Source	N	Birth	3	6	9	12
Gaultier, 1979 (130)	52	48	44	39	34	29
Tepper, 1986 (8)	117	47	38	31	27	24
Taussig, 1977 (132)	34	–	31	31	31	31
Weighted mean	203	47	38	33	29	26

Reference values and interpretation. Three recent studies (8, 131, 133) providing reference values of respiratory rate in infants during quiet sleep are shown in table 1. Two of these show different rates of decrease in respiratory rate from birth to 1 yr of age, whereas the third shows little or no change from 3 months to 1 yr of age. These disparate results reflect the sources of variability inherent in the respiratory rate, some of which were not considered in the reported measurements.

Four studies (9, 10, 131, 133) reporting reference values for VT are shown in table 2. VT in the first year of life is roughly constant at 7 to 9 ml/kg. These results are much more consistent than those for respiratory rate. However, all these studies were performed with a pneumotachograph and thus the values may differ from VT values obtained without the use of a mask by inductive plethysmography.

Reference values for TI/Ttot in infants are limited. A longitudinal study of 15 normal infants reported in 1979 (224) measured TI/Ttot during quiet sleep from birth to 4 months of age. A barometric chamber method not requiring the use of a face mask was used to avoid facial stimulation. The mean TI/Ttot (0.32 ± 0.07

TABLE 2

PREDICTED VALUES OF TIDAL VOLUME (ML) FROM SELECTED STUDIES OF INFANTS

		Age (*months*)				
		Birth	3	6	9	12
		Weight (*kg*)				
		3.2	5.5	7.5	9.0	10.0
		Length (*cm*)				
Source	N	50	60	67	72	75
Gaultier, 1979 (130)	65	22.0	48.9	67.7	81.2	89.3
Tepper, 1986 (8)	117	24.0	51.0	69.9	83.4	91.5
Taussig, 1977 (132)	34	–	47.8	75.1	94.7	106.4
Hanrahan, 1990 (9)	148	24.4	47.9	64.4	76.1	83.2
Weighted mean	364	23.8	49.1	67.8	81.1	89.1
ml/kg		7.4	8.9	9.0	9.0	8.9

SD) did not change during the study period. The authors therefore concluded that the increase in minute ventilation seen with growth was due primarily to an increase in mean inspiratory flow rather than in the respiratory duty cycle. Challenging similarly aged infants with 2% carbon dioxide resulted in an increase in minute ventilation but no change in mean Ti/Ttot (0.36) (225). In a study of 62 healthy children aged 4 to 16 yr, values of 0.40 to 0.50 have been observed (226).

Although adults with COPD have decreased Ti/Ttot (227), infants with severe BPD do not (211, 228). A study of 103 healthy infants and 24 infants with BPD, using a face mask and pneumotachograph to measure flow, found that age-corrected mean Ti/Ttot in the healthy babies at 3.7 months (0.43 ± 0.04 SD) did not differ from that measured in the babies with BPD (0.42 ± 0.05) (211). Indeed, it was reported (228) that hypercapnic infants with BPD had higher respiratory rates, shorter inspiratory times, and smaller VT than did normocapnic infants with BPD. Nevertheless, no significant difference in Ti/Ttot was found between the groups. In contrast to the results in infants with BPD, children with chronic airway problems do have a decreased Ti/Ttot and an increased mean inspiratory flow (217–219).

Abnormally shaped tidal expiratory flow-time curves, demonstrating a rapid, early expiration of VT, were first reported in infants with airway obstruction from bronchiolitis (161). The altered shape returned to normal as the disease resolved. Similarly, adults with obstructive lung disease (229) reach the peak tidal flow earlier in expiration than do normal subjects or subjects with restrictive lung disease. Reference values for Tme/TE in infants are very limited. In 103 healthy infants from Tucson, Arizona (211), studied using a face mask and a pneumotachograph to measure flow, age-corrected mean Tme/TE was 0.27 ± 0.08 SD at 3.7 months of age. The value was significantly lower (0.18 ± 0.09) in 24 infants with BPD. Reduced Tme/TE in early infancy also appears to predict later wheezing illness, suggesting that tidal expiration analysis may be useful in detecting mild to moderate levels of airway dysfunction (11).

Future directions. Rigorous studies are needed to define the determinants of tidal breathing pattern in infants in health and disease. Continued work is needed to reduce the effects of measurement conditions such as dead space, orofacial stimulation, or posture and head position, especially on VT. The interactions of sources of measurement variability such as sleep state, time since feeding, and time of day need to be better understood. Longitudinal studies of VT and respiratory rate are needed to determine the progression of these measures during normal development, taking into account gestational age, weight, and length. Measures of inspiratory timing (TI/Ttot) and drive (VT/TI) also merit further investigation in health and disease.

The observed relationship between diminished Tme/TE values and obstructive airway disease remains to be clarified. As for VT and respiratory rate, the factors governing measurement variability must be investigated. Further, these results (11, 211, 229) need to be replicated in infants with different ages, ethnicities, and lung conditions. For example, the analysis of tidal expiration in intubated neonates may be confounded because they cannot control expiratory flow by laryngeal adduction (230). If tidal breathing analysis can be shown to be useful, then this simple, noninvasive method could become a powerful epidemiologic tool.

Measures of Chest Wall Motion

Introduction

In preterm and newborn infants, Cw may exceed CL by 5- to 7-fold (231). The functional consequence of this high Cw for the infant is that the respiratory pump is less efficient in moving VT. Part of the applied pressure is used to draw in air, but another part is used to distort the chest wall (232). This is particularly true in active sleep (233). An understanding of chest wall mechanics is thus important in assessing the overall respiratory function of preterm and full-term infants. Chest wall properties that have been measured in infants include Cw (49, 231, 234), the contribution to VT of the separate rib cage (RC) and abdominal (AB) compartments (235), and the relative timing of the RC and AB compartments (synchronous, asynchronous, and paradoxic) (236, 237). This section discusses the last two measurements.

Surface measurements offer the potential for noninvasive assessment of ventilation (e.g., frequency, VT, Ti/Ttot) at the chest wall (238). They may prove useful in the study of the normal physiology of the chest wall, chest wall abnormalities (e.g., thoracic deformities and neuromuscular disease), control of breathing (e.g., central versus obstructive apnea [239]), and chest wall motion. Excessive negative intrapleural pressure associated with obstructive lung disease can affect the rib cage, delaying its outward movement relative to that of the abdomen or causing paradox. Quantitation of this asynchrony appears to be a promising noninvasive approach in assessing the severity of underlying lung disease (236, 237, 240).

Methods

Respiratory inductive plethysmography (RIP) is the most widely used method to assess chest wall motion. The amplitude-frequency response of RIP has been shown to be flat to 13 Hz (232) and thus is adequate to assess breathing patterns even in very tachypneic infants. Alternative methods include the use of strain gauges and magnetometers. If calibrated, these instruments can be used to differentiate the contributions to VT of the RC and AB chest wall compartments. Care must be taken to minimize shoulder girdle motion, to place the RIP bands and strain gauges properly, and to keep them from slipping during the study, as this will affect calibration. Two methods of calibration are commonly used: an isovolume maneuver during airway occlusion (241) or a least-mean-squares regression to solve the equation $VT = I_{RC} \times k_{RC} + I_{AB} \times k_{AB}$, where I is the pen displacement in volts (V) and k is the calibration factor in milliliters per volt. Given the two unknowns (k_{RC}, k_{AB}), simultaneous equations must be solved by choosing two ventilatory strategies that differ in the RC/AB contribution to breathing. A change in body position or from quiet to active sleep is commonly used to accomplish this (242–244). A third method, a modification of the isovolume calibration equations, has recently been described that allows calibration during single-posture natural breathing (245). Most workers accept agreement of RIP and pneumotachograph measurements of VT within 10 to 20% (242–244) as evidence of adequate calibration.

Although calibration is difficult in infants, the timing (phase relationships) between RC and AB movement can be inferred without volume calibration. This can be done by calculating a "phase angle," Φ, between RC and AB motion. If the AB and RC compartments are plotted on the *x* and *y* axes, respectively, of an oscilloscope, with time as an implicit variable, the resulting "Lissajous" figure can be analyzed, and a phase angle calculated. Synchronous motion ($\Phi = 0°$) is reflected in a closed loop with a positive slope. As asynchrony develops, the loop opens, becoming progressively wider as asynchrony increases. Counterclockwise loops indicate that outward AB motion precedes outward RC motion; clockwise loops indicate the opposite. Pure paradoxic motion ($\Phi = 180°$) is represented by a closed loop with a negative slope. This method of analysis assumes sinusoid RC and AB wave

forms, but in most cases motion that is not purely sinusoid does not introduce substantial errors (236).

Current Controversies

Limited data are available on the relative accuracy of measurements obtained by RIP, strain gauges, and magnetometers (246). Although all three methods detect abdominal motion equally well, magnetometers may be less accurate than RIP or strain gauges in representing changes in overall chest wall volume because they are more influenced by local events (e.g., proximity to the area of apposition of the diaphragm).

The major problem with all of these methods is calibration to volume. The underlying assumption that the system has only two degrees of freedom (241) may not be true, especially in premature infants with highly distortable chest walls (247). Furthermore, calibration performed during one sleep state may not apply in a different sleep state (248). Phase relationships between RC and AB movement may be measured independently of volume calibration. However, increased chest wall asynchrony is observed in active sleep; to allow for inferences about the underlying lung mechanics from chest wall motion, the measurements should be taken during quiet sleep determined using behavioral criteria (64). Furthermore, to be most informative, phase angle values should be analyzed along with the volumetric contributions of the RC and AB compartments. For example, a phase angle of 180° with substantial RC motion has greater functional consequences for the infant than a phase angle of 180° with minimal RC motion.

Reference Values and Interpretation

Rib cage contribution to VT. The mean RC contribution to VT during quiet sleep is 35% (range = 20 to 50%) in the first 3 months and approaches adolescent values by age 1 yr (mean = 60%, range = 30 to 80%) (235). No data from preterm infants have been published.

Phase relationships of RC/AB movement. Normal chest wall motion is synchronous in full-term infants and children (mean phase shift = 8°, range = 0 to 25°) in quiet sleep (236, 237). Normal chest wall motion in preterm infants may be asynchronous, with a mean phase shift of 58° (range = 0 to 157°) in quiet sleep (outward AB motion preceding outward RC motion) (249). In this age group, chest wall motion is more synchronous in the prone than in the supine position (250). Pulmonary disease has marked effects on chest wall asynchrony that can be related to the degree of abnormality in Crs and Rrs. Again, outward AB motion usually precedes outward RC motion (251). Asynchrony improves significantly after bronchodilators in infants with lower airway obstruction (236) and after racemic epinephrine in children with upper airway obstruction (237). These changes in asynchrony correlate with the improvement in lung mechanics (236).

Future Directions

Relative to the infant lung, little is known about the infant chest wall. Promising noninvasive techniques of assessing chest wall function have recently been introduced. The methodologic issues that require further study include the relative value of RIP, strain gauges, and magnetometry and the comparison of different methods of calibration, especially in preterm infants. In calibration methods, the assumption of only two degrees of freedom needs to be critically evaluated, as does the stability of calibration between sleep states and body positions. Further development of the recently described performance index (248) will better enable workers to assess agreement between RIP and pneumotachographic measurements of VT. The accuracy of RIP in tracking changes in FRC merits study. The effects of chest wall mechanics on other measures of lung function in infants (e.g., PEFV curves by the RTC technique, esophageal manometry) need to be investigated. The accuracy of differentiating measures of chest wall volume changes to obtain flow measurements should be further assessed as a promising method of producing tidal flow-volume curves without a face mask (252).

Further reference data need to be generated to describe the changes with development in static and dynamic Cw in preterm and growing full-term infants, and in the relative magnitude and timing of RC and AB contributions to VT. The intrasubject variability of these measurements needs to be established.

Chest wall mechanics should be studied in infants with neuromuscular disease, chest wall abnormalities, and primary lung disease, and the role of chest wall instability in overall respiratory pump malfunction should be assessed. The use of the phase angle as a promising, noninvasive index of airflow obstruction needs to be further evaluated. Chest wall motion should be investigated as an indicator of control of breathing (e.g., to differentiate central from obstructive apnea). Chest wall muscle function (e.g., electromyographic activity, $P_{0.1}$, maximal inspiratory and expiratory pressure) should also be studied.

Measures of Gas Mixing

Introduction. Gas mixing is measured during tidal breathing of either washout or washin of a gas. Studies using measures of gas mixing have found them to be sensitive indicators of obstructive lung disease in infants, children, and adults. The sensitivity of these measures in infants with respiratory disease is highlighted by the results of three studies. In a study of infants with hyaline membrane disease, gas mixing measures discriminated between those infants who completely recovered with no subsequent lung disease and those who developed BPD (253). In two other studies, a measure of gas mixing discriminated between normal infants and those with CF (254) and between infants with CF with and without pulmonary symptoms (255).

Tests of gas mixing present a different view of the lungs than do the measures mentioned in previous sections in that they assess homogeneity of ventilation. The combination of measures of lung mechanics and measures of gas mixing may provide a better picture of lung function than either type of test alone. This idea is supported by a study in older subjects in which normal subjects, patients with mild or moderate asthma, and patients with CF could be discriminated only by using measures of both lung mechanics and gas mixing (256).

Methods. Measures of gas mixing are usually performed during a measurement of FRC by either nitrogen washout or inert gas equilibration. All such techniques take measurements from the resulting exponential decay curve of gas concentration. Numerous methods of analysis have been proposed and tested in adults. Some methods normalize a measurement taken at the end of the washout by lung volume—that is, the pulmonary clearance index (257) is the ratio of the ventilation required to achieve 2% end-tidal nitrogen concentration and the FRC. Because such single-point measures can be variable even in cooperative adults, they are infrequently performed in young subjects, who are commonly less cooperative and predictable.

The five measures for which data from infants or young children have been published are mixing index (258), pulmonary clearance delay (259), ventilatory efficiency (260), multiple-compartment model fitting (261), and moment analysis (262). In the first three techniques, once the diluted volume (FRC) and the diluting volume (VT) are known, the washout values for a one-compartment

ideal lung (a lung with perfect gas mixing) can be calculated and compared with the observed values. Both the mixing index and the pulmonary clearance delay compare the observed number of breaths to reach a given mixing value with the expected number from an ideal lung. The ventilatory efficiency compares the ventilatory volume needed to achieve 90% mixing in the patient's lungs to the ventilatory volume required of an ideal lung.

The final two techniques analyze the shape of the washout curve. In multiple-compartment model fitting, compartments of different time constants are derived by fitting two or more linear approximations to the log-linear plot of washout gas concentration over expired volume. In moment analysis, the distribution of the dilution number (expired volume/FRC) versus end-tidal nitrogen concentration is characterized by the moment ratios M_1/M_0 and M_2/M_0.

Current controversies. These methods have no standardized technique or terminology. Two studies have compared the sensitivity (263) and reproducibility (264) of multiple methods of performing gas mixing measurements in adults, but no such studies have been performed for infants. The question of the most appropriate method for this age group thus remains open.

When gas measurements are performed, the issues of equipment dead space, gas analyzer response, and synchronization with flow measurement require careful attention (265). In infants these issues are compounded by the smaller size and faster breathing patterns (265). The best strategy for overcoming such equipment effects continues to be debated.

Gas mixing measures are reportedly sensitive in detecting disease (263). Whether and how such measures change with age remain controversial. The lack of standardized methods or equipment impedes any generalization about normative data or demonstration of the utility of such measures in observing the course of infant lung disease.

Reference values and interpretation. A few studies have produced reference values in infants. Mixing index (i.e., the theoretic number of breaths needed to achieve 90% mixing in an ideal lung expressed as a percentage of the number of observed breaths) has a positive correlation with body length over the first year of life and averages about 61% (218). Infants with little or no disease have a pulmonary clearance delay of 47%, which corresponds to a mixing index of 68% (253). These data suggest less even mixing in infants than in adults, whose pulmonary clearance delay of 21% (259) corresponds to a mixing index of 82%. The ventilatory efficiency (i.e., theoretic ventilation to achieve 90% mixing in an ideal lung expressed as a percentage of observed ventilation) of reference subjects has been found to be about 50% in infants versus 70% in adults (267). In two similar analyses that took anatomic dead space into account, the ventilatory efficiency increased over the first day of life from 47 to 76% (185) and from 51 to 60% (268).

In multiple-compartment analysis studies newborn infants have less even ventilation than do adults, having a slow lung space that represents 10 to 20% of total alveolar ventilation (185, 253, 268, 269). These results are contradicted by one report that found more even ventilation in normal newborns than in normal adults (270). Although no results from moment analysis in infants have been published, one study in children found a significant difference in moment ratios between normal subjects and those as young as 3 yr of age with CF (271).

Future directions. The techniques for testing and analyzing gas mixing need to be standardized so that results from different studies can be compared. As the simultaneous calculation of all proposed measures of gas mixing is possible, comparative studies are needed to determine the best way to characterize gas mixing in health versus disease. The use of inert gases for gas mixing studies may yield different results from nitrogen washout with oxygen and should be evaluated. Continued work is needed to design equipment that operates quickly enough to analyze the rapid breathing patterns of infants and is small enough to provide dead spaces appropriate to the infant's size. Longitudinal studies are needed to determine how measures of gas mixing change with age and whether they are useful indicators of early lung disease in infants and young children. When these goals are met, gas mixing measures may be useful in characterizing lung function from birth to adulthood in health and disease.

Conclusion and Recommendations

It is now possible to perform a variety of measurements of respiratory mechanics in infants. These have already proved valuable in revealing the normal functional development of the lungs and in predicting and tracking infant respiratory disease and responses to therapy. However their full potential is still unrealized because of the lack of standardized methods and reference values. Further, some uncertainty remains about the physiologic basis of some of these tests. On the basis of its discussions and the scientific information summarized in this statement, the Committee makes the following recommendations.

Standardization

The measurement procedures for infant pulmonary function testing must be standardized. Equipment standards like those established for pulmonary function testing in adults and children are needed for the instruments used in infants. A committee needs to be established for the express purpose of setting standards for tests of infant pulmonary function in accordance with current knowledge of these measurements. Standards should be revised as new information about these tests is acquired. Patient safety must be assured in all aspects of the development of standards and investigation of respiratory mechanics. This statement does not attempt to address the relative safety of the various sedatives used during infant pulmonary function testing. The risk versus the benefit of any medication given should be assessed on an individual basis.

Physiologic Investigation

It is important to define further the physiologic basis underlying pulmonary function tests in infants in order to clarify what the tests can and cannot measure. For example, the following specific issues need to be addressed: (*1*) The question of whether or not flow limitation is reached during measurements of forced expiration needs to be resolved. (*2*) The effect of active respiratory responses (including the upper airway, chest wall, and other respiratory muscles) on tests performed during assumed passive conditions needs to be investigated. (*3*) The reasons for the consistent discrepancies in measurements of lung volumes in healthy infants by plethysmographic versus gas dilution techniques need to be defined. Although not addressed in this report, the Committee recognizes the need to develop methods for evaluating pulmonary function in preschool children.

Reference Values

Normal reference values for tests of infant pulmonary function need to be obtained from sufficient numbers of subjects. This will require collaborative efforts using equipment and procedures that meet the established standards. Age, gender, race, and other

genetic and environmental factors will need to be considered. The appropriate basis on which to compare the results of the various tests at different stages of growth and development will need to be determined.

Scientific Interaction

The continued development of currently useful tests of infant pulmonary function will be optimized by the exchange of scientific information at regular intervals between investigators working in this area both nationally and internationally. Workshops are recommended both to foster the exchange of scientific information and to educate practitioners of all levels. Constructive interaction must be fostered between scientific investigators in the field and the manufacturers of testing equipment.

Collaborative Investigations

Because of the complexities involved in obtaining reliable pulmonary function data in infants and the relatively small number of subjects available for study in any single center, multicenter collaborative studies and clinical trials should be undertaken to investigate:

(1) The functional development of respiratory mechanics in healthy infants
(2) The impact of prenatal and postnatal factors, including tobacco smoke and drug abuse on respiratory system development
(3) The natural history of the major respiratory disorders of infancy, including CF, asthma, neonatal lung disease, and disease from respiratory syncytial and human immunodeficiency viral infections
(4) The effects of major therapeutic interventions on these disease processes

If tests of pulmonary function in infants are developed in parallel with new diagnostic and therapeutic approaches being derived from the rapid advances occurring in cell and molecular biology, great potential exists to make substantial progress in the diagnosis and treatment of respiratory disorders of early childhood.

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