CONSENSUS STATEMENT ON MEASUREMENTS OF LUNG VOLUMES IN HUMANS

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1. INTRODUCTION

Inspired and expired lung volumes measured by spirometry are useful for detecting, characterizing, and quantitating the severity of lung disease. Measurements of absolute lung volumes, residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC), are technically more challenging and their clinical usefulness is more controversial.

In contrast to the relative simplicity of spirometric volumes, a variety of disparate techniques have been developed for measurements that include the "inaccessible" space of RV. These include gas dilution (e.g., the helium (He) or argon dilution techniques), nitrogen (N_2) washout measurements, body plethysmography using various methodologies, and radiographic imaging methods using standard posterior-anterior and lateral chest radiographs and computerized tomography (CT).

As part of ongoing efforts by the American Thoracic Society (ATS) to develop recommendations and standards regarding clinical testing, a workshop was convened by the ATS and charged with developing recommendations for measuring absolute lung volumes in humans. In order to provide the diversity of expertise necessary to meet these challenges and develop recommendations that could be endorsed by the European Respiratory Society (ERS) as well as the ATS, many from "across the Atlantic" were invited workshop participants.

We decided to integrate input from experts with both adult and pediatric experience in order to share perspectives regarding specific measurement techniques unique to either adult or pediatric patients. This facilitated clearer definition of optimal techniques and clinical limitations for subjects of all ages.

Since selection of appropriate reference values can be as important as correct measurement techniques, a review of predictive values of lung volumes has also been included. In addition, because clinicians face increasing pressure to limit the use of increasingly expensive medical technology, we reviewed the pathophysiology of changes in absolute lung volumes in order to better define the clinical indications for these measurements and their clinical usefulness.

The scope of the resultant review was considerable. Had all of the background information and recommendations developed by consensus been compressed into a single document of length suitable for publication as a Statement endorsed by the ATS and ERS, much valuable information would have been lost. It was therefore originally decided that, in addition to this consensus document, the background papers developed by workshop participants would be submitted for publication.[1] This also permitted a more representative account of workshop participants' input prior to the integration of differing viewpoints into a single consensus document. After the original consensus document was developed, it was still considered too long for publication in the American Journal of Respiratory and Critical Care Medicine, but many felt that it could not be shortened to the target length without sacrificing information that led to consensus

conclusions. To resolve this impasse, it was finally decided to publish this consensus document as a web-based document and that a shorter standardization document would be written and published by the joint ATS/ERS Task Force on standardizing pulmonary function testing in the European Respiratory Journal. In both the published ATS/ERS document and in this web-based broader consensus document, we have referred readers to the background papers published in the European Respiratory Journal for more in-depth review or citation of supporting references. [1-11]

Development of the recommendations in this document required balancing the performance of instrumentation currently in widespread clinical use versus the costs of purchasing improved but often-expensive new technology. We anticipate that in some laboratories wishing to comply with these recommendations that the compromises reached will mean that some older instruments will need replacement and some existing automated instruments will require relatively inexpensive software upgrades.

Systems will be available in the future which through new technology will offer potential advantages (e.g., ease of use, rapidity of testing, improved accuracy) over the methodology recommended in this document. The ATS and ERS encourage such innovation. However, it is the responsibility of manufacturers to demonstrate that the lung volumes reported by new technology do not differ substantially from those obtained by the standard techniques; such comparisons must be made using subjects with varying severities of obstructive and restrictive lung disease as well as healthy subjects.

Future updates of the recommendations in this document can then more readily take into account the improvements in technology.

In addition to the fiscal and administrative support of the workshop by the ATS, grant support from the National Heart, Lung, and Blood Institute (Grant # R13-HL-48384) was invaluable and appreciated.

2. TERMINOLOGY

The term 'lung volume' usually refers to the volume of gas within the lungs as measured by body plethysmography, gas dilution or washout. In contrast, lung volumes derived from conventional chest radiographs usually are based on the volumes within the outlines of the thoracic cage and include the volume of normal and "abnormal" lung tissue (e.g., interstitial fibrosis) as well as the lung gas volume. Lung volumes derived from CT scans can include estimates of abnormal lung tissue volumes as well as normal lung tissue volumes and the volume of gas within the lungs.[12]

By convention, lung “capacities” have been defined as "volumes which are combined"[13] or "lung volumes which are formed of two or more sub-volumes".[14] Thus, total lung capacity (TLC) represents the sum of residual volume (RV), expiratory reserve volume (ERV), tidal volume (V_T or TV), and inspiratory reserve volume (IRV).[11]

In this report, we will use the term lung volumes to mean volumes which represent the *total* amount of gas in the lungs (e.g., RV, FRC, TLC, thoracic gas volume) in contrast to subdivisions of lung volumes measurable with a spirometer (e.g., vital capacity, ERV, inspiratory capacity).

Recommendations for specific abbreviations were made to be as much as possible in accord with recommendations developed for terminology regarding respiratory function in infants recently endorsed by the ATS and ERS [15,16] and the editorial board of

Pediatric Pulmonology.[17] This includes the use of subscripts to better define parameters, commas to separate multiple subscripts, and ordering of multiple subscripts according to location (where), time (when), condition, or quality (what, how)[15,16] (e.g., F_{I,O_2} [or $F_{I,O2}$ if it is easier to use smaller type on the same line for subscripts of subscripts]; P_{a,CO_2} or $P_{a,CO2}$). In this document we have also followed the convention that vital capacity (VC) can refer to either inspiratory (IVC) or expiratory (EVC) vital capacity; the maneuvers used to measure VC, IVC, or EVC are presumed to be "slow" or "non-forced" unless preceded by an F (e.g., FVC, FIVC) in which case the entire expiratory or inspiratory maneuver is performed with sustained maximal expiratory or inspiratory efforts. [17]

Total Lung Capacity:

Total lung capacity (TLC) is the volume of gas in the lungs after maximal inspiration, or the sum of all volume compartments.

Vital Capacity (VC):

Vital capacity (VC) is the volume change at the mouth between the positions of full inspiration and complete expiration. The measurement may be made in one of the following ways:

1. Inspiratory vital capacity (IVC): the measurement is performed in a relaxed manner, without undue haste or deliberately holding back, from a position of full expiration to full inspiration.

2. Expiratory vital capacity (EVC): the measurement is performed in a relaxed manner, without undue haste or deliberately holding back, starting from a position of full inspiration to full expiration.

3. Forced vital capacity (FVC): the volume of gas which is exhaled during a forced expiration starting from a position of full inspiration and ending at complete expiration.

Residual Volume:

Residual volume (RV) is the volume of gas in the lungs after maximum voluntary expiration (regardless of the lung volume at which exhalation was started). In most healthy young adults RV is set by a static balance between the compressive forces from expiratory muscles (and a small contribution from lung elastic recoil) and the expansive force from the elastic recoil of the chest wall. In older healthy adults, RV is determined more by dynamic than static mechanisms due to decreases in elastic recoil of the lung and associated decreases in maximal expiratory flow resulting in gradual increases in RV with aging. In individuals with obstructive airway diseases, expiratory flow limitations can be even more marked. In such cases, RV may vary with the lung volume at which the expiratory maneuver starts and the duration of the expiratory maneuver. Decreases in expiratory flow due to alveolar gas compression and true negative effort dependence may also influence RV in such cases. Additional causes of variations in RV include external resistance and changes in the respiratory exchange ratio during expiration [18] and inhibition of increases in RV by maximal inspirations to TLC [19;20] or increases in transpulmonary pressure during inspiratory efforts. The resultant

dependence of RV on volume history raises the question of whether RV should be strictly defined as "the volume of gas remaining in the lungs after maximal expiration from FRC" or whether other RV measured after other volume histories should be accepted.

Recommendation for RV:

RV is defined as the lung volume after complete expiration regardless of the lung volume at which expiration started. Although not implicit in the general definition of RV, it is, however, preferred that RV be reached by a slow expiration and that this expiration start from FRC rather than from TLC. The volume history used during RV measurements should be described in lab protocols and methodology sections of reports.

Valid measurements of TLC and RV require maximal inspiratory and expiratory efforts and hence cannot be obtained in non-cooperating subjects such as infants or comatose adults. In such subjects, volumes approaching RV or TLC can be measured after application of compressive or expansive forces to the chest wall, or of positive or negative pressures to the airways. [21] The procedures and pressures used, and the relation of the resulting volume extremes to those achieved by voluntary efforts, are not well established. In such subjects, volumes related to TLC and RV can also be defined by maximum and minimum lung volumes achieved during spontaneous activities like sighing, crying, or hyperpnea but the relationship of these volumes to 'actual' RV and TLC is poorly defined.

Tidal Volume:

Tidal volume (TV or V_T) has been defined as "that volume of air inhaled or exhaled with each breath during quiet breathing".[13] However, the term tidal volume is commonly used to describe tidal breathing under a variety of other conditions (e.g., during exercise, during labored breathing).

Recommendation for Tidal Volume:

Tidal volume is defined as "the volume of gas inhaled or exhaled with each breath". The preferred abbreviation is V_T but TV is acceptable. If measured under conditions other than quiet relaxed breathing that should be indicated. Since the breath-to-breath inspiratory and expiratory V_T can differ under some circumstances, it occasionally may be appropriate to specify which is used (e.g., $V_{T,I}$ for inspiratory tidal volume). Often tidal volume denotes the "averaged" tidal breathing volume (e.g., when minute ventilation is divided by respiratory rate in order to compute tidal volume).

Functional Residual Capacity:

Functional residual capacity (FRC) is the volume of gas present in the lung at end-expiration during tidal breathing. “Relaxation volume” ($V_{rel\ or}\ V_r$), “passive “ and “elastic equilibrium volume” (EEV) are terms that have been used to identify the equilibrium volume of the 'relaxed' respiratory system under static conditions when the recoil pressures of lung and relaxed chest wall are equal and opposite in sign. FRC in healthy humans approximates the V_{rel}. In infants, FRC is usually maintained above V_{rel} by the active processes of increased tone of inspiratory muscles, glottic braking of expiration

(which lengthen the expiratory time), and a relatively high respiratory rate (short expiratory time) which results in initiation of inspiration before V_{rel} is reached.

FRC also differs from V_{rel} under other conditions and can be set by both passive and active processes. During exercise in younger healthy adults, for example, increased activity of expiratory muscles commonly drives FRC below the V_{rel}. In obstructive lung diseases, relaxed expiration may still be 'incomplete' when it is interrupted by the next inspiration; FRC then exceeds V_{rel}, especially with hyperpnea (such as may occur during exercise or mechanical ventilation). Under such conditions, FRC has been called "dynamic FRC" (FRC_{dyn}) or "end-expiratory-lung volume" (EELV).

Recommendations for FRC:

FRC is the lung volume at end expiration during tidal breathing. If the intent is to describe the FRC under other conditions, the condition should be described. Subscripts can be used to denote FRC measured during conditions other than quiet breathing (e.g., FRC_{crying} during crying in infants, or FRC_{exer} for FRC measured during exercise). If the intention is to describe the static equilibrium volume of the "relaxed" respiratory system, the abbreviation 'V_{rel}' should be used. We discourage the use of such terms as dynamic (FRC_{dyn}) or end expiratory lung volume (EELV).

Since in individuals with lung disease lung volumes measured by different methods may differ (e.g., multiple-breath N_2 washout vs body plethysmography in those with severe COPD), the method should be specified. Abbreviations can be described with a subscript (e.g., FRC_{pleth}). Similar subscripts can be used for identifying the type of

measurement for RV and TLC (e.g., TLC_{sbN2} for TLC measured by single-breath N_2 washout).

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Thoracic Gas Volume:

The term “thoracic gas volume” (abbreviated TGV or V_{TG}) generally refers to the volume of gas measured by body plethysmography. Most commonly, patients are presumed to at FRC when TGV measurements are made; however, TGV can be used to describe plethysmographic measurements of lung volumes at any level of thoracic expansion and at any level of alveolar gas compression or expansion and can also refer to gas volumes determined by non-plethysmographic methods. Because of the nonspecificity of the term, it has been recommended in official statements adopted by both the ATS and ERS regarding respiratory terminology in infants that the use of the term TGV be abandoned.[16;17]

Recommendation for Thoracic Gas Volume:

The term "thoracic gas volume" is defined as the absolute volume of gas in the thorax at any point in time and at any level of alveolar pressure. Because the term is too nonspecific, it is recommended that the use of this term be discontinued and be replaced with more specific terminology (e.g., plethysmographic lung volume [abbreviated $V_{L,pleth}$]; FRC by plethysmography for TGV at FRC [abbreviated FRC_{pleth}].

Hyperinflation:

The term “hyperinflation” has several meanings. When used to describe pulmonary function test (PFT) results, hyperinflation can refer to elevations of RV, FRC, or TLC.

Hyperinflation is also used to describe radiographic evidence of a larger than expected TLC and can, in this context, refer to a specific lung region (e.g., "hyperinflation of the right lower lobe").

Recommendation for Hyperinflation:

Hyperinflation is defined as a larger than expected lung volume. When the term is used, the volume or region being described should be specified (e.g., "hyperinflation of the right lower lobe" or "hyperinflation of RV").

Restriction:

The term “restriction” also has several meanings. The 1975 ACCP-ATS joint committee provided the following definition: "Restrictive Pattern (Restrictive ventilatory defect): Reduction of vital capacity not explainable by airways obstruction".[13] Many, however, find this definition unsatisfactory and use the term 'restrictive pattern' as a synonym for a reduced TLC.

Reductions in TLC are usually accompanied by reductions in vital capacity. Reductions in vital capacity not accompanied by reduced maximal expiratory flows are highly suggestive of a restrictive process, but this assumption is not always valid. For example, reduced VC and normal or elevated TLC can occur in a variety of patients [6] including those with bullous or cystic lung disease in the absence of obstructive airway disease. [22] In children with scoliosis, an elevated RV, resultant from a stiff chest wall, can reduce vital capacity even though TLC is normal.

Recommendation for Restriction:

The terms "restriction" or "restrictive pattern" refer to conditions in which TLC is reduced.

Gas Trapping:

The term “gas trapping” has a variety of uses (e.g., differences between body plethysmographic and gas washout lung volumes; differences between FRC measured after conventional N_2 washout to 2% N_2 and after five additional inspiratory capacity (IC) maneuvers [23]; differences between slow and forced expiratory vital capacities; hyperinflation of dynamic FRC during exercise; radiographic evidence of regional or localized hyperinflation of the lung). This workshop was not able to achieve a consensus for one or more specific definitions of "gas trapping" likely to be universally accepted. It was also recognized that regardless of the specific definition, estimates of the volume of gas trapped vary substantially because of the dependence on breathing patterns and methods of measurement (e.g., whether radiographs are imaged at end expiration or inspiration, the duration of multiple breath N_2 washouts). The abbreviations that have been used include TAV for trapped air volume, V_{tg} for trapped gas volume, and TG for trapped gas.

Recommendation for Gas Trapping:

When the term "gas trapping" or "trapped gas" are used, the context should be described [e.g., "Gas trapping following a FVC maneuver", "gas trapping during exercise", "gas trapping evidenced by differences between body plethysmographic and N_2 washout measurements"; "lobar hyperinflation indicates gas trapping" (as seen on radiographs)].

If an abbreviation is needed, the term "V_{tr}" is recommended for the volume of trapped gas; $V_{tr, exer}$ for the volume of gas trapped during exercise. The abbreviation V_{tg} should not be used because it is sometimes confused with thoracic gas volume.

Controversies:

Differences in volume histories can influence the magnitude of the RV. In healthy subjects the differences when RV is reached from an expiration from FRC rather than TLC are usually small. In patients with significant obstructive disease, however, the RV reached when slow expiration is started from TLC may be significantly larger than when expiration is started from FRC. And RV reached after a FVC rather than a EVC from TLC can be even higher. Although the RV calculated from the FRC-ERV will most likely represent the smallest RV, it may not be as sensitive for the early detection of hyperinflation as the RV computed from the TLC-FVC. In order to minimize such differences, it was proposed that the definition of RV include specifics as to how the expiratory effort was performed. This was rejected in favor of the more general definition recommended with attention directed to the method of expiration in the sections on optimal methods of testing.

3. EFFECTS OF NUTRITION, GROWTH HORMONE DISTURBANCES, TRAINING, AND ALTITUDE ON LUNG VOLUMES

Readers interested in more extensive literature citations for this section are referred to the background paper by Gaultier and Crapo.[8]

3.1 Effects of Nutrition

Knowledge of the effects of nutrition on lung growth has been provided mostly by animal studies. [8] Adequate studies of humans are not available for the first two years of life. Based primarily on results of animal research, adverse effects in humans should be greatest when malnutrition occurs during late gestation and the two first years of life and is expected to be associated with low lung volumes, low lung compliance, and an increased ratio of maximal expiratory flows to lung volume. Intra-uterine growth retardation does not appear to modify lung volumes in children. [24] Information is scarce with regard to the potential effects of generational changes in diet such as may occur in migrating populations. Third-generation Japanese-Americans have lung volume corrected for height more comparable to Caucasians than native Japanese. [25] Environmental factors other than changes in diet may also explain anthropometric and pulmonary function changes.[8]

3.2 Effects of Growth Hormone

In children who had growth hormone deficiency, VC, FRC, and TLC are appropriate for the small statures of the patients; after treatment, compensatory growth occurs associated with increases in TLC and VC appropriate for the increase in standing height. [8] Individuals with adult-onset hypopituitarism have reduced lung volumes. [26]

In acromegalic adults all lung volumes are increased and pulmonary distensibility is normal suggesting that large lung volumes of acromegalic patients are from increases in alveolar number rather than size. [8]

3.3 Effects of Training

Animal studies show conflicting data with regard to the effects of sustained exercise on enhancement of lung growth. In humans a number of studies have observed that lung volumes are larger than expected in young swimmers. [8, 95] Elevated lung volumes have been noted before the start of swimming training suggesting that large lungs may be a characteristic of those selected for swim teams [8], perhaps because of improved buoyancy as well as larger oxygen (O_2) reserves during breathholding. Swim training may also increase absolute lung volumes even further.[8] Studies of athletes training in other sports (football, gymnastics, tennis, runners, rowing) [8] as well as musicians trained as wind instrument players and singers [27] have generally not shown increased lung volumes although a few studies have shown small increases in VC associated with enhanced physical education programs in children. [8]

In adults, five weeks of ventilatory muscle strength training led to only small increases in VC despite more than a 50% increase in maximal static inspiratory pressures at FRC. [28] Another study showed that healthy subjects can increase their VC and TLC over a 6-week training period by performing multiple daily sustained inhalations to TLC, increases attributed to greater maximal shortening of the inspiratory muscles. [29] Such a mechanism could explain increased VC seen in breath-hold divers. [8]

3.4 Effect of Altitude

No consistent differences in lung volumes attributable solely to altitude have been reported in studies of residents at altitudes from sea level to 1800 meters. Increased lung volumes are, however, an adaptive response to high altitudes (at or above 3,000 meters).[8;30-32] Studies consistently show larger lung volumes in natives of high altitudes which are not explained by race or body size.[30;31] The magnitude of the increases in lung volume is hard to quantify because of differences in body size and race of the subjects and the variability between studies. TLC in highland natives compared to lowland natives are in the range of 7-15% larger.

In residents of high altitude, the increase in lung volume varies depending upon the age at which acclimatization occurred and the duration of the exposure to high altitude. Children over 5 years of age living at high altitudes have larger VC than lowlanders and the differences increase through age 21. VC does not appear to change if the stay at high altitude is less than three years. The increases in vital capacity are about the same for individuals who acclimatize and live at high altitude during growth regardless of whether or not they were born at high altitude; native lowlanders who acclimatize to high altitude as adults have smaller vital capacities than highland natives.[8] These observations suggest that larger lung volumes in highland natives are acquired as a result of exposure to hypoxia during growth rather than being genetically determined. An increase in the number and size of the alveoli when lungs of highlanders were compared with sea level controls has been observed [8], results also noted in newborn

rats exposed to hypoxia. [33] The increased lung volumes observed in animals raised at high altitudes are associated with both an increase in air within the lung and an increase in the fine septal tissue and the internal surface area of the lung. [32] Thus, the larger lung volumes seen in high altitude natives appear to be the result of accelerated and/or prolonged lung growth in response to a hypoxemic stimulus at an early age rather than over-inflation of the lung.

The findings concerning changes in lung volumes associated with acute exposure to high altitudes are variable. Average vital capacity decreases (about 200 mL in adults) and total lung capacity and residual volume increase with the initial exposure to altitude, but return to baseline values within a month. [8]

4. DETERMINANTS OF LUNG VOLUMES IN HEALTH AND DISEASE

An understanding of the physiologic determinants of absolute lung volumes is important for optimizing the accuracy of these measurements, as they are often highly dependent on conditions of the testing such as posture or volume history. It is also important for defining the clinical usefulness of these tests.

Changes in lung volumes impact on the efficiency and effectiveness of gas exchange, on respiratory muscle function, and on the sensation of dyspnea. The physiologic determinants of these changes are, however, incompletely understood.[34,35] Changes in surface tension and reflexes which may limit maximal inspiration and expiration may play a more important role in changes of lung volumes with disease than has been previously appreciated. [6] Improving our understanding of the pathophysiology of these changes may lead to more effective modes of therapy.

In healthy adults, absolute lung volumes at rest generally do not differ appreciably when measured by different techniques even though the results represent fundamentally different volumes (communicating gas volumes for gas dilution and washout, compressible gas volume for plethysmography, volumes within thoracic cage margins for radiographic lung volumes). In healthy newborn infants and patients with disease, however, these measurements are more dependent upon methodological differences, which must be considered when reviewing the literature regarding the pathophysiology of lung volume changes.

4.1 Determinants of Lung Volumes in Healthy Infants, Children and Adults

Measurements of RV and TLC in infants are virtually impossible because of the lack of cooperation. Absolute volume measurements in infants, therefore, are usually limited to static and dynamic FRC.

Though the highly compliant thoracic cage of newborn infants facilitates the birth process, it provides an unstable structure for maintaining adequate lung volumes. The relatively high chest wall compliance in infants is coupled with a number of other factors which result in the FRC at the end of spontaneous expiration being substantially larger than that FRC measured under conditions of no flow following relaxation of inspiratory and expiratory muscles (V_{rel}). V_{rel} is commonly as low as 10-15% of TLC[36] (as compared with a V_{rel} of 30-35% of TLC in supine adults).

At the low volumes of V_{rel} in healthy infants, peripheral airway resistance is relatively high, the time constants for lung emptying are lengthened, and gas exchange is impaired. FRC is maintained above the V_{rel} in infants by the combination of reduced expiratory flows from increased laryngeal resistance, maintenance of some diaphragmatic inspiratory muscle tone during expiration, and rapid respiratory rates with initiation of inspiration well before expiration reaches V_{rel}. [6] Immediately after birth, glottic braking during expiration provides the additional advantage of promoting reabsorption of lung fluid during the first few minutes of life. [37]

During the growth of infants, the diameters of distal airways increases, as does the distending pressures surrounding them as a result of stiffening of the chest wall. Expiration becomes more passive with less dynamic elevation of FRC between the ages of 6 and 12 months.[38] In children, FRC increases as stature increases; in adults, the changes in FRC with aging are minimal. [2]

In older healthy children and adults, FRC is generally considered to represent the volume at which the outward recoil of the chest wall is balanced by the inward recoil of the lung parenchyma and FRC during voluntary chest wall relaxation are the same as those observed during quiet tidal breathing. Although observed decreases in FRC during sleep or anesthesia (discussed later) raise questions as to whether awake FRC is indeed an entirely passive state, these decreases may also be due to atelectasis or intrathoracic shifts in fluid or blood rather than reduced inspiratory muscle tone during sleep or anesthesia. [6] Though clearly an important determinant of FRC in infants, in adults, the role of the upper airways is more controversial. Glottic narrowing in adults is usually considered to affect expiratory flows during tidal breathing but not FRC. [6]
In most healthy young adults RV is determined by the balance between expiratory muscle force and the outward recoil of the chest wall.[6;21] As healthy adults age, RV increases reflecting an increasing contribution of airflow limitation and airway closure. TLC is determined by the balance of inward elastic forces of the chest wall and lung parenchyma and the outward forces generated by inspiratory muscles. Increases in TLC in children reflect primarily the growth of the chest wall. In healthy adults, the TLC changes little with aging. [2]

4.2 Changes in Absolute Lung Volumes in Respiratory Dysfunction and Disease

There are two general patterns of lung volume changes in disease: restriction and hyperinflation. These terms are widely used because they facilitate the recognition of characteristic patterns of lung disease. They do not, however, enjoy universally accepted definitions.

4.2.1 Restriction

Restriction is a condition in which TLC is reduced as discussed in the section on terminology. Though frequently interrelated, causes of restriction can be attributed to six basic categories: lung growth; gas volume displacement; lung compliance and elastic recoil; pleural changes; neuromuscular; and thoracic cage abnormalities. Surgical resection of lung tissue and lung scarring are additional causes of restricted lung volumes.

Alterations in Lung Growth

In infants and children, a key determinant of lung volume is lung growth.[6] A number of pathologic processes can interfere with lung growth during intrauterine development (e.g., oligohydramnios) or after birth (e.g., excessive pleural fluid). [6]

Gas Volume Displacement

At birth, the lung is filled with fluid that is, in normal circumstances, reabsorbed into the pulmonary circulation and lymphatics within a few hours. Under certain conditions, including birth by Cesarean section, pulmonary artery hypertension, and cardiac failure, reabsorption is delayed interfering with the normal expansion of lung volumes. Decreased FRC at birth can also result from increased pulmonary blood volume due to

obstruction of pulmonary venous return, left to right cardiac shunting, hypervolemia due to late clamping of the umbilical cord, or to diaphragmatic hernia.

Additional specific causes of gas volume displacement at any age include: pulmonary edema; inflammatory fluids and tissue in the alveoli, pleural space, or interstitium; interstitial fibrosis; engorgement of the pulmonary vascular bed and cardiomegaly; hypertrophy and hyperplasia of the pulmonary vascular bed in chronic pulmonary hypertension; tumors; and pneumothorax. In addition to reducing lung volumes from the simple displacement of gas by fluid or tissue, such processes may also affect the size and surface tension of alveoli with resultant additional impact on the distensibility of the lung. [6;39] Decreases in lung volumes by displacement of gas volume can result in discrepancies between absolute lung volume measurements when results of radiographic techniques are compared with either plethysmographic or gas dilution/washout methods. [3]

Decrease in Lung Compliance, Increases in Lung Recoil

The specific determinants of changes in lung elasticity are multifactorial, complex, and incompletely understood. Data from a variety of mammals [40] and studies of alveolar micromechanics [41] indicate that air-fluid surface forces, rather than tissue elasticity, are the major determinants of variations in the distensibility of aerated lung. Surface activity may increase or decrease depending on the amount, distribution, and quality of surfactant and related surface-active substances and can also be affected by interfering substances such as proteins from inflammation or pulmonary edema fluid. [6] There are also indirect causes related to the relationship between alveolar size and surface

tension. External chest strapping results in shifts of lung pressure-volume curves to the right [42], presumably through the effects of decreased alveolar size on surface forces. Additional evidence of support is derived from CT scans of the lungs of patients with chronic respiratory muscle weakness which indicate that alterations in lung elasticity are more important determinants of reduced lung volumes than microatelectasis.[43] In addition, agents which alter tissue elasticity may also have direct effects on surface forces as illustrated by the increase in lamellar bodies observed in the cells of the alveoli treated with bleomycin. [44] Changes in lung elasticity in interstitial processes may also result from the "gluing" together of denuded alveolar walls, so called "collapse or atelectatic induration", which has been described as an integral part of the process of pulmonary fibrosis. [45] In addition, lung distensibility may be altered by the complex effects of stretching and unfolding of pleats of septal tissue [41] as well as deformations of parenchymal boundaries from accumulation of fluid within the lung.[46] Lastly, the complex interactions between release and distribution of surface-active lipoproteins and surface tension are also potentially affected by stress failure of pulmonary capillaries. [47] This may result in release of plasma proteins which interfere with action of surfactant and related surface-active substances.

In the newborn, the most common cause of respiratory failure is respiratory distress syndrome, characterized by diffuse alveolar collapse and decreases in FRC. The main underlying mechanism seems to be alveolar collapse secondary to decreased production and inactivation of surfactant on the alveolar surface, although data from premature monkeys suggests that inadequate clearance of fetal lung liquid and leakage

of fluid and "glue-like" fibrinous exudate into the alveoli as well as other factors may play prominent roles.[48] A variety of other conditions can alter lung compliance and thereby reduce lung volumes, including bronchopulmonary dysplasia, pulmonary edema, pneumonia, neuromuscular disease, alterations in corticosteroid levels, and pulmonary hypertension.[6]

The pressure-volume curves published for some subjects with restriction attributed to increased lung elastic recoil, demonstrate lung elastic recoil pressures at maximal inspiration which are not as subatmospheric as expected if lung expansion was limited by increased lung elastic recoil; this may be due to alterations in reflex inhibition of inspiration, possibly as a result of inflammatory activity. [6,49]

Abnormalities of the Pleura

In addition to lung volume reductions from decreases in lung and chest wall compliance attributable to disease involving the visceral and parietal pleura, pulmonary gas volumes can be reduced by fibrosis, tumor, inflammation, blood or fluid filling adjacent pleural spaces.

Neuromuscular Disease

In neuromuscular disease involving the respiratory muscles, in addition to the expected decreases in TLC from the direct effects of decreases in maximal inspiratory muscle force, FRC may decrease secondary to multiple factors. These include reduction in resting inspiratory muscle tone at FRC, microatelectasis, and alterations in surface tension forces of the alveoli and airways associated with sustained reductions in lung

volumes [50,51] The FRC may be further reduced in patients with coinciding interabdominal processes (e.g., ascites, pregnancy), obesity, or atelectasis. Decreases in maximal inspiratory and expiratory pressures of around 50% can occur with only mild decreases in TLC (e.g., 5%) or mild elevations in RV (e.g., 15%).[52] In more severe disease, the lung volume restriction is more substantial and often exceeds that expected for the degree of muscle weakness observed.

The normal postural changes in lung volumes can be altered in neuromuscular disease. Reductions in VC, which average 7.5% and are usually less than 20%, are seen in normals when posture is changed from erect to supine.[53] These decreases have been primarily attributed to shifts in blood from the legs [54] to the thorax and presumably reflecting decreases in TLC. In patients with diaphragmatic paralysis the postural decreases in VC are usually substantially greater (e.g., 50%). In tetraplegic subjects, VC increases by approximately 15% upon assuming the supine position, changes attributed to the failure of the anterior abdominal wall to support the abdominal contents during expiration in the upright positions, with resultant increased RV when upright than supine.[54] In non-obese subjects, transdiaphragmatic pressures of at least 3 kPa (30 cm H_20) are needed to overcome the hydrostatic effects of the abdominal contents in the supine position. [55]

Thoracic Cage Abnormalities

Alteration in the mechanical properties or configuration of the chest wall can have a marked influence on lung volumes. A number of intra-abdominal processes can push the diaphragm up or limit its caudal movement during inspiration including ascites, intra-

abdominal tumors, severe obesity, pregnancy, and even normal gastric filling from eating. These reductions in lung volumes will be even more pronounced when the patient is supine or prone.

Available studies of children indicate that obesity must be substantial (e.g., 147-300% ideal body weight) before reductions in ERV (and presumably FRC) are observed.[8] In adults, TLC is reduced only when obesity is severe [6], though more extensive data from spirometry studies indicate decreases in VC (and presumptively, decreases in TLC) are associated with lesser degrees of obesity. [56] More significant reductions in TLC may occur at lesser degrees of obesity in patients with neuromuscular disease or in the elderly. Patients with the obesity hypoventilation syndrome have substantially greater reductions in TLC and VC than equivalently obese subjects without evidence of hypoventilation. [57] This restriction is frequently reversible following either weight loss [58] or effective treatment of sleep apnea, suggesting that the decreases in TLC may be secondary to increased pulmonary blood volume and lung water and biventricular enlargement secondary to cor pulmonale resultant from nocturnal hypoxemia and acidemia associated with apnea or hypoventilation during sleep.[58] Additional possible causes include impaired load compensation secondary to impaired respiratory neuromuscular coupling [57], alterations of the reflex limitation of inspiration, or relative inspiratory muscle weakness from fatty infiltration of the diaphragm. [6]

Kyphoscoliosis can result in profound reductions in TLC and VC (though the RV is often close to normal), changes attributable to respiratory muscle dysfunction as well as

deformities in the thoracic cage.[6] Lung compliance is reduced similar to the pattern resulting from chest wall strapping of healthy subjects. [42]

4.2.2 Hyperinflation

Hyperinflation of RV, FRC, or TLC is commonly observed in patients with obstructive lung disease. Because of impaired distribution of ventilation in severe obstructive airway disease or bullous disease, measurements of absolute lung volumes by gas dilution or washout techniques may be lower than the same measurements by plethysmography or radiographic techniques even when plethysmography is performed using techniques to avoid artifactual measurements. [59;60] Others have reported good agreement between plethysmographic and He dilution TLC [61] in the presence of airway obstruction. Reported inaccuracies of gas dilution and plethysmographic techniques reduce our confidence in many previous observations regarding hyperinflation.

Hyperinflation of TLC:

The pathophysiology of hyperinflation of TLC remains incompletely understood.[34,35] The traditional explanation attributes elevations of TLC in emphysema primarily to reductions in elastic recoil of the lung parenchyma. Decreases in tissue elasticity are a primary determinant of the observed decreases in lung recoil in emphysema. Though decreases in surface forces resultant from increase in the sizes of airspaces may play a role in reducing lung recoil [62], animal data on experimentally induced hyperinflation from pneumonectomy refute this role. [63] There is also increasing evidence that airspace enlargement is a response of the lungs to a wide variety of injuries rather than a specific effect of elastin destruction. Increased TLC in emphysema could also be in part

secondary to remodeling and an increase in the relaxed volume of the chest wall from chronic hyperinflation of FRC. [6]

Observations of hyperinflated lung volumes as an early manifestation of alpha-1 antitrypsin deficiency in children are complicated by the challenges of predicting lung volumes in growing children. [6] Although TLC is elevated to some degree in most adults with alpha$_1$-antitrypsin deficiency and evidence of obstructive airway disease, it is well within normal limits in some patients, despite severe obstructive disease and the apparent absence of restrictive processes. Conversely, although the loss of elastic recoil in emphysema is usually also associated with evidence of airway obstruction, there are some patients who have evidence of a larger TLC associated with bullous disease or reduced recoil from emphysema, without clinically recognizable reductions in maximal expiratory flows.[22]

Long-term elevations of TLC are frequently seen in patients with asthma, elevations which may be secondary to developmental increases in alveolar size when asthma starts in childhood [62,64], alterations in pulmonary elastance attributable to changes in surface tension forces , lung injury, or alterations in reflexes limiting maximal inspiration.[6] Small acute elevations in TLC in asthmatics have been confirmed by radiographic TLC measurements [65,66] although, in keeping with reports based on physiologic measurements, more substantial acute changes in TLC were observed in only a minority of patients. Resolution of the controversies regarding the magnitude and

frequency of acute and reversible elevations of TLC in asthmatics await more definitive studies using appropriate techniques for measuring TLC.

Hyperinflation of FRC:

FRC is generally increased in infants with diseases which cause an increase in airway resistance such as bronchopulmonary dysplasia, bronchiolitis, or asthma, especially when the resultant prolonged expiratory time constants are coupled with increased respiratory rates and decreases in time available for expiration.[6] However, low values may be obtained by gas dilution and washout methods which will underestimate FRC in the presence of airway obstruction.

FRC can also increase above the V_{rel} due to active closure of the upper airway during expiration, as reported in healthy infants and those with RDS.[67,68] In RDS, this allows maintenance of more normal lung volumes in the presence of surfactant deficiency and chest wall instability. This mechanism for beneficial elevations in lung volume is lost during endotracheal intubation and must be replaced with positive end-expiratory pressure. Post-inspiratory activity of the inspiratory muscles has been demonstrated which in adults asthmatics as well as healthy newborn infants causes retardation of expiration and increased end-expiratory lung volume.[6] However, this mechanism may not be important in asthmatics with prolonged rather than acute bronchoconstriction or in patients with COPD.[69] Airway closure and prolonged expiratory time constants may also contribute to the association between obstructive airway disease and hyperinflation of FRC. In patients with asthma or COPD, decreases in FRC after bronchodilators occurred in those with flow limitation during tidal breathing but not in those without [70],

despite significant increases in maximal expiratory flows in all groups, indicating that bronchodilation alone may not result in reversals of hyperinflation of FRC. These and other observations suggest that flow limitation during tidal breathing may cause elevation of FRC though the mechanisms are not clear.

In contrast to acute and reversible changes of FRC, causes of chronic elevations of FRC may include persistent increases in inspiratory muscle force, changes in length-tension relationships of inspiratory muscles [35,71,72], reduction of chest wall expansion during contraction of the diaphragm [71], and remodeling of the chest wall secondary to prolonged and repeated episodes of hyperinflation. [6]

Although there are a number of benefits of hyperinflation of FRC including decreased airway resistance and increased lung recoil, the adverse consequences are also considerable and include: increased inspiratory work of breathing from increased lung and chest recoil; reduced diaphragmatic power and efficiency; increased fatigue of mechanically disadvantaged inspiratory muscles; and possibly inspiratory muscle dysfunction secondary to reduced blood flow because of persisting contractions of intercostal and accessory muscles throughout the respiratory cycle. [6,69,71]

Hyperinflation of RV:

In obstructive lung disease (and to a much lesser extent in elderly healthy subjects), early closure or compression of small airways during expiration results in the elevations of RV so frequently observed. Reflex increases in diaphragmatic tone at the end of expiration may also play a role.[73] Under some conditions, volume history plays an

important role. In healthy subjects, the increase in RV observed after inhalation of methacholine is greater if RV is reached from end-tidal lung volumes rather than following expiration after maximal inspiration to TLC; a similar modulation of RV by inspiration to TLC was not observed in asthmatics. [19] Although maximal expiratory flows are greater if measured after rapid inspirations to TLC than after a slow inspiration followed by a 4-6 second pause at TLC, RV was not affected by these differences in flow histories.[74]

Modest increases in extracellular fluid volume have been shown to increase RV and closing capacity and to reduce VC without a significant change in FRC or TLC. These changes are attributed to narrowing of small airways.

4.2.3 Change in FRC During Exercise

Dyspnea during exercise is probably the most common symptom of chronic lung disease and improvements in this symptom are an important outcome measure of treatment. In part because of the obvious difficulties in measuring absolute lung volumes during exercise, alterations in lung volumes and volume-adjusted tidal breathing flows during exercise have in the past been neglected, especially in children. Radiographic techniques are potentially the most appropriate option for assessing changes in absolute lung volumes during exercise but present their own technical challenges and have rarely been used.

In adults, TLC does not change during exercise, either in normals [75,76] or subjects with obstructive lung disease. [77] Observations which facilitate volume-adjusting analyses of tidal volume flows during exercise are obtained from spirometric measurements of inspiratory capacity. In younger healthy adults, as exercise levels increase, FRC decreases secondary to expiratory muscle activation. This decrease in FRC shifts the diaphragm to a more optimal portion of its length-tension curve. The decrease in FRC has the additional advantage of allowing the recoil of the compressed thoracic cage to "assist" the inspiratory muscles during the subsequent.[6] In contrast, in older healthy adults, the changes in FRC_{exer} are more variable and related to limitations in maximal expiratory flows. Elderly subjects with a progressive decrease in FRC_{exer} have significantly higher forced expiratory flows (FEFs) than elderly subjects with progressive increases in FRC_{exer}. [78] Similarly, whereas middle-aged controls without airway disease decreased their FRC_{exer}, in patients with mild-to-moderate expiratory flow limitation FRC_{exer} increased.[79]

Increases in FRC_{exer} in patients with COPD are generally attributed to reductions in expiratory flows from decreased lung recoil, increased airway resistance, and insufficient time for complete expiration before the next inspiration as respiratory rates increase during exercise. Increases in respiratory drive from stimulation of J receptors may also play a less direct role.[80] An increase in FRC_{exer} decreases resistive work of breathing, increases inspiratory and expiratory flows, and improves the distribution of ventilation in subjects with airflow limitation. A higher FRC_{exer} should also decrease dyspnea in patients with obstructive airway disease because of reductions in

"unpleasant" respiratory sensations associated with dynamic airway compression [81] and by delaying the conscious need to inspire, as inferred from the observation that the time to the break-point of breathholding under conditions of hypoxia or hypercapnia is substantially extended if lung volumes are elevated.

However, increases in FRC_{exer} in those with COPD have the negative effects of increased inspiratory work from higher recoil pressures from the lung and chest wall and inspiratory muscles shifting to a less optimal position on the length-tension curve. Increases in FRC are the strongest predictor of worsening of the sensation of dyspnea during exercise in patients with COPD. [82] A lower FRC during exercise has been shown to relate better to decreases in dyspnea following bronchodilators than improvements in resting PFTs [83] and may be an important outcome of lung volume reduction surgery.

4.2.4 Changes in FRC During Sleep

In infants, the findings have been inconsistent and the potential influence of sleep stage (e.g., active or REM stages of sleep versus quiet or NREM stages) controversial. [8] Some studies saw slight decreases in FRC during sleep[36], some decreases only when the rib cage and abdominal motion is out of phase, while others reported no changes.[6] Plethysmographic studies have shown larger decreases in FRC during sleep but may represent errors in measurement resultant from airway closure during sleep. [84] At least in preterm infants, decreases in FRC during sleep seem to be primarily due to decreases in FRC after apneas, changes which are reversed by sighs[85]. The observation that decreases in FRC occur primarily following apneas not followed by sighs may also explain some of the conflicting results of earlier studies.

Decreases in FRC during sleep in infants are thought to be secondary to decreases in tone of inspiratory muscles and also possibly a decrease in active braking during expiration from glottic narrowing or closure. Such decreases make infants precariously susceptible to rapid decreases in O_2 saturation during apnea.

In healthy adults, mean decreases in FRC of 10-17% have been reported during sleep which contrast with larger decreases in FRC reported in adult asthmatics.[6] We did not find studies which measured absolute lung volume during sleep in obese subjects.

4.2.5 Other Conditions

During mechanical ventilation, intrinsic PEEP and resultant dynamic hyperinflation is commonly inadvertently induced as a consequence of insufficient duration of expiration. Measures of dynamic hyperinflation have been shown to be better predictors of the risk of complications from mechanical ventilation than measures of tidal volume or peak airway pressures.[86]

FRC decreases by approximately 20% during anesthesia when subjects are in the supine, but not seated, positions.[87] These changes are not reversed following repeated lung inflations. The causes are unclear and probably multifactorial (e.g., changes in lung surface forces, relaxation of inspiratory muscle tone with resultant decrease in chest wall dimensions, increased intra-abdominal blood or intrathoracic fluids distortion of the lung, and trapped gas or atelectasis). [6] Morbidly obese patients have been observed to

have much larger decreases in FRC (~50%) during anesthesia, in some patients to levels below awake RV.[88]

Head injuries are often associated with decreases in FRC changes which result from microatelectasis, closure of small airways, increased lung water, or increases in alveolar surface tensions secondary to stress failure of pulmonary capillaries.[47]

In healthy adults [89,90] in infants [91], breathing 100% O_2 for less than 10 minutes has been shown to reduce FRC. Such decreases are readily reversible and different from the more serious decreases in lung volumes after 5 or more days of 100% O_2 breathing attributed to lung injury.[92]

5. CALCULATIONS OF RV AND TLC FROM MEASUREMENTS OF FRC

As discussed in more detail in the controversies section of the Terminology Section, there are a number of ways to calculate lung volumes once FRC has been determined and a consensus on the "ideal" method proved difficult to achieve. Most, but not all, of the workshop participants favored RV measurements derived from expirations from FRC rather than TLC.

It also proved difficult to identify a single method of measuring and calculating RV and TLC applicable to the He dilution, N_2 washout, and body plethysmography techniques which was both efficient in the clinical setting and performable by patients with severe obstructive lung disease and patients with severe dyspnea. The following are the recommendations and rationales which evolved from review of these issues.

The **standard recommended method** (which can be applied to the He dilution, N_2 washout, and body plethysmographic measurements) utilizes the performance of ERV maneuvers immediately after the acquisition of the FRC measurement(s) followed by slow IVC maneuvers, all performed as "linked" maneuvers (i.e., without the subject coming off the mouthpiece prior to the completion of the maneuvers).

The reported value for FRC is the mean of the technically satisfactory FRC measurements linked to the technically satisfactory ERV and IVC maneuvers used for calculating RV and TLC. The reported value for RV is the reported value for FRC minus the mean of the technically acceptable ERV measurements linked to the FRC

determinations used to compute the reported FRC. The reported value of TLC is the reported value for RV plus the largest of technically acceptable IVCs.

The **acceptable alternative method** utilizes the performance of IC maneuvers immediately after the acquisition of the FRC measurement(s) to measure TLC. This method may be necessary in patients with severe obstructive dysfunction or severe dyspnea who are unable to follow the FRC measurements with a linked ERV maneuver because of dyspnea. The subjects can come off the mouthpiece between linked FRC and IC determinations and also between the separate VC maneuvers needed to calculate RV. The VC measurement can be derived from either a ERV maneuver followed by IVC maneuver (as used in the standard recommended method), or from an IC maneuver followed by a slow expiratory VC. The latter can be linked with the FRC/IC measurements if patient discomfort does not preclude optimal performance.

A previous recommendation has been that ERV is defined as the largest of several measured values. [9,93] However, the largest ERV may be a consequence only of the subject's having started expiration from the largest starting FRC which would then bias the results to the smallest RV and TLC. We consider that it is appropriate to account for spontaneous variation in FRC at the start of the ERV maneuver and thus recommend the use of the mean ERV of three acceptable maneuvers. Similarly, the use of the mean of technically acceptable IC measurements is recommended for computations of TLC instead of the largest IC**.**

6. MEASUREMENTS OF LUNG VOLUMES BY MULTIPLE BREATH HELIUM DILUTION

6.1 In Adults and Children

6.1.1 Introduction and Theory

This method for measuring lung volumes is based on equilibration of gas in the lung with a known volume of gas containing helium (He).[96] The lung volume (V_L) at the time the subject is connected to the spirometry apparatus of known volume (V_{app}) and He concentration (He1) is calculated from the He concentration at the time of equilibration (He_2) by the conservation of mass:

$$V_{app} \times F_{He1} = (V_{app} + V_L)(F_{He2})$$

$$V_L = V_{app}(F_{He1} - F_{He2})/F_{He2}$$

The European Community for Steel and Coal (ECSC) developed standardization recommendations for multiple-breath He dilution methods in 1983 [97] in adults and the updated ECSC [93] standards were adopted by the ERS in 1993. The following recommendations for adults are largely derived from the 1993 ERS standards. [93] Substantive differences, where they exist, have been added to the description of the method and a detailed section on problems/controversies has been added. Although one can also derive measurements of gas mixing [98] from this procedure, these aspects of lung function will not be covered in this document.

6.1.2 Equipment

For systems which utilize a volume displacement spirometer, the capacity of the spirometer should be at least 7 L (although 7-10 L is ideal). Inaccuracy of static volume measurements should be less than 3% over the entire range; minimal resolution should be equal to or less than 25 mL. The gas volume in the spirometry apparatus with the bell at zero volume including the circuit tubing to the mouthpiece valve should preferably not exceed 4.5 L**.** The smaller the V_{app} at the time the patient is switched into the circuit, the larger the changes in He concentration during the FRC measurement and the smaller the random errors will be relative to the signal. The recommended equipment specifications and procedures will establish an advantageous starting He concentration near full scale deflection of the meter. The mouth pressure needed to initiate a change in spirometer volume should be < 0.03 kPa (< 0.3 cmH_20). The spirometer should be equipped with a mixing fan, CO_2 absorber, O_2 supply, a gas inlet and outlet, and a water vapor absorber in the line to the He analyzer. The mixing fan should mix the gas throughout the circuit within 8 s after the end of exhalation into the circuit. Typically, breathing circuit flows of about 50 L/min are utilized to ensure adequate mixing of He concentration measurements which are reported every 15 s. If pneumotachometers or other flow devices are used instead of volume displacement spirometers, and if they are not isolated from variations in gas properties (e.g., by bag-in-box systems), then appropriate calibrations and corrections may be necessary to accommodate the changes in gas properties.

A thermal conductivity He analyzer is the type utilized most commonly. Other types of He analyzers may be used[99] and other inert gases may replace He.[100-102] The He analyzer should have a range of about 0-10% He, a resolution $\leq$ 0.01% He over the entire range**,** and a 95% response time of less than 15 s to a 2% step change in He concentration in the breathing circuit. The meter should be stable with a drift of 0.02% or less for measurement periods of up to 10 min. For systems in which $F_{I,O2}$ changes substantially because of O_2 consumption during measurement of FRC, the He analyzer must be calibrated over the range of $F_{I,O2}$ encountered. Because thermal conductivity He analyzers are sensitive to temperature changes, it should be assured that the temperature of the gases entering the He analyzer is the same as during calibration. Some of the problems associated with various types of He analyzers can be avoided by the use of a respiratory mass spectrometer, often employing other inert gases such as argon.

A small pump samples gas from the breathing circuit just beyond the CO_2 absorber pushes it through a desiccant chamber, through the He analyzer and back into the main circuit [103]; for most analyzers at least 200 mL/min flow is necessary. Since changes in the flow of gas through the analyzer or in the pressure of gas in the analyzer circuit will affect response time or accuracy, variations in flow and pressure should be minimized. Similarly, since thermal conductivity analyzers also respond to changes in concentration of CO_2, O_2, N_2 and water vapor pressure, CO_2 and water are removed before the sample is introduced into the He analyzer and the O_2 concentration is maintained relatively constant by adding O_2 to the circuit as necessary (see below). The activity of

the CO_2 and water absorbers should be assured before each test (either from visual or photocell detection of indicator color changes or by replacing the absorbent after a specified number of tests (or accumulated minutes of equilibration time). The breathing circuit CO_2 level during testing should be kept below 0.5% to avoid patient discomfort and hyperventilation.

Lung volumes are reported at BTPS conditions. When TLC and subdivisions thereof are measured, the temperature of gas inside the system differs from both BTPS and the ATPS condition computed using room temperature since the conditions are variably affected by exhaled warm gas, room temperature, and heat generated by absorption of CO_2 in the soda lime canister. Therefore, the temperature of the gas in the breathing circuit should be measured so that these lung volumes can be corrected to BTPS conditions. The temperature sensor should have an accuracy of better than 0.5° C over the range 12-30° C and should have a 90% response time of less than 30 s to a 5° C step change of temperature of the gas inside the breathing circuit.

The breathing valve and mouthpiece should have a combined deadspace of less than 100 mL and should be easy to disassemble for sterilization. The size of this deadspace should be available from the manufacturer or measured by water displacement.

Errors in O_2 supply can be prevented by continuously measuring the O_2 concentration. This also provides a means to adjust the output of thermal conductivity He analyzers for the effect of different O_2 concentrations and to assure a satisfactory $F_{I,O2}$.

6.1.3 Quality Control

All quality control checks should be retained for review and trend analysis.

Daily QC checks:

1. Before each patient is tested, the following items should be checked: water level of water-sealed spirometers, status of all CO_2 and water absorbers, operation of the circuit fan (assessed by listening), and the baseline stability of He and volume signals.

2. Systems that can be pressurized conveniently (e.g., by placing a weight on top of an upright water-sealed spirometer) should be checked for leaks at least once during the 24 hours prior to patient testing and after tubing or canister changes. In some systems, this can be accomplished by injecting about 3 L of air into the system, closing the breathing valve, then pressurizing the breathing circuit to about 0.4 kPa (4 cm H_20). With the system closed and the circulating fan operating, there should be no detectable leaks (i.e., < 50 mL volume change) over a span of three minutes.

Weekly and Monthly checks:

The stability of the He meter should be confirmed weekly. The meter should not drift more than 0.02% in 10 min. The temperature sensor should be checked periodically (e.g., monthly) to ensure that it remains accurate to within 0.5^o C. After overnight equilibration and before the spirometer is used, its temperature should be compared to room temperature measured with a thermometer known to be accurate to within 0.1° C.

Linearity check:

To establish the linearity of the He meter, the spirometer is thoroughly flushed with air until the He reading is stable. With the spirometer in its lowest position and closed, He

is added, and F_{He1} read after mixing; then after addition of a precisely known volume of air with a calibrating syringe, the initial spirometer volume is calculated from the new concentration, F_{He2}, the known volume of added air, and F_{He1}. Subsequently more air is introduced with the syringe in precisely known volumes (e.g., in 1.00 L increments), and new computations are performed; this is repeated until the spirometer is full. BTPS corrections should not be made for these computations. Volumes added with the syringe and calculated changes in volumes should agree throughout the range to within 3%.

Contemporary He meters usually have very stable linearity. If the stability of the linearity has been demonstrated (e.g., by weekly checks over a few months), then quarterly or semi-annual checks seem sufficient, as data are not available to support more frequent linearity checks for all instruments. It is important to recognize that the linearity test as described tests the function of the entire system including that of the He meter.

From the determinations of He concentrations during set up, the integrity of the entire system is checked within a limited volume range prior to each FRC measurement of patients. The second He concentration after addition of a known and constant volume of air should be very reproducible from day-to-day. Departures of greater than 0.2% He during setups or changes in V_{app} (at the end of the setup) greater than 3% of the mean value obtained from multiple sessions[7] suggest technical problems such as an incorrect gas volume having been added, a leak, or He meter malfunction.

Biologic reference standards:

Periodic testing (e.g., monthly) of "reference" subjects is useful [104] in that it tests not only the equipment but also the procedures used by the technicians. Criteria for "out-of-limits" tests vary among different subjects tested (some perform the test more reproducibly than others) and with the degree of precision desired. Data related to variability within and among subjects are provided in the sections on reference values and reproducibility of lung volume measurements.

A healthy non-smoking individual with normal lung function (biologic reference standard) should be tested at least once per week. If at any time the FRC value is more than 5% (or greater than ±3 standard deviations) from the mean of the 10 previous measurements), the instrument should be checked and repaired with appropriate documentation. The biologic reference standard should be tested again before testing any subjects.

6.1.4 Measurement Procedure

Specific details of procedures will vary with different types of equipment and degrees of automation.[7] A recommended procedure for non-automated lung volume measurements is as follows:

Prior to measurements, the status of the CO_2 absorber in the spirometer and the CO_2 and water absorbers in the line to the He meter should be checked and absorbers changed when appropriate; in addition, the water level should be checked in water

sealed spirometers. The mixing fan should be turned on and the He analyzer warmed up sufficiently to achieve stable output.

The next steps are to flush the spirometer with room air then place the bell in its lowest position and close the circuit. Rolling seal spirometers should be emptied and then about 1 L of air added. O_2 is then added so after all additions of gas in the procedure, the final O_2 concentration will be about 25-30% (higher values are acceptable). When a stable He reading is obtained (< 0.02% change over 30 s), the He meter is adjusted to zero. Then He is added to raise the F_{He} (fractional concentration of He after mixing) to nearly full scale deflection (e.g., 10%) on the analyzer. This initial He concentration (F_{He1}) is noted, where F is either the fractional concentration or an arbitrary meter reading proportional to this fraction. Then a precise volume of room air is added (e.g., 3.00 L from a calibrated syringe) and the second meter reading (F_{He2}) noted after the He reading stabilizes. V_{app} under these conditions is the volume of the apparatus prior to the addition of air, and V_{air} the precise volume of air added during the last step. Then

$$V_{app} = V_{air} \cdot F_{He2}/(F_{He1} - F_{He2})$$

V_{app} need not be calculated for assessing FRC; its value is substituted by the right-hand part in computations of FRC (see below). However, the reproducibility of values of F_{He1} and F_{He2} obtained for the same V_{air} introduced on different days is a useful check on quality of measurements. It should be noted that because the lung volumes are derived from changes in F_{He}, the absolute accuracy of the He analyzer is not key assuming that the output of the He analyzer is linear over the operating range and passes through zero. If measurements of ERV and IC are to be linked to the FRC

measured, it should be insured that when the patient is at FRC that the position of the bell is appropriate to allow for the full ERV and IVC maneuvers.

As when defining predicted values for a variety of pulmonary function tests, standing height should always be carefully measured: shoes off, heels together with weight distributed evenly across both feet, standing erect with back and heels against a metal ruler which has been plumbed vertical, head looking straight ahead (specifically: head in the Frankfort horizontal plane, the horizontal plane which includes the lower margin of the bony orbit of the eyes and the most forward point in the supratragal notch, the notch just above the anterior cartilaginous projection of the external ear), height measured to nearest half centimeter down using a solid level at 90° angle to the ruler and placed snugly but not tightly on top of the head.

During measurements, the subject should be seated and at rest so that both the O_2 uptake and the FRC are stable. Dentures need not be removed, but a nose clip should be worn.

The subject is asked to breathe quietly for 30-60 s to become accustomed to the apparatus and attain a stable breathing pattern; subsequently the subject is connected to the closed system (“turn-in”) at the end of a normal tidal expiration.
During the equilibration period, compensation must be made for the subject's O_2 consumption (see section below). The F_{He} is noted every 15 s and equilibration is considered complete when the decrement in F_{He} is less than 0.02% in 30 s (i.e., over

the span of three consecutive readings). At equilibration, F_{He} decrements are likely to be due mostly to continued gas mixing since the best estimates suggest that He absorption and N_2 excretion can cause a decrement of F_{He} of approximately 0.01% He per minute, equivalent to an increase of about 20 mL/min in the calculated FRC. These changes in F_{He} are near the resolution of modern He meters. For systems which display FRC directly, the equivalent end-of-test criterion is an increase in FRC of less than 0.04 L per 30 s. There is no clinical value in prolonging testing after these end-of-test criteria have been met. In practice, the test rarely exceeds 10 min even in patients with severe gas exchange abnormalities.[7]

After the end-of-test criterion is met, the volume display should be examined to be sure the value is stable over several breaths. The subject should then be instructed to exhale slowly and fully to RV. Variations in subject effort, flow limitation, exhalation time, and FRC will all influence the magnitude of each ERV measurement. It is recommended that three satisfactory ERV maneuvers be performed and the mean value reported. Factors which lead to unsatisfactory maneuvers include cough, glottis closure, gas leak from the nose or mouth, and too brief an effort.

During each ERV maneuver, once RV has been achieved, the subject should be coached to inhale completely to TLC (inspiratory vital capacity, IVC, maneuver). The observer should monitor subject performance to ensure a maximal effort. Three satisfactory IVC should be obtained and the largest reported.

6.1.5 Adjustments For Oxygen Consumption

Failure to adequately account for the effects of O_2 consumption can result in significant errors in the calculation of lung volumes. During the measurement, O_2 can be added to the circuit at a flow rate equal to the patient's estimated O_2 consumption (usually 250-300 mL/min or 3-4 mL/(kg/min) for adults). Alternatively, boluses of O_2 can be added as needed (every 15-30 s) to keep spirometer volume constant at end exhalation.

Because CO_2 is removed from the breathing circuit, the amount of O_2, which is added, approximates O_2 consumption. It is important with the bolus method that the subject has been at rest sufficiently long to assure that a stable end expiratory level has been attained before turn-in. A third method utilizes servo-controlled addition of O_2 to keep the O_2 concentration constant during the test as measured by an O_2 analyzer. The measurements of O_2 concentration at the beginning and end of the test also facilitate appropriate adjustment of the He measurements for changes in O_2 concentration. A fourth method starts with elevated concentrations of O_2 in the circuit; CO_2 is not absorbed nor is O_2 added. O_2 concentration is monitored to ensure an adequate F_{I,O_2} and for correction of the He meter. This method can only be used in subjects with rapid equilibration times because the rising levels of CO_2 may change the subject's ventilatory pattern, increase the FRC in patients with obstructive lung disease and cause breathing discomfort. Because of these limitations and the absence of data indicating that this approach will not cause problems, this method is not recommended.

Recording of the duration of the test is not required but is useful for assessing between-test variability on a single day and for estimating the degree of ventilatory inhomogeneity.

6.1.6 Reproducibility and duplicate analyses

Same-day duplicate measurements of FRC using multiple breath He dilution in population studies have coefficients of variations (CVs) of 5%, with only somewhat larger CVs (e.g., 6%) in individuals with COPD. [5,7,105] Data are not currently available to allow us to conclude whether the expected variability is best expressed in absolute volumes or as a percent of the observed.

Because of the extra costs incurred by making multiple breath gas dilution or washout lung volume measurements in duplicate or triplicate, and the relatively good inter-day variability in adults as noted above, it is recommended that in adults two or more measurements of FRC need be done only when necessitated by clinical or research needs.[7] For infants and young children, however, it is recommended that at least two technically satisfactory measurements be performed.[10]

For purposes of computing reported results, the software should allow the technician to set aside technically unsatisfactory individual tests so the averages of TLC, FRC, and RV can be reported from the remaining acceptable tests. The results of all individual tests, however, should be retained in the database.

6.1.7 Calculations

The lung volume (V_L) at the time the patient was connected to the spirometer is obtained as follows:

$$V_L = V_{air} \quad F_{He1} \quad (F_{He2} - F_{He3})/[(F_{He3} \quad (F_{He1} - F_{He2})] - V_{ds}$$

where F_{He3} is the He concentration at the end of the determination and V_{ds} is the valve and mouthpiece deadspace.

The temperature (room temperature) and water vapor saturation of gas (estimated or measured water vapor pressure of room air) in the calibrating syringe and not in the spirometer should be used to convert the results to BTPS conditions. The ERV, IC and IVC should be corrected according to the temperature inside the spirometer and assuming saturation with water vapor. This is true even for "dry" spirometers as the gas within the spirometer is saturated with water vapor from the lungs during the measurement.

If more than one FRC measurement is made, the value reported for FRC should be the mean of technically acceptable results.

Residual volume and TLC are obtained as follows: RV = FRC – ERV (mean FRC if more than one maneuver is done); ERV = mean of three or more satisfactory ERVs linked to the FRC determination(s). TLC = RV + largest IVC (the preferred method) but the combination of TLC = FRC + IC (means of acceptable **linked** measurements if more than one maneuver is made) and RV = TLC - largest IVC is also acceptable. The

reader is referred to the controversies section of the Terminology Section (2) and the Calculation Section (5) for more detailed discussions of calculation options.

The technician should document the following for each subject: history of eardrum perforation, problems with leaks around the mouthpiece and nose clip, excessive swallowing during the test, posture changes, and apparent adequacy of effort during the IVC and ERV maneuvers.

Review of the volume/time tracings is essential for recognizing sudden or slow inward or outward leaks and for assessing the reproducibility of the end-tidal volumes, ICs, and IVC. A difference of more than 0.3 L of spirometer volume when the subject was turned into the apparatus (switch-in) and at the end of the FRC determination (switch-out) suggests a leak. The time to equilibration (or the lack of equilibration after 10 min) should be reported. It is also helpful to review a recording of the He/time signal to assure that during the test there was a smooth decline and plateau. Sudden changes in He concentration also suggest a leak.

The measured equipment volume used in the calculations should be compared with prior measurements, which establish the acceptable variability for that instrument. Values which fall outside the expected range (e.g., 95% confidence limits) should be brought to the operator's attention as possibly indicating a leak (or a change in the water level or amount of CO_2 absorber).

Helium loss, effects of N_2 excretion, and need for correction factors:

During the measurement, He concentration changes because of (a) gas mixing between the lung-spirometer system (b) N_2 excretion from body fluids and tissues (c) imperfect balance between O_2 consumption and supply (d) He uptake in body fluids and tissues (e) any leaks in the circuit including those at the mouthpiece or through perforated eardrums (f) swallowing and (g) solution of He in the water in the spirometer. He loss during the test will cause an overestimation of volumes and may lead to failure to achieve equilibration.

He is a gas with low solubility in body tissues although the precise rate of He absorption within the body is not well defined. A variety of estimates have been published [7], and adjustment of the FRC (for example, about 100 mL) has been recommended based on these estimates. However, because of the small magnitude of corrections in FRC that would result from using current estimates of helium absorption and uncertainty about the true magnitude of these uptakes, it is recommended that no corrections for He absorption be made.

Similarly, in part because the F_{IN2} during the He testing is generally 0.55-0.80 and in part because N_2 excretion is only approximately 20-30 mL/min [7], N_2 excretion during the He equilibration will cause only a small increase in system volume and dilution of He, thus we recommend that no correction be made for N_2 excretion. In addition, in both the multiple bolus method for addition of O_2 and the continuous O_2 flow method, the effects of N_2 excretion are accounted for and correction for N_2 excretion is not necessary. [7]

The effects of changes in He concentration when the respiratory quotient differs from 1.0 is extremely small, hence correction for this can also be ignored.[7]

Switching error and changes in lung and spirometer volume during the test:

In practice, subjects are not always at FRC when they are switched into the spirometer circuit, resulting in differences between measured V_L and FRC (switching error). Corrections for this should be made from the spirometer trace when reporting FRC. Some computerized equipment reports and accounts for the switch-in-error automatically obviating the need for continuous recordings of spirometry. During the period of He equilibration, the subject's FRC may be stable or vary steadily or intermittently. Such variations do not change the total volume of the system (apparatus plus lung) nor do they affect the rate at which O_2 is added when it is at a constant flow equal to the subject's estimated O_2 consumption. However, in systems in which O_2 is added in boluses, variations in actual FRC during the equilibration will affect the rate at which O_2 is added. When the subject's actual FRC decreases or increases during the test, the added O_2 will be less than or greater than O_2 consumption, respectively. This will lead to respective under or overestimation of FRC at switch-in. Additional examples of these problems are provided in the background paper.

6.1.8 Controversies

In most subjects, He will equilibrate more rapidly if the patient being tested takes deep breaths intermittently. If, however, the equilibration times or difference between plethysmographic or radiographic volumes and He dilution volumes are used to assess

disease severity, intermittent deep inspirations during equilibration may alter the results.[7] There is evidence that in some subjects deep inspirations will not open compartments behind occluded airways.[107] In these subjects, deep inspirations will not affect equilibration times. Deep breaths may affect the results in those with dynamically determined FRC. Hence, equilibration during regular tidal breathing is recommended without intermittent IC maneuvers.

6.2. Multiple Breath Helium Dilution Lung Volume Measurements in Infants

This technique is the most widely used method for determining resting lung volume in spontaneously breathing infants[91,108-120] (for children over the ages of 6-7 years, the methodology is the same as for adults). The equipment needed to perform the test is simple, reliable, relatively inexpensive (compared with plethysmography), and suitable for bedside measurements, but still requires considerable operator training if reliable results are to be routinely obtained.

6.2.1 Procedure

Details of how to perform these measurements in infants have been published elsewhere. [109] After establishing a stable end-expiratory level, the infant is switched into a spirometer which contains a known volume of gas with known concentration of He and allowed to rebreathe from this mixture until equilibration is complete. Attachment to the spirometer is normally via a face mask. Careful attention is required to minimize leaks; use of a probe attached to the He meter may be useful for defining optimal mask fits. The volume of the spirometric system should be as low as possible and preferably

not significantly exceeding that of the infant's FRC [110] although this is often extremely difficult, if not impossible, to achieve. Commercially available 1-liter spirometric bells should suffice for older infants and toddlers but a smaller size is recommended for neonates. The circuit must, however, contain sufficient air to accommodate the large sighs (2-3 times normal V_T), which frequently occur in young infants. The spirometer should be carefully balanced so that pressure within the enclosed system remains as close as possible to atmospheric. The reliability of the system can be checked with a calibrated syringe by adding known volumes in the range of the infant's FRC as described earlier in Section 5, taking care *not* to correct to BTPS.

The desired initial concentration of He in the circuit can range between 6% and 15%, although concentrations as low as 3% have been used. This means the He dilution method can be used on patients with lung disease requiring markedly elevated inspired O_2 concentrations (e.g., F_{I,O_2} as high as 0.97) compared with F_{I,O_2} of < 0.70 required for N_2 washouts.

Geubelle et al. [91] observed that breathing 100% O_2 for relatively short periods (e.g., 1-3 min) was associated with a decrease in lung volume in all 14 infants tested; FRCs were ~30% lower after breathing 100% O_2 (e.g., from a mean of 72 mL to 50 mL). Reductions in FRC after breathing 100% O_2 have been observed in additional studies in adults as well as infants [90,121,122] but not in other studies [123,124,126]. Alternative causes for observed reductions in lung volumes after breathing increased concentrations of O_2 include inadequate times for equilibration with room air between repeat N_2 washouts.[121]

Although there are clearly controversies regarding whether, or in what settings, breathing enhanced concentrations of O_2 results in reductions in lung volumes, when such changes occur, they are in accord with lung volumes being smaller as a result of loss of "nitrogen-splinting" of lung volumes. For N_2 washout studies in which 100% O_2 is administered only during the testing procedure, if decreases in lung volumes do occur, they should not affect the measurement of the "turn-in" volume unless the decreases in lung volumes result in "trapped" volumes which limit the washout of N_2. Time to equilibration in healthy infants and young children is usually between 13-60 s [127-130], but may be considerably longer (between 3 and 5 min) in the presence of airway disease.[108] It is, therefore, recommended that rebreathing continue until He concentration has been stable for at least 30 s (specifically, < 0.02% change in He concentration over 30 s).

An interval is required between measurements to allow all He to be cleared from the lungs. Ideally, the system should allow continuous monitoring of He in the exhaled air, so that measurements can be repeated once concentrations return to zero. If it cannot, an interval of at least 5 minutes should be given. The goal should be to obtain two measurements of FRC which agree within 10% of each other (i.e., maximum difference between repeat measurements equivalent to approximately 2 mL kg^{-1}). Since rebreathing needs to be continued for 3-5 min in some infants with airway disease, this technique can require a lengthy testing period.

Alternative methods of measuring FRC_{He} using a rebreathing bag are not recommended due to the complexities of the equilibration of O_2 and CO_2 between bag and lung during this process when breathing spontaneously. The inherent errors can be minimized when mechanical ventilation is being used, which shortens the time for gas mixing. Another alternative for measuring small lung volumes is the helium washout method described by Roy et al.[132] for which a four fold greater sensitivity at FRC around 25 mL than conventional helium dilution techniques and is less affected by small lung to spirometer volume ratios.

6.3. Helium Dilution Lung Volume Measurements During Mechanical Ventilation

The closed-circuit He dilution method has been adapted to measure FRC on ventilated patients. For details, the reader is referred to both the background paper on this section [10] and the original description by Heldt et al.[133] Although the technique offers the capability of measuring lung volumes on patients requiring $F_{I, O2} > 70\%$, the technique has a number of limitations[10] and is not widely used. In addition to the He dilution technique, a dilution technique for measuring FRC in small-volume lungs has also been described using sulfur hexafluoride during mechanical ventilation as well as spontaneous breathing.[134] Other approaches have included the use of multiple gas washouts.[135]

7. MEASUREMENT OF LUNG VOLUMES BY MULTIPLE BREATH NITROGEN WASHOUT

7.1. In Adults and Children

7.1.1 Introduction and Theory

The technique is based on washing out the nitrogen (N_2) from the lungs by giving the subject 100% O_2 to breathe. The initial alveolar N_2 concentration and the amount of N_2 washed out can then be used to compute the lung volume at the start of the washout. Additional details and literature citations about the various nitrogen washout techniques and related washout measurements using other gases are available in the background paper.[10] Although these washout techniques also provide potentially useful indices relevant to the distribution of ventilation [136-138], these issues will not be addressed in this document.

The N_2 washout method was originally developed into a clinical technique by Darling, Cournand and Richards in papers published in 1940.[139] Prior to and immediately after the N_2 washout, subjects made complete expirations and samples of end expiratory gas were obtained for measurements of alveolar N_2 concentrations. For the N_2 washout, the subject was connected at FRC to a system containing 100% O_2 through a system of one-way valves directing the exhaled gas to a collection bag or large spirometer. The total N_2 volume exhaled was measured from these two variables after subtraction of N_2 excreted from tissues and adjustments for STPD/BTPS conversions and the differences between alveolar N_2 before and after the washout. The technique originally utilized gas

collections for a 7-min period, a period deemed adequate for washout of N_2 from the lungs of healthy subjects (e.g., alveolar N_2 < 2.5%). After the relative consistency of the alveolar N_2 concentrations between subjects was demonstrated, the initial alveolar $F_{I, N2}$ was usually not measured and assumed to be 0.81.

With this technique, the FRC is calculated from the following equation:

FRC = [(volume N_2 washed out) – (N_2 tissue excretion)] / (initial N_2 fractional concentration – final N_2 fractional concentration)

This technique has the disadvantages that any inaccuracy in the measurement of the bag volume or the final N_2 concentration will cause a significant error. Since the final N_2 concentration may be very low because of the gas dilution with a large amount of O_2, even an error of less than 1% of full-scale N_2 concentration will cause significant inaccuracies in calculated FRC.

The difference between TLC computed from body plethysmography and 7-min N_2 washout in those with severe obstructive airway disease was often referred to as "trapped gas". It has been pointed out [121] that the primary cause of the underestimation of FRC by the N_2 method is not from actual gas trapping but rather the inability to obtain an accurate measure of mean alveolar N_2 concentration after 7-min of breathing O_2. This is because measurements of alveolar N_2 during a forced exhalation are highly weighted in favor of the more normally ventilated regions of lung, thereby underestimating the true mean alveolar N_2 concentration.

To overcome these problems, Emmanuel et al. [121] has suggested modification of the 7-min N_2 washout method to monitor N_2 excretion over 15 min. Extrapolation of the late exponential component of the continuous N_2 excretion curve eliminates the need to include in the calculations measurements of final alveolar N_2 concentration [121]. Emmanuel noted a mean underestimation of FRC of 32% (range up to 48%) in individuals with emphysema in whom FRCs were measured by the standard 7 min technique as compared with the extrapolation 15-min technique. In addition, it was noted that second determinations after a 30-min wait were approximately 9% lower than the first and it was therefore recommended to wait at least 1 hour between duplicate measurements in individuals with severe COPD. This technique reduces the underestimates of lung volumes in those with severe emphysema as compared with the standard 7-min washout but required longer washout periods. However, no commercial systems available at the time this document was written use this method.

N_2 washout techniques were further refined with the availability of rapidly responding N_2 analyzers including respiratory mass spectrometers[140,141] and microprocessors which permitted continuous integration of measurements of expired flows and N_2 concentrations.[142] These approaches require appropriate adjustments for delay times of the analyzers [143] and synchronization with flow measurements. The methods were also adapted for use in infants.[10] Rapid N_2 analyzers also allowed more accurate estimates of the rates of N_2 tissue elimination from healthy subjects while breathing O_2.[121,144]

In the resultant open-circuit method, when at FRC, the subject is switched to inspiring 100% O_2 and from this point the volume of N_2 exhaled is determined by integration with respect to time of the instantaneous N_2 concentration flowing in the exhalation circuit multiplied by the instantaneous flow (after appropriate phase shift corrections) as calculated from the following equation:

$$V_{N2} = \int V'_{N2}(t) * dt$$

where V_{N2} = Volume of N_2 exhaled

V'_{N2} = the instantaneous flow of N_2 in the exhaled air [V' is the word-processor friendly abbreviation recently recommended by the ATS and ERS for instantaneous flow, the first time derivative of volume, previously expressed as V].

For details regarding these calculations and also the extrapolation method, the reader is referred to the background paper [10] and Emmanuel et al.'s original paper [121].

7.1.2 N_2 Excretion

N_2 excreted from the tissues can be estimated from tables or complex exponential equations.[145] Because the differences in the correction when these different sources are used is small, we recommend the relatively simple equation developed by Cournand et al. for N_2 tissue excretion (C) adjusted for body size after 7 min of washout is estimated[146] as :

$$C = [(BSA \times 96.5) + 35] / [0.8]$$

Where BSA = Body surface area

Darling and Cournand et al.[146] recommended adding 10 mL of N_2 to the correction for each minute of washout after 7 min.

Assuming that the initial F_AN_2 is 0.81 rather than using actual measurements of the initial alveolar N_2 concentration resulted in errors in calculating tissue N_2 excretion of < 50 ml of FRC in 95% of determinations.[147]

Studies are not available which have compared the accuracy, reproducibility, and efficiency of the open-circuit methods utilizing continuous measurements of N_2 until specific end-of-test criteria are met (e.g., end-tidal N_2 < 1.5%) versus the 15-min exponential method described by Emmanuel. Systems currently commercially available utilize continuous direct or indirect measurements of N_2 and airflow rather than the exponential method**.**. Accordingly, no single method for measurement of lung volumes by N_2 washout can be recommended. Described below is the suggested methodology for the directly measured N_2 technique.

7.1.3 Equipment

N_2 analyzers should be linear with an inaccuracy $\leq$ 0.2% of full range throughout the measuring range (0-80%), resolution of $\leq$0.01%, and have a 95% analyzer response time less than 60 ms after correction for phase shift. Linearity can be best assessed using precision dilution systems, but the use of four or five certified calibration tanks spanning the range of 0-80% N_2 is an acceptable, albeit somewhat impractical and expensive alternative.

In testing for accuracy and linearity, compensation must be incorporated for delay times for N_2 sampling and analysis. If a needle valve is in the N_2 measuring circuit, the needle valve should be regularly inspected and cleaned. If measurements of N_2 concentration are made indirectly by subtracting measurements of O_2 and CO_2, the accuracy, drift and linearity characteristics of the O_2 and CO_2 analyzers should result in indirect calculations of N_2 with comparable performance characteristics to the direct measurements of N_2 specified above.

Note: Some workshop participants thought that in following this approach the resultant requirement for the accuracy of O_2 and CO_2 measurements is too demanding (e.g., inaccuracies of O_2 and CO_2 would need to be < 0.7x 0.2% = < 0.14%.). Mass spectrometers should meet the above specifications for all three gases and have <1% drift over 30 minutes and a molecular weight resolution of < 1.0.

Pneumotachographs or other flow measuring devices (e.g., ultrasonic flow meters, turbines, etc) incorporated into the breathing circuits to measure gas flows should have inaccuracies $\leq$ 3.0% or flow rates from 0-6 L/s. Potential inaccuracies from condensation of water from expired gases, changes in gas temperature, changes in gas viscosity or density over the range of O_2/N_2 mixtures encountered during testing must be considered and controlled in meeting the above performance specifications. Corrections for viscosity/density of the exhaled gas are necessary. The manufacturer

should demonstrate that appropriate corrections have been made (e.g., using a known-volume syringe to assure accurate tidal volumes are measured during the washout.

The system should have a sampling rate of at least 40 samples/s per channel for flow and N_2 signals. Amounts of N_2 exhaled should be calculated at least every 25 ms or less with appropriate corrections for phase differences between flow and N_2 measurements. [143]

The breathing valve for switching the patient from breathing room air to 100% O_2 should have a dead space < 100 mL and < 2 mL/kg in smaller children. O_2 can be provided either from a gas-impermeable bag filled with dry 100% O_2 or a source of O_2 connected to a demand valve. Demand valve trigger pressure should be <10 cm H_20. However, lower trigger pressures are advantageous, especially for those with neuromuscular weakness.

7.1.4 Quality Control

Daily Check:

Before each subject is tested, the N_2 analyzer should be zeroed using 100% O_2 and then exposed to room air to confirm calibration. The percent N_2 for room air should be within 0.5% of the expected reading for room air (78.08%).[148,149] The accuracy of the flow and volume output of the flow measuring device should be confirmed at least once a day with a calibrating syringe using pumping frequencies which will result in flow rates in the same range as tidal flows. Volumes should be within 3.0% of expected values

(ATP). Initially and periodically, exhalation volumes should be checked with the syringe filled with room air and inhalation volumes with the syringe filled with 100% O_2.

Linearity Check:

Before the initial use and once every 6 months thereafter, the linearity of the N_2 analyzer should be confirmed by also measuring the $\%N_2$ of a calibration gas mixture whose N_2 concentration is around 40%, either from a certified calibration tank or as created using precision dilution techniques. Observed values should be within 0.5% of expected. If greater alinearity is observed, readings must be corrected for the observed alinearity.

Temperature Check:

The temperature sensor should be checked periodically (e.g., every 6 months) to ensure that it is accurate within 0.5° C at room temperature as compared with a thermometer known to be accurate to within 0.1° C.

Biologic Reference Standards:

A healthy non-smoking individual with normal lung function (biologic reference standard) should be tested at least once per week. If at any time the FRC value is more than 5% (or greater than ±3 standard deviations) from the mean of the 10 previous measurements), the instrument should be checked and repaired with appropriate documentation. The biologic reference standard should be tested again before testing any subjects.

7.1.5 Procedure

Turn the N_2 analyzer on and allow adequate time for the pump to reach operating vacuum levels and calibrate at both 0 and 80% N_2 concentrations (100% O_2 and room air). Check the calibration of the pneumotachometer with a calibrating syringe. Attach a disinfected mouthpiece to the system. If a droplet barrier filter is not utilized between the mouthpiece and the pneumotachometer, the pneumotachometer should be disinfected between subjects. If a barrier filter is used, dead space should be adjusted to compensate.

Measure the subject's height (see detailed discussion in section 6.1.4.). Ask the subject if he or she has a perforated eardrum (if so, use an earplug). Explain the procedure to the patient emphasizing the need to avoid leaks around the mouthpiece during the washout.

With the system connected to room air, attach nose clip and ask the subject to breath quietly on the mouthpiece. When breathing is stable and appears to be at FRC the subject is switched into the circuit so 100% O_2 is inspired instead of room air. Switch-in errors can be compensated as described in the section on He dilution technique.

Switching Error:

In practice, subjects are not always at FRC when they are switched into the spirometer circuit, resulting in differences between measured lung volume and FRC (switching error). Corrections for this should be made from the spirometer trace when reporting FRC. Some computerized equipment report and account for the switching error automatically, alleviating the need for continuous recordings of spirometry.

End of Test:

During the washout, the N_2 concentrations should be monitored. A change in inspired N_2 >1.0% or sudden large increases in expiratory N_2 indicate a leak and the test should be stopped and repeated after a 15-min period of breathing room air. The end of test criteria is when the end-expiration N_2 concentration is < 1.5% for at least three successive breaths. Using "alveolar" samples (after exhalation to RV) for assessing the end-of-test criteria was considered but rejected because of larger variability and the inability of some patients to comply (e.g., young children and infants).

At the end of the washout, the subject should be switched back to inspiring room air and, after placing a tissue below the mouthpiece to catch accumulated saliva, allowed to come off the mouthpiece. Because of the duration of some prolonged washouts and the need to clear accumulated saliva, for computations of RV, it is considered better to measure the slow inspiratory or expiratory vital capacities as separate maneuvers after taking a short break after completion of the N_2 washout. The reader is referred to the discussion of options for computations of RV in both the Terminology Section 2 and the earlier Calculations Section 5.

Repeat Testing:

Although repeat measurements of FRC can be made in healthy subjects after only a few minutes of breathing room air, in those with obstructive or bullous disease, the equilibration time breathing room air is considerably longer. Based on reductions in volumes that averaged 9% in subjects with severe COPD when 15-min N_2 washouts

were repeated with a 30-min wait period between repeat testing, Emmanuel et al. recommended a waiting period between tests of at least 1 hour for patients with emphysema.[121] In practice, most labs seldom do these measurements in duplicate or triplicate in spontaneously breathing adult subjects.

An alternative method to hasten the washout of N_2 is the "forced rebreathing" N_2 washout technique in which N_2 is washed out using large tidal breaths.[93;107] The method offers significant advantages for epidemiologic studies of healthy subjects and those with mild obstructive disease. In those with severe airflow limitation or cystic fibrosis, the method may still underestimate volumes as compared with body plethysmography.

7.2. In Infants

For studies in infants (especially when inspired gas mixtures include He), the problem of changes in pneumotachometer output related to variations in gas temperature and viscosity has been overcome by placing the infant in a face-out body box. [150] The method, however, has never been widely accepted because the system is cumbersome, has only recently been automated in commercially available systems, and is difficult to use outside research environments.

In 1985, Gerhardt, Bancalari, and co-workers described a method using a constant background flow of a heated and humidified He/O_2 mixture.[151] The infant breaths the gas from the circuit through a T-tube and gas leaving the circuit is mixed in a mixing

chamber at the end of the system. The N_2 concentration of the gas leaving this chamber was measured using a mass spectrometer and the signal integrated avoiding the necessity of gas collection. The amount of N_2 washed out from the lungs is proportional to the integrated N_2 as long as the flow through the circuit is unchanging. Gas flow is adjusted to the estimated peak tidal inspiratory flow of the infant to prevent rebreathing. Under these conditions, if flow is constant, the volume of N_2 washed out is obtained by:

$$V_{N2} = V' * {}^{t}\int_{0} \%N_2 * dt$$

Adjusting the background flow to just slightly higher than peak inspiratory flow allows flows to be lower and thus makes the system more sensitive to the smaller amounts of N_2 exhaled as will occur in small infants. Background flow during calibration must equal the flow selected for testing.

Subsequently, 100% O_2 has been used in all but premature infants for the N_2 washout measurements as the possibility of significant lung injury from exposure to 100% O_2 is considered negligible considering the relatively short exposures to high O_2 concentrations during FRC measurements. Any subject in which there is a specific concern regarding O2 toxicity can be tested using He and O_2 gas mixtures as originally described .

The resolution and thus the accuracy of N_2 washout method depend not only on the stability of the N_2 analyzer but also on the level of the alveolar N_2 concentration before the test. If the subject is breathing gas with a relatively high F_{I,O_2} before the test, the

volume of N_2 to be washed out is much smaller, which will reduce the accuracy of the results. Very high $F_{I,O2s_2}$ (e.g., 90 - 100%) prior to testing preclude use of this technique as is also the case in patients with reduced lung volumes from disease (e.g., ARDS) where an $F_{I,O2} \leq 0.7$ is usually required for accurate measurements.

The technique was made more reproducible and accurate by the development of a two-point calibration system. [141,152] This is typically performed prior to the procedure. According to the weight of the infant to be tested, a “low” and “high” volume can be chosen for the two-point calibration. Other considerations during the measurement include a tight seal on the facemask, and eliminating any other sources of leak. Putty can be used around the mask for a tighter seal. A child with tubes in his/her ears may need putty placed in the ear to prevent a small, but constant leak of room air into the system. Occasional sighs will cause the N_2 elimination curve to ”jump up” a small amount, and then resume decreasing. Frequent elevations in the N_2 concentration or a washout period that extends beyond two minutes are signs of leaks.

Infants with tracheostomies present additional problems. Leaks are obviously inherent. It is possible to either use a cuffed tracheostomy tube or an uncuffed tube that is large enough to approximate the trachea and form a tight seal. It is good practice to also occlude the mouth and nose of the infant in case a leak is present around the tube. Other detailed reports regarding measurements of FRC in infants using N_2 washout are available. [152,153, 308]

The time required for washout of the N_2 from infants with normal lungs spontaneously breathing room air prior to washout is about 2 min.[151] Subjects with restrictive lung disease and those breathing elevated inspired O_2 concentrations may wash out in less time. Conversely, those with obstructive airways disease will take longer, sometimes up to 3 min.

There are relatively few studies which have compared lung volume measurements using the He and N_2 techniques. In a limited number of spontaneously breathing preterm infants [123], older infants[126], and children [153] there was no significant difference between measurements made with the He and N_2 methods. Similar comparisons between He and N_2 washout techniques in spontaneously breathing adults are not available but in ventilated adults there were no significant differences between the two techniques. [154]

7.3. Nitrogen Washout Lung Volume Measurements During Mechanical Ventilation

The N_2 technique described for infants above is not suitable for ventilated subjects because there is no way to assure constant gas flow in this situation and because the flow during calibration differs from that during the test because the compliance of the tubing of the ventilator and the calibration apparatus differing from that of the subject's respiratory system.

Techniques have been developed for measuring FRC during mechanical ventilation using N_2 washout .[123;151;152;155;156] A review of these methods is included in the background paper.[10] The lung volumes for those on mechanical ventilation have also been described by a number of other gas washout techniques.[135;138]

7.4 Controversies

1. With all techniques there is controversy regarding how many measurements should be made and regarding the way in which results should be expressed. Whereas it is relatively simple and quick to obtain 3-5 repeat measurements of FRC with the plethysmograph, this is less feasible with gas dilution or washout techniques due not only to the duration of rebreathing or washout required, but the necessary interval between tests. Results during mechanical ventilation based on a single recording are more likely to be reliable than in spontaneously breathing infants because of generally slower rates of controlled (mechanical) ventilation allowing greater precision in switching-in to washout gas at FRC. A CV of < 5% can be expected for repeated measurements in a ventilated patient.[150]

Recommendation:

The minimum for acceptable measurements of FRC in infants or during mechanical ventilation is the mean of two technically satisfactory measurements which are within 10% of each other; greater confidence would be obtained if three such measurements were available. [109]

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2. Geubelle et al.[91] reported that breathing 100% O_2 reduced lung volume in infants. In adults it has been concluded that breathing 100% O_2 for about 3 min had little effect on FRC either in spontaneously breathing subjects or those requiring mechanical ventilation[154] ; other studies have not confirmed these findings and instead observed reductions in volumes.[90;157] Whether or not such reductions do occur remains controversial and may depend upon differences in the patterns of ventilation and perfusion in the subjects studied.

3. Subjects who have lung volumes determined while mechanically ventilated have an endotracheal tube in place which bypasses the volume of the nasopharyngeal area. This volume has been measured post-mortem in adults [158], and while dependent to a degree on head position, the volume represents approximately one-half the anatomical dead-space. The infant head is relatively much larger in proportion to body-size than is the adult's, and the relative contribution to total dead-space is as great as 2-3 mL/kg in early infancy.[159] Thus, "normal" FRC on mechanically ventilated children will be lower than in their spontaneously breathing counterparts, but exact corrections can be difficult to define.

4. Unlike the observations in healthy adults, the FRC obtained using gas dilution or washout techniques in healthy infants are generally lower [126;160] than those reported using body plethysmography. [2;161] The differences between the gas and plethysmographic methods are often suggested to be secondary to non-communicating spaces measured by plethysmography although overestimation of

volumes secondary to methodologic problems with plethysmography cannot be excluded. In addition, little evidence has been found for such “non-communicating” spaces when volumes are measured above FRC by progressive addition of volume to the lungs.

There are, as yet, no published studies in small infants and young children comparing FRC's obtained by N_2 washout to the He dilution technique in the same subjects while mechanically ventilated. In cats, FRC measured during mechanical ventilation by both N_2 washout and He dilution techniques in animals with normal lungs (n = 128) and those with pulmonary edema (n = 80) were comparable (range of FRC = 40 to 150 mL). Similar comparison studies on mechanically ventilated adults (either under neuromuscular blockade or heavily sedated) also confirm that there is no significant difference between the two gas equilibration methods under these conditions. [154;162]

5. As was the case with the He dilution measurements, it was also proposed that the recommended methods for N_2 washout include IC maneuvers during washouts for measurements of TLC from the linked FRC and IC maneuvers. This approach was also rejected by the group as it deviated too much from conventional testing to be recommended without firmer evidence of feasibility and improved comparability and reproducibility.

8. BODY PLETHYSMOGRAPHY

8.1 In Adults and Children

8.1.1 Introduction and Theory

Full details of plethysmographic measurements are available in the background paper by Coates et al. [9] The abbreviation $V_{L,pleth}$ (previously frequently referred to as the thoracic gas volume or TGV) refers to a plethysmographic measurement of intrathoracic gas at the time of airflow occlusion. The volume measured is the compressible gas within the thorax. Although $V_{L,pleth}$ is most frequently measured at or near FRC, it can refer to any lung volume at which the measurement is made.

In infant plethysmography there is controversy as to the benefits of measuring $V_{L,pleth}$ at end inspiration as opposed to end expiration (FRC).[163] Irrespective of where in the tidal volume cycle $V_{L,pleth}$ is measured, FRC_{pleth} can be derived by subtracting or adding the appropriate volume.

In healthy children and adults, there are usually minimal differences in FRC measured by gas dilution techniques and plethysmography. However, in individuals with lung disease associated with gas trapping and normal healthy infants, most, but not all, studies indicate that FRC_{pleth} often exceeds FRC measured by gas dilution.[2; 94; 108;161] Discrepancies may also occur in those with pneumothoraces or poorly communicating bullae.

Although earlier versions of body plethysmography were described in the 1800s, it was not until the papers by DuBois and colleagues [164] that the technique was used clinically. The measurements are based on Boyle's law which states that, under isothermal conditions, when a constant mass of gas is compressed or decompressed, gas volume decreases or increases and gas pressure changes such that the product of volume and pressure at any given moment is constant.

Isothermal conditions imply that during either compression or rarefaction of gas, heat is exchanged across the walls of the container so that the temperature of the gas does not change. In body plethysmographs, isothermal compression and rarefaction can only be achieved at frequencies which are one or two orders of magnitude below normal breathing frequencies. Conditions are considered to be adiabatic if no heat is lost from the chamber during gas volume changes and therefore temperatures change; the volume and pressure changes are then described by the ideal gas law, which states that the product of pressure and volume divided by temperature remains constant. Adiabatic compression is the predominant condition in body plethysmographs. Conditions in between these two extremes are polytropic.

For the determination of $V_{L,pleth}$ the subject is placed in the plethysmograph chamber and is instructed to pant or breathe via a mouthpiece connected to a device which can occlude flow and measure changes in pressures at the mouth. Panting results in the rarefaction and compression of the gas in the thorax. During such maneuvers, changes in thoracic volume are measured from changes in pressure within the variable pressure

plethysmograph (or from measured flows or volumes of gas exiting and entering the chamber with flow or volume plethysmographs). Pressures measured at the airway opening (P_{ao}) are simultaneously recorded. Assuming that P_{ao} is representative of alveolar (P_{alv}), $V_{L,pleth}$ can be calculated using the following application of Boyle's law:

$$(P_{alv1}-P_{H20}) \times V_{L,pleth\ 1} = (P_{alv2}-P_{H2O}) \times V_{L,\ pleth\ 2} \qquad \textit{Equation 1}$$

where the subscripts denote differing values of pressure and volume during the respiratory maneuver. P_{alv1} and P_{alv2} are expressed as absolute pressures and not the differences between barometric pressure (P_{bar}) and P_{ao}. Water vapor pressure is subtracted from all pressures because under fully saturated conditions, water vapor does not behave as a compressible gas. (For the sake of clarity in the following review of the theoretical basis of plethysmography, P_{H2O} will not appear in the subsequent equations, but must be subtracted from all measurements of P_{alv} or P_{bar}). For additional details of the derivation of the equations, the reader is referred to the background paper [9].

A more common expression of the above equation is:

$$-\Delta P \times V_{L\ ,\ pleth1} = \Delta V(P_{alv1} + \Delta P) \qquad \textit{Equation 2}$$

where P_{alv1} is the alveolar pressure at the start of the maneuver and ΔP is the change in alveolar pressure measured at the mouth under conditions of no flow during the panting maneuver so $\Delta P = P_{alv2} - P_{alv1}$. ΔV is the resulting change in volume of the thorax and is equal to $V_{L,\ pleth\ 2} - V_{L,pleth\ 1}$.

Equation 2 can be further simplified to

$$V_{L,pleth\ 1} = -(\Delta V/\Delta P) \times P_{alv2} \qquad \textit{Equation 3}$$

When doing a panting maneuver, it is frequently assumed that the pressure changes are small (± 1 kPa). Under these conditions, it is customary to ignore the small product of $\Delta P \times \Delta V$, the last term in equation (2), and the solution becomes

$$V_{L,pleth\ 1} = -(\Delta V/\Delta P) \times P_{alv1} \qquad \textit{Equation 4}$$

As previously noted P_{alv1} represents the alveolar pressure at the start of a panting maneuver and it is generally assumed that the discrepancy between P_{alv1} and P_{bar} during a panting maneuver is small so the solution for $V_{L,pleth}$ is reduced to

$$V_{L,pleth} = -(\Delta V/\Delta P) \times P_{bar} \qquad \textit{Equation 5}$$

The term $\Delta V/\Delta P$ is the slope of the pressure volume relationship and is always negative. While technically a hyperbola, over the range of pressure changes of interest, it is so close to being a straight line that few errors are introduced when it is treated as such. This "simplified" equation (5) is the one used in most automated plethysmographs.

Because of problems experienced by some subjects in making satisfactory pants at a frequency of 1 cps, measuring pressure and volume changes during a single inspiratory effort has been proposed as an alternative [165]. However, this method of determining $V_{L,pleth}$ may give rise to changes in mouth pressure that are of sufficient magnitude (i.e., up to 5 kPa or 51 cmH_2O) that the product of ΔP and ΔV cannot be ignored. This technique has the additional disadvantage that it is more difficult to recognize and compensate for drift of the plethysmographic signal if only single inspiratory efforts are displayed.

An additional consideration when calculating $V_{L,pleth}$ is that where P_{alv1} differs from P_{bar} such as will occur if the occlusion is not performed at FRC, a proportional correction factor to adjust for this difference may need to be implemented, hence, equation 3 can be rewritten as:

$$V_{L,pleth} = -(\Delta V/\Delta P) \times P_{alv2} \times (P_{alv1}/P_{bar}) \qquad \textit{Equation 6}$$

This is the "complete" equation and it contains both the $\Delta P \times \Delta V$ term and volume correction necessary should P_{alv1} be different from P_{bar}. With today's modern computing capabilities, the use of the "complete" equation is markedly facilitated. The errors introduced by the simplified version during panting are small (in the order of 3%) and centered around zero. For the single inspiratory maneuver, they are generally in the order of 5%, systematically greater than zero, and related to the magnitude of the pressure generated during the maneuver. [166]

The plethysmographic method of determining FRC_{pleth} is based on a number of assumptions, which are as follows:

1. There is no gas flow, and hence no flow-resistive losses of pressure in the airways during the respiratory efforts against an occluded airway. Hence, P_{ao} is equal to P_{alv}.

In adults, it has been demonstrated that under circumstances of increased resistance of the airways, excessive compliance of the upper airway, and possibly intrapulmonary gas flow from non uniform alveolar pressures, the upper airway acts as a shunt capacitor allowing gas flow back and forth in the airway during the panting maneuver resulting in P_{ao} underestimating P_{alv}, leading to an overestimate of FRC_{pleth} as has

been observed in subjects with asthma [167], in healthy subjects with experimentally induced increases in airway obstruction from balloon inflation in the lower trachea[168], or severe COPD [61;169]. Panting at slower frequencies (i.e., ~1 cps vs ~4 cps) [61], 0.5-1.0 cps vs > 1.5 cps)[169] and (0.8 vs > 2.0 cps)[170] may reduce but not completely eliminate the error. There are few studies concerning flow resistive losses during FRC_{pleth} measurements in infants and neonates, but work done in older children with extensive disease[165] suggests that panting frequencies around 1 cps reduce the error as in adults[61;169;170].

2. The pulmonary parenchyma is either sufficiently compliant or gas containing spaces are freely in communication with each other so that changes in pressure are uniform throughout all the gas containing areas of the lung.

This assumption, while probably reasonable in most adults, has been challenged in infants with airway disease. Godfrey et al.[171] found values of FRC_{pleth} that were much lower than expected from clinical findings in infants recovering from bronchiolitis and, by a process of elimination, suggested that areas in the lungs of these infants have such high resistance and low compliance that they act as little "spheres" whose contents do not undergo volume changes during the panting maneuver. Helms [172] provided evidence that more accurate measurements of FRC_{pleth} were obtained if airway occlusions were performed at lung volumes above FRC.

An alternative explanation of discrepancies in FRC_{pleth} is that changes in pleural pressure during panting are non-uniform. This is controversial in adults; some evidence

supports it[61], other workers have found no evidence of it. [173] The suggestion of non-uniform distribution of pleural pressure changes in neonates [59;174] has not been supported by recent work.[175] This would suggest that the effects of non-uniform pleural pressure changes, if they exist, are likely to be small. Part of the problem with this argument is that there is no "gold standard" technique which would allow for adequate comparison of values measured.[176] Since the discrepancies are usually seen only in infants with gas trapping, measurements of FRC by gas dilution techniques would also be likely to give unreliable estimates. Though perhaps more useful for detecting changes in lung volumes from serial measurements, as discussed later, radiographic methods in infants have yet to be validated with respect to quantitative estimates of absolute volumes.

3. Only gas in the thorax undergoes rarefaction and compression.

This assumes that the volume of gas in the gastrointestinal tract is insignificant, not compressed, or both. In infants [171;172] and adults [61] this appears to be a valid assumption, since the changes in intra-abdominal pressure when panting around FRC or higher lung volumes are relatively small compared with changes in mouth pressure.

8.1.2 Types of Plethysmographs

The changes in thoracic volume which accompany compression or decompression of the gas in the lungs during respiratory maneuvers can be obtained using a body plethysmograph by measuring the changes in: 1) pressure within a constant volume chamber (variable pressure plethysmograph), 2) volume within a constant pressure

chamber (volume displacement plethysmograph)[177] or, 3) air flow in and out of a constant pressure chamber (flow plethysmograph).

1. Variable Pressure Plethysmograph

The advantages of the variable pressure plethysmograph [164] are simplicity and accuracy of the measurement of small changes in volume as are seen during panting. Whether the changes within the plethysmograph during panting are isothermal, adiabatic or polytropic depends on the rapidity of the changes, the size of the subject in relation to the volume of the chamber, and the thermal conductivity of the materials in the walls of the plethysmograph. The conditions in variable pressure plethysmographs are usually predominantly (if not entirely) adiabatic.

The smaller the volume of a plethysmograph with respect to the subject, the better the signal to noise ratio of the volume signal. Small chambers, however, may be cramped, uncomfortable, claustrophobic, and allow an excessive build up of heat. The smaller the chamber, the more likely polytropic temperature conditions during compression of gas; polytropic compression is very unlikely above 0.1 cps in an adult plethysmograph unless the chamber volume is near to the body volume of the subject being tested. Providing no attempt is made to air condition the system, current infant plethysmographs also appear to operate under adiabatic conditions. [178;179]

Plethysmographs for use in adults and older children should have a volume between 100 and 300 times the volume being measured so that the pressure changes in the plethysmograph will be small compared to alveolar pressure changes and will not

interfere with normal breathing but will still be large enough to result in accurate measurements. A plethysmographic volume of 600 to 1000 L generally meets these requirements. For infants, plethysmographic volumes must be in the order of 50 to 100 L. [178]

The plethysmograph is usually connected to the atmosphere by a small leak of controlled dimension (e.g., tubing with an internal diameter of 0.05-2 mm and a length of 30-60 cm) which results in a mechanical time constant (i.e., the compliance of the gas in the plethysmograph times the leak resistance) between 10 and 50 s (ideally in the order of 10 s). This controlled leak minimizes slowly occurring pressure changes such as may occur as the chamber temperature increases when occupied by a person. The shorter the time constant, the less the problems with thermal drift, but at the cost of inaccuracies in the measurement of slowly occurring events. Inadvertent leaks caused by poorly fitting doors or other open orifices may lead to serious errors.

In order to accurately measure the small changes in plethysmographic pressure resulting from thoracic volume changes associated with compression and decompression of the lungs during breathing or panting against the closed shutter, the transducer measuring changes in the chamber pressure must be capable of measuring accurately in the range of 0.001 to 0.01 kPa (0.01 to 0.1 cmH_20). Transducers of this sensitivity also respond to the small changes in atmospheric pressure that accompany events such as opening or closing of a door in the room. This "noise" can be minimized by referencing the pressure changes within the interior of the plethysmograph to

pressure changes within a reference chamber which is open to the room by a constant leak of controllable magnitude so that the reference chamber has the same time constant as the plethysmograph.[180] Thermal drift, particularly in infant plethysmographs, may give rise to pressure changes as much as 1.0 kPa (10.0 cmH_2O), which might necessitate a larger working range of the transducer.
Two time constants influence the behavior of the plethysmograph and it's combined time constant, one due to the controlled leak (the mechanical time constant), and the other due to the volume of the chamber and thermal conductivity of the walls (the thermal time constant). Both influence the lower range of the frequency response characteristics. Details of how these time constants can be measured are in the background paper by Coates et al. [9]

The greater the resistance of the controlled leak, the greater the mechanical time constant; this results in more accurate measurements of pressure changes during low frequency maneuvers such as tidal breathing but greater problems with slowly occurring non-respiratory changes such as temperature increases within the chamber. In practice, it is the total time constant that is important; when the thermal time constant is long compared with the panting or breathing cycle, changes in pressure within the chamber are completely adiabatic; when it is of the same order of magnitude, they may be polytropic and when it is much shorter they may be isothermal as is the case within the lungs.

Adiabatic conditions have a simple predictable relationship between pressure and volume within the plethysmograph, whereas predicting polytropic conditions requires more complicated mathematical manipulation.[180] The equation that relates changes in pressure and volume under adiabatic conditions is slightly more complicated than Boyle's Law because it includes the ratio of the specific heat of air at constant volume and constant pressure. However, if the calibration is performed under adiabatic conditions, the measurements are made under the same conditions, and changes in pressure and volume are relatively small, the relationship between P_{pleth} and V_{pleth} can be adequately approximated as a linear function.

Plethysmographs used in adults or older children commonly have a thermal time constant in the order of one minute combined with a leak time constant between 10 and 20 s. Using appropriate transducers, this will result in a flat frequency response from as low as 0.1-0.2 cps to as high as 10-20 cps. Specifically, if the combined time constant (leak plus thermal) is at least 10 s, the transmission of the signal at a frequency of 0.1 cps will be 0.98 and for 0.2 cps, 0.995, clearly adequate for virtually any respiratory maneuvers. For a more complete description of the thermal process, the reader is referred to the monograph by Bates.[181]

In order to measure lung volumes other than $V_{L,pleth}$ as well as any difference between the volume at the time of occlusion (V_{tg}) and the normal end expiratory volume, there must be either an external spirometer, or a pneumotachograph (that may vent either inside or outside the chamber, depending on design).

2. Volume Displacement Plethysmograph

The modern volume displacement plethysmograph described by Mead [177] is a rigid chamber between 300 and 600 L in volume. Part of the chamber opens directly into the base of a spirometer with low inertia. With the subject breathing air from outside the chamber, the spirometer will measure large changes in thoracic volume such as forced vital capacity maneuvers. When the airway is occluded and the subject pants, small changes in thoracic volume due to thoracic gas compression and expansion are also measured; the accuracy in the latter conditions depends on the frequency response of the spirometers and particularly its inertia.[9]

In addition to steps to physically minimize the effects of inertia [9], the plethysmograph can be "pressure compensated" by the adding to the volume signal of the spirometer a signal which is proportional to the small variations of internal pressure that accompany the rapidly changing volumes because of the inertia of the spirometer. Pressure compensation should improve the frequency response from the order of 4-5 cps in the uncompensated plethysmograph to the order of 8 cps.

Within the chamber of the plethysmograph, the subject produces heat which gives rise to thermal drift which is usually controlled by air conditioning the chamber. Difficulty in achieving control over thermal drift and the need for frequent adjustments of the bellows position has limited the use of volume plethysmographs.

The major advantage of the volume displacement plethysmograph is its ability to measure larger changes in lung volumes (i.e., vital capacity maneuvers). Furthermore, during forced expiration, such body boxes can measure both the volume of gas that the subject expires and the "true" volume changes of the thorax which include the volumes from compression of the chest [182] during the maneuver (if the frequency responses of the system are adequate).

3. Flow Plethysmograph

In theory, the flow plethysmograph should be an ideal compromise between variable pressure and volume displacement plethysmographs. Absolute rigidity of the walls is not necessary, problems with thermal time constants are minimized, and the frequency response, after pressure compensation, should be close to that of a variable pressure plethysmograph. Changes in lung volume are measured by integrating the gas flow in and out of the chamber as measured by the differential pressure across either a capillary type pneumotachograph or a wire mesh screen (e.g., 25 μm mesh) mounted on the wall of the plethysmograph. The sensitivity of the screen type pneumotachograph to low flows can be increased by adding several layers of low resistance screen but this also increases resistance and hence the time constant, thereby reducing the frequency response.

Pressure compensation increases the frequency response as in volume displacement plethysmographs.[180] The use of a reference chamber with time constant characteristics similar to those of the plethysmograph can decrease the influence of ambient pressure variations. One of the problems with flow plethysmographs can be caused by thermal

drift of the chamber or electrical drift of the integrator, the effects of which are minimal if the respiratory maneuver happens over a very short period of time (i.e., the panting maneuver). Alternatively, there are a variety of ways to compensate for thermal drift. [9] With proper pressure compensation, flow plethysmographs should have an adequate frequency response to 15-20 cps.

4. Variable Pressure-Flow Plethysmograph

A flow plethysmograph can be converted into a variable pressure plethysmograph by simply occluding the pneumotachograph orifice making it adaptable to the particular respiratory maneuver of interest. For example, measurements of $V_{L,pleth}$ could be made using the variable pressure mode and flow volume curves measured using the flow mode.

8.1.3 Equipment

Regardless of plethysmograph type, a transducer capable of measuring P_{ao} up to at least ± 5 kPa (50 cmH_2O) with a flat frequency response in excess of 8 cps is essential. [180] Spirometers or pneumotachographs used for the measurement of lung volumes and forced inspiratory and expiratory volumes should meet published standards for accuracy and frequency response of spirometric devices [182.]

Thermal drift due to temperature changes in the interior of the plethysmograph is common to all types and can be detected and compensated for from the plot of V/ P during an occlusion showing a systematic difference in slope between compression and

expansion.[9] A second approach for compensation is to use an iterative method as described by Peslin et al. [183]

The frequency response of commercial plethysmographic systems should be stated by the manufacturer and the user should be given detailed instructions on how to verify it. The frequency response is most commonly accomplished by the application of a sinusoidal volume signal where the frequency can be varied.[9;180] It is generally recommended that the minimum adequate frequency response be 5 times the frequency of the signal being measured. For a pant at 1 cps, this means fidelity of the signal at 5 cps. To ensure that panting frequencies slightly above 1 cps will not lead to problems, the minimum acceptable frequency response should result in accuracy at 8 cps.

8.1.4 Quality Control

The P_{ao} transducer should be physically calibrated daily. Linearity of the P_{ao} transducer over the range of physiologic signals should be confirmed at least every six months. Similarly, the plethysmograph signal should also be calibrated daily using a volume signal of similar magnitude and frequency as the respiratory maneuvers during testing. This is usually achieved with a small reciprocal pump that, for adult plethysmographs, delivers a sinusoidal volume signal of 20 to 50 mL, the same order of magnitude as the compressive/decompressive volume changes in the subject. If the calibration is done with the subject in the plethysmograph holding his breath, no further adjustment in the calibration is needed. If the plethysmograph is calibrated empty, the data from the

plethysmograph can be adjusted by multiplying the measured $V_{L,pleth}$ by the following correction factor:

$$\text{Correction factor} = \frac{\text{Plethysmographic volume - subject volume}}{\text{Plethysmographic volume}}$$

The subject's volume in L is estimated from the weight in kg divided by 1.07.[184] The linearity of the plethysmographic signals should be checked periodically (e.g., every 6 months) by injecting known small amounts of air into the box, (i.e., 5, 10, 20, 30, 50 mL).

Calibration of the pneumotachograph should be checked daily with the use of a calibrating syringe with a displacement that is of the same order of magnitude as the VC of the subjects (e.g., 3.0 L for adults).

Ideally, the frequency response should be measured at least once every six months and after any significant change in the apparatus, for example, repairs or replacement of a transducer, unless absolute reference volumes are checked at the same frequency (e.g., by the flask method, see below, over the range of frequencies encountered clinically).

A validation of accuracy using a known volume should be performed periodically. This can be done using a "model" lung of known volume.[9;185] Filling the flask with thermal mass (e.g., copper wool) is essential in order to simulate the isothermal conditions

within the lung; care should be taken to adjust the calculated volumes to ambient (or model) temperature and saturated conditions rather than to BTPS conditions during the calculations. The accuracy of adult plethysmographs in measuring the gas volume of the container ("V_{flask}") should be ±50 mL or 3%, whichever is greater, based on a mean of 5 determinations.[9]

At least monthly, or whenever plethysmographic errors are suspected, two reference subjects (biological standards) should have FRC_{pleth}, RV_{pleth}, and TLC_{pleth} measured. Values that differ significantly (>10% for FRC and TLC or > 20% for RV) from the previous established means for measurements on the same subject suggest errors of measurement. These criteria are approximately twice the reported coefficients of variation for repeat measurements of these parameters, hence tighter standards can be adopted at the cost of more frequent "false alarms" suggesting equipment malfunction.

8.1.5 Measurement Procedure

Because of the dependence of predicted values of lung volumes on height, the subject's height should be measured with care (see detailed discussion in section 6.1.4.). The equipment should be adjusted so that the subject can sit comfortably in the chamber and reach the mouthpiece without having to flex or extend the neck. For children, this may require special equipment. The volume of gas between the mouthpiece and shutter should be minimized. The door is closed and time is allowed for thermal transients to stabilize and the subject to relax during tidal breathing so that a base line representing the "relaxed" FRC can be determined. Testing may commence once the

initial rapid temperature rise has occurred and the continuing thermal drift is less pronounced and constant.

During the more rapid initial phases of chamber temperature increases, the variable pressure plethysmograph is vented to atmosphere using a valve. In a volume displacement plethysmograph the spirometer must be returned to the mid-line position prior to any respiratory measurements.

Changes in the volume and pressure of the intrapulmonary gas are usually achieved by panting against an occlusion at the airway opening.[186] The panting maneuver has been used for the determination of both FRC_{pleth} and airway resistance. The original [131, 164] justification for the shallow panting maneuver was three fold: to minimize temperature, saturation and respiratory quotient effects; to improve signal to thermal drift ratio, and to minimize the contribution of resistance from narrowing of the upper airways.

Many young children have difficulty with the standard panting maneuver but can generate adequate rarefaction of intrathoracic gas during an inspiratory effort against an obstruction at end expiration.[165] Two potential disadvantages of this technique are that any leaks, which usually present as a loop in the volume vs pressure ($\Delta V/\Delta P$) tracing during the panting maneuver, are hard to detect during a single inspiratory effort, and that excessive thermal drift, which presents as a difference in slope between the inspiratory and expiratory phase of a pant, may not be appreciated without the expiratory phase. The maneuver must result in a rapid change in pressure and volume

to avoid problems due to thermal drift. If the duration of the inspiratory maneuver is less than 0.8 s, then thermal drift may not be a factor.[166] A slower inspiratory maneuver invites errors due to both thermal drift and polytropic conditions within the plethysmograph.

The subject is instructed to support his cheeks and chin firmly with both hands. Breathing is continually monitored by the operator in order to establish a baseline representing FRC. When the subject is at or near FRC, the shutter is closed at end expiration. The subject makes a series of gentle panting maneuvers (approximately $\pm$ 1.0 kPa) at a frequency between 0.5-1.0 cps (30-60 pants/min). Panting at this low frequency has been shown to greatly reduce or eliminate errors[61;169;170] due to flow resistive losses caused by the upper airway acting as a capacitive shunt, yet is sufficiently fast to avoid errors related to polytropic conditions within the interior of plethysmograph. One option for assisting patients in achieving this specific range of panting frequencies is the use of a metronome (an instrument readily available in music stores designed to mark exact time by either display of flashes or auditory tics) to assist patients in panting at an exact frequency. For example, with a metronome setting at 120, a panting frequency of 60 is achieved if the patient makes each inspiratory and expiratory effort in time with the metronome.

During the panting maneuver, the operator monitors the X/Y plot of ΔP vs ΔV. The panting should result in a series of almost superimposable straight lines separated only by small thermal drift.

For subjects unable to perform appropriate panting maneuvers (e.g., young children), an alternative is to perform a rapid inspiratory maneuver against the closed shutter. In this situation, it is essential that the complete rather than the simplified version of the V_{TG} computation equation be used [9] in the calculation of V_{TG} . If a computerized system is used for such measurements, the user must confirm that the complete equation is used by the computer during such measurements.

Selection of technically satisfactory measurements:

Preferably, users should be able to review a time-based recording of tidal breathing preceding shutter closure. After shutter closure, there should be at least two recognized pants displayed on a X/Y plot at a frequency between 0.5 and 1 cps and where P_{ao} does not exceed 2 kPa. (With only one maneuver, it is extremely difficult to ascertain the existence and magnitude of thermal drift). The plots of the ΔP / ΔV relationship should be linear over at least 80% of the plot including all portions that will be used in calculations. Following corrections for thermal drift, calculations of goodness of fit using at least squares linear regression of ΔP_{ao} on ΔV_{pleth} is desirable. Low correlation coefficients (e.g., $r < 0.95$) may result from improper technique. The X/Y plot may show looping if the upper airway acts as a shunt capacitance in patients with severe obstructive disease when panting at a high frequency [167] or if there is a poor frequency response of the equipment. Single inspiratory maneuvers should yield virtually superimposable X/Y plots and values of FRC_{pleth} within 5% of each other. For recordings where shutter closure occurs significantly above or below what appears to

be FRC, the measured volumes can be appropriately corrected; usually, however, skilled technicians will recognize inappropriate shutter closures and repeat the measurements until an adequate number of appropriate shutter closures are achieved.

After each set of 3-5 technically satisfactory panting maneuvers, the shutter is opened and the subject instructed to expire to RV (request as complete an expiration as possible but not a rapid forced expiration) followed by an inspiratory vital capacity maneuver (IVC) to TLC. If need be, the subject can come off the mouthpiece and rest between TGV/ERV/IVC maneuvers. Subjects with severe pulmonary disease and/or dyspnea may, however, have difficulty with performing complete expirations RV followed by a maximal inspiration to TLC after completion of technically satisfactory TGV maneuvers. To overcome this problem, a subject can be instructed to take two or three tidal breaths after the panting maneuver in order to lessen the sense of dyspnea prior to performing the linked ERV and IVC maneuvers.

Obtain at least 3 and preferably 5 technically satisfactory TGV/ERV/IVC maneuvers. The recordings of tidal breathing immediately prior to shutter closure need to be reviewed and a line drawn representing the best estimate of the stable end tidal level which represents FRC. (With most computerized systems, this line is drawn by the computer; the technician needs to confirm the accuracy of this line placement and if need be, adjust the position). If shutter closure occurs above or below the estimated FRC position of the tidal breathing recording, the computed TGV value should be adjusted by the appropriate shutter closure correction factor for calculation of FRC.

The reported value for FRC is the mean of technically satisfactory recorded values of FRC from maneuvers with both technically satisfactory FRC and ERV maneuvers. The reported value for RV is the reported value for FRC minus the mean of technically satisfactory and linked ERV maneuvers. The reported value for TLC is the reported value for RV plus the largest of technically satisfactory IVC maneuvers.

> Rationale: Errors from shutter closure significantly above or below the stable end-tidal volume display are usually small but can be more substantial in patients with severe obstructive lung disease who may “staircase” their end-tidal volumes especially when breathing at higher frequencies (e.g., as can occur during open-shutter R_{aw}/TGV measurements. The reader is referred to the fuller discussion of calculation options in the controversies of the Terminology section 2 and in the earlier Calculations Section 5.

A proposal considered was that the reported value for FRC be the mean of technically satisfactory FRCs from the maneuvers used for calculation of the mean TLC *and which do not differ by more than 10% from the lowest of the technically acceptable FRCs*. Rationale: Occasionally one or more FRC measurements will be significantly higher than the others, measurements almost always associated with smaller linked ICs. In such cases, although the resultant TLC measurements may be reproducible and presumably valid, the mean FRC may be substantially higher than the "true" FRC. This proposal was rejected because of the lack of data proving that the benefits outweigh the added complexity.

For subjects with severe pulmonary disease or dyspnea who have difficulty with performing complete expirations RV followed by a maximal inspiration to TLC after completion of technically satisfactory TGV maneuvers, the following acceptable alternative method is suggested: Following the recording of TGV maneuvers the subject is instructed to inspire maximally (but not necessarily rapidly) to TLC. The resultant IC is added to the linked FRC to compute the TLC value for that maneuver. The subject can come off the mouthpiece and rest between TGV/IC maneuvers. After recording a minimum of three technically satisfactory FRC/IC maneuvers, the subject can again rest and then perform a series of ERV maneuvers followed by IVC maneuvers. The largest of technically satisfactory IVC maneuvers is subtracted from the mean of technically satisfactory TLC maneuvers to compute the reported value for RV.

When using a variable pressure plethysmograph, the pneumotachometer used for measuring flows for airway resistance measurements or an external spirometer is used to measure IC and EVC with the plethysmograph vented to atmosphere to avoid overloading the plethysmograph pressure transducer. In the volume displacement plethysmograph, the subject breathes via tubing connected to the outside of the chamber and the plethysmograph measures the total change in thoracic volume of the subject. This change in volume includes both the volume of inspired or expired gas and any volume of compression or expansion[182] resulting from positive or subatmospheric pressures in the pleural space. While the volume change due to compression will be

small in a healthy subject, it may be considerable in a subject with marked airway closure at low lung volumes who generates large positive pleural pressures. [182]

8.1.7 Selection of Reported Values

For the *standard recommended method*, the reported value for FRC = the mean of the technically satisfactory FRC measurements linked to the technically satisfactory ERV and IVC maneuvers used for calculating RV and TLC. The reported value for RV is the reported value for FRC minus the mean of the technically acceptable ERV measurements linked to technically acceptable FRC determinations. The reported value of TLC is the reported value for RV plus the largest of technically acceptable IVCs.

For the *acceptable alternative* method for patients unable to perform the standard recommended method, the reported value for the FRC is the mean of technically acceptable FRC measurements used for the calculation of TLC. The TLC is the mean of the three largest sums of technically acceptable FRC and linked IC maneuvers.

The largest values from at least 3 acceptable VC maneuvers should be reported. The average IC and ERV values from acceptable maneuvers should be reported.

There is insufficient evidence regarding optimal recommendations for reproducibility criteria for ERV and IC used for computing TLC and RV. Until better information is available, the following are interim recommendations:

FRC measurements should be within 5% of each other. TLC measurements should be within 10% of the highest of technically acceptable TLCs, and RV measurements should be within 10% of the lowest of technically acceptable for RVs .

8.2. In Infants

Detailed descriptions of measurements of FRC_{pleth} in infants have been published. [171;178;186-188;309-314]

Volume and frequency characteristics of the infant plethysmograph must be known and shown to be adequate (i.e., at least five times the frequency of the respiratory maneuvers being measured).[178] Generally, most infant plethysmographs are the variable pressure type, although a flow plethysmogaph suitable for measuring FRC has been reported. [187]

In the first month of life, measurements can be made during natural sleep, but in older infants sedation is usually required. Display of time-based traces is strongly recommended as this makes it possible to assess variations in end-expiratory level more accurately, correct for thermal or metabolic drifts during airway occlusion, and occlude the airway at any phase of the tidal breath and subsequently correct to the end-expiratory level. A reduction in upper airway tone such that ΔP_{alv} does not equal ΔP_{ao} during the occlusion may be reflected as a phase lag between P_{pleth} and P_{ao}.

Infants do not pant but usually make relatively low frequency respiratory efforts (around 0.5 cps) against the occlusion, which increases the problems of thermal drift when compared to adults panting at 1 cps. With a variable pressure plethysmograph, the combined thermal and mechanical time constant should be at least 10 s which will provide an adequate frequency response down to 0.1-0.2 cps . If the system is calibrated at the approximate frequency of the respiratory efforts against the occlusion, any errors introduced by polytropic conditions will be cancelled out in calibration.[179] Unless efforts are specifically made to reduce the thermal time constant (metallic walls, fan, etc.) conditions in infant plethysmographs are adiabatic over the range of frequencies encountered (i.e., 0.3-2 cps). This can be verified by the operator by calibrating the system over the desired frequency range and establishing that the recorded signal remains constant. Alternatively, appropriate software can be used for signal corrections.[189]

8.2.1 Procedure

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 5 tidal breaths before occlusion to establish a stable end-expiratory level, then briefly closing the shutter at end-inspiration. If the seal is adequate, mask flow will be zero throughout the occlusion and the volume recorded will return to the expiratory baseline after the release of the shutter. Any increase in the volume baseline after release of the occlusion or decay of P_{ao} signal during occlusion suggests a leak.[178;190] After eliminating leaks, the plethysmograph is closed. If a

pressure plethysmograph is used, it is allowed to reach thermal equilibrium. At least five tidal breaths (more, if end-expiratory level is unstable) should then be recorded before the airway is occluded. FRC_{pleth} is conventionally measured by closing a shutter at end-expiration and allowing the infant to make two to four respiratory efforts against the occlusion. In practice, occlusion is frequently performed at end-inspiration. This improves the signal to noise ratio, is better tolerated by most infants and reduces the incidence of glottic closure. The volume at which occlusion should occur is still under debate. [163;172] In healthy infants, measurements made at end-inspiration and end-expiration agree within 5% after correcting for the inspired tidal volume, thereby providing a simple and effective in vivo method of validating the accuracy of the measurements. [125]

During the occlusion, the changes in box volume and P_{ao} should be strictly in phase. A loop appearing on an 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 obtained during quiet sleep. [192]

In healthy infants, FRC_{pleth} measurements should be very reproducible, with a coefficient of variation of less than 5%. [186; 106] Variability may be greater in infants with respiratory disease [193], those who are not in quiet sleep [194], or those without a stable end-expiratory level before occlusion.

9. MEASUREMENTS OF ABSOLUTE LUNG VOLUMES BY IMAGING TECHNIQUES.

Qualitative assessments of lung volumes are done unconsciously by most clinicians during review of chest radiographs, but more precise quantitative measurements of lung volumes can also be gained from these images. Although radiographic methods for measuring lung volumes have their own assumptions and limitations, they overcome some limitations of physiologic measurements of lung volumes such as the impact of poorly communicating spaces on gas dilution techniques or plethysmographic errors secondary to failure of dynamic pressures measured at the mouth to reflect changes in alveolar pressures. Radiographic methods can be applied to standard routine chest radiographs obtained for clinical purposes. Such applications may useful when serial chest radiographs are available for a patient but previous physiologic measurements of lung volumes are not available for comparison. These techniques are also useful for epidemiologic studies in which chest radiographs have been obtained for other purposes. [3]

9.1 Radiographic Methods for Adults

The ellipsoid technique[195;196] considers the thorax as a stack of five ellipsoids. From these ellipsoids, volumes can be calculated from transverse diameters and heights of the ellipsoids measured from PA and lateral chest radiographs after adjustments for magnification factors, and volumes of the heart, intrathoracic tissue and blood, and infradiaphragmatic spaces.

The planimetric method as described by Pratt et al[197;198] measures the surface area of the lungs on PA and lateral chest radiographs using planimeters (engineering devices designed to measure the area of irregularly shaped spaces). The surface areas are then converted to TLC through the use of equations developed from subjects who underwent both physiologic measurements of lung volumes and measurements of radiographic lung surface area by planimetry. Unlike the ellipsoid technique, the magnification factors are not routinely measured and the radiographs are assumed to be exposed following the standard 6-foot posterioranterior and lateral techniques.
As reviewed in the background paper [3], comparisons of planimetry and ellipsoid and related computerized radiographic techniques[315] with physiologic measurements of TLC indicate high correlation coefficients (e.g., r= 0.93) and low mean differences (e.g., 0.8%), but differences up to 15-20% in individual subjects.

A number of papers have described automation or computerization of both the ellipsoid and planimetric techniques. Pierce et al. described a modification of the ellipsoid method which used a computerized digitizer [199] and Bush and Denison later proposed improvements for estimating magnification when using the Pierce method.[200] In a comparison of techniques, Rodenstein et al.[201] concluded that the Pierce/Bush technique was more accurate than the Barnhard/Loyd technique when compared with plethysmography and offers the advantages of computer-assisted data reduction. Because of a lack of studies which have compared the three basic radiographic techniques (Harris, Barnhard, and Pierce) with physiologic measurements (e.g., He dilution and/or plethysmography), participants in the ATS/ERS workshop concluded that

no single radiographic technique could be recommended over another. Whichever method is used, careful attention must be paid to matching the techniques originally described, especially with regards to magnification factors and specific anatomic guidelines for defining thoracic outlines.[3] Studies of the reproducibility of radiographic lung volume measurements on the same radiographs demonstrate intraobserver coefficients of variation (CV) of 0.56% and interobserver CV of 4.9%.

Ries et al. described a technique for measuring FRC or TLC in supine subjects using portable radiography; this paper also described radiographic techniques which reduced radiation exposure for these measurements by approximately 90% as compared with conventional chest radiographs. [202] X-ray source to film cassette distances were standardized; adoption of different distances would require adjustment for changes in magnification. Assessment of the effects of inter-subject differences in magnification secondary to differences in thoracic size indicated these variations in magnification had no significant on the accuracy of radiographic measurements. A technique for measuring FRC in supine patients using portable chest radiographs has also been described by Block et al.[203] However, comparisons of the two portable techniques are not available.

Although plethysmographic, gas dilution, and radiographic techniques can give lung volumes, which are reasonably similar in healthy subjects, they measure fundamentally different spaces which can differ substantially in individuals with lung disease. In a subject with lung disease with significant amounts of airspace-occupying tissue (e.g.,

pneumonia with consolidation; severe interstitial fibrosis), planimetric lung volumes may be substantially greater than the compressible-gas volumes measured by plethysmography or communicating gas volumes measured by gas dilution .

9.2 Radiographic Methods for Children and Infants

For pediatric applications, available studies are more limited[3]. Both the planimetry and elliptical methods developed for adults have been shown to result in substantial errors when used in children. In infants, variations in thymus size are especially problematical. As is the case with adults, no specific radiographic technique for measuring lung volumes can be recommended for children and infants as the "gold-standard" at this time. [3] The technique developed by Fumey et al.[204] for infants using AP chest radiographs alone or combined with lateral views is promising as is a more recently described technique.[316] For older children, the method of choice is that reported by Salam and Warwick. [205]

9.3 Computerized Tomography (CT) and Magnetic Resonance (MR) Imaging

CT and MR imaging techniques offer the potential for improved accuracy of volume measurements by allowing for variations in individual chest wall shapes and by measuring specific regions or sections of lung.[3] CT also offers the possibility of being able to estimate the air and tissue volumes of the lungs separately. Not all CT scanners are equally suited for quantitative applications and results on one machine may not be comparable with those of another unless correction factors are used.[206] If fine detail of parenchymal images is not needed, CT procedures can be modified to substantially

reduce radiation dose. In addition to reducing radiation doses, advances in ultra-fast or spiral CTs offer assessments of regional lung volumes in the future for units as small as individual lobules. There are a paucity of studies comparing CT volumes with those measured physiologically but those currently available[317;318] observed substantial (e.g.,> 1.1 L) differences in mean values of lung volumes determined by CT and plethysmography. However, the CT measurements are made in the supine position whereas the physiologic measurements are made in the sitting position.

MR also offers the potential for measuring the volume of specific regions of the lungs and for estimating lung water and tissue. For both CT and MR, advances in the speed of imaging and thoughtful selection of the number of images required, will significantly affect the potential of these techniques for lung volume measurements in the future. Use of both CT and MR for measuring thoracic volumes is, however, substantially limited by the cost of these procedures. Since both CT and MR techniques are done with the subjects supine, lung volumes may differ from conventional physiologic measurements secondary to postural differences, especially in those with neurologic disease or marked obesity.

9.4 Controversies

1. Are the inspirations to TLC achieved during routine chest radiographs sufficiently close to those achieved in PFT labs where subjects are specially instructed to make maximal inspirations?

Crapo et al.[207] observed that, in 19 healthy subjects, radiographic TLC taken after routine coaching instructions for chest radiographs averaged 95.5% of the radiographic TLC measured after special coaching. In contrast, Kilburn et al. noted that 13% of subjects had radiographic evidence of inadequate inspirations; 90% of these subjects achieved better inspiration after encouragement to maximize inspirations. [208] It is therefore likely that the adequacy of inspiratory efforts during "routine" radiographs is highly site and subject specific. If optimal accuracy is required, both the subject and the radiology technician should be instructed regarding the importance of exposing the radiographs at times of maximal inspiration.

2. Are single radiographic lung volume measurements in individual subjects sufficiently accurate to be clinically useful?

Differences between plethysmographic and radiographic TLC as much as 20% in healthy subjects have been reported [185;195;198;201;209] presumably reflecting primarily errors in the radiographic measurements attributable to variances of chest shape, although inaccuracies in plethysmographic measurements contribute. Such discrepancies would limit the clinical usefulness of single radiographic measurements.[3]

10. REFERENCE VALUES FOR RESIDUAL VOLUME, FUNCTIONAL RESIDUAL CAPACITY AND TOTAL LUNG CAPACITY

The best reference value is the value previously observed in a subject in a period when disease was absent. Most often, however, such data are not available. The alternative, reference values derived from healthy subjects, allow conclusions regarding whether an individual's measured volumes fall within a range expected for a healthy person of the same sex, similar stature, age, and other characteristics. There are a number of publications on selection and interpretation of reference values for respiratory function and the associated concepts of "normality". This section will review reference values for absolute lung volumes and represents a distillation of the background paper.[2]

Not surprisingly, lung volumes are related to body size. In infants, this is best defined as body length when stretched.[210] For children and adults, standing height (distance from the sole of the feet to the top of the head with the subject standing erect and looking straight ahead) has consistently been shown to be the best factor for narrowing the range of predicted values for individual subjects (a more detailed description of the optimal technique for measuring standing height is in section 6.1.4). In children and adolescents, lung growth appears to lag behind the increase in standing height during the growth spurt and there is a shift in relationship between lung volume and height during adolescence. [211;212] Appropriate statistical modeling to adjust for alinearity of various growth spurts or non-linear change in ventilatory function with aging of infants and children may increase the sensitivity of lung volume measurements in the early detection of reduced lung function. TLC does not change with aging in healthy adults;

RV increases linearly in adults, whereas the age dependence of FRC in adults is relatively small (if it exists at all). [2]

10.1 Reference Values for FRC in Infants

Although attempts have been made to assess TLC from measurements of crying VC and RV[2], the only lung volume that can be measured routinely with accuracy and reliability in infants is FRC. In the past there has been reasonable agreement between the mean values of FRC (mL/kg) in newborn infants published from various studies for the same basic measurement techniques (approximately 23 mL/kg from He dilution techniques and 30 mL/kg from plethysmographic measurements).[2] However, these limited differences in means do not reflect the wide scatter of results observed within many of the studies. The significant discrepancies between FRC measured by gas dilution and plethysmographic techniques has been largely attributed to the presence of trapped gas which is not detected by gas equilibration methods. [91;130;161;213] However, better comparative studies on sufficiently large numbers of infants are needed to clarify this issue.

Studies with both adequate measuring techniques and sufficient numbers of normal healthy infants for defining optimal predictive values for FRC in infants are not available. Accordingly, Stocks and Quanjer compiled data measured at several different centers in which at least 25 healthy Caucasian infants had been studied and all raw data and details of methodology were available. [2] Table 1 presents the prediction equations derived from these data for FRC measured by either He dilution or plethysmographic

techniques; Table 2 presents representative values and 95% confidence limits for infants for a range of lengths and body weights.

Table 1- Prediction equations for FRC (in mL) in infants and young children.

Index	Equation	RSD	90%CI	95%CI
FRC_{He}	$0.0036\ L^{2.531}$	0.177	75-134%	71-144%
FRC_{Pleth}	$2.36\ L^{0.75}\ W^{0.63}\ k$	0.140	79-126%	76-132%

RSD = residual standard deviation; L=crown-heel length(cm), W = body weight (kg), k = constant to describe laboratory interaction: k = 1.0 for data from Dezateux et al [191], **1.01 for references by Doershuk et al [214;215]; 1.07 for references by Stocks and Godfrey[188], Hatch and Taylor [216], and Phelan and Williams [217].**

Table 2 - Representative values (mean+95% CI) of FRC at arbitrarily chosen values of length (supine) and body weight in infants, derived from collated data

Length cm	50	60	70	80	90
Weight¶ kg	3	6	9	11	-
FRC_{He} mL	72	114	168	236	318
95% CI mL	51-102	81-161	119-237	166-333	226-448
FRC_{Pleth}mL§	89	157	228	286	-
95% CI mL	68-117	119-207	173-301	217-377	-

¶: only used for predicting FRC_{Pleth} ; §: calculated from equation in Table 1. For abbreviations see legends to table 1.

Although these equations are currently considered the prediction equations of choice, it must be recognized that these equations have not yet been tested by enough centers with sufficiently varied subjects to allow confirmation of their robustness. Therefore, caution is urged when interpreting results with respect to these (or other) reference values for infants and additional studies defining predicted values are encouraged.[2]

As reviewed in detail in the background paper [2], a large proportion of variance of the FRC for infants was explained by body size but a simple linear regression of FRC on either weight or length was found to be inadequate in view of the heteroscedastic scatter of the residuals around the regression. Logarithmic transformation provided the best model.[2]

During recent years, a progressive decline in the magnitude of plethysmographic volumes in infants has been noted. This is probably attributable to a combination of factors including improved equipment with reduced deadspace, more accurate correction for apparatus and mask deadspace, and data collection under baseline conditions, rather than immediately following airway resistance measurements which required rebreathing heated humidified air from a bag or circuit, and which was inevitably accompanied by a degree of hyperventilation and potential hyperinflation. Thus predicted values of FRC pleth from the equation above are approximately 7% lower than those quoted in earlier publications [188;216;217]. Following a recent ERS/ATS initiative to develop guidelines for infant lung function software and equipment [319;320], a new generation of infant lung function equipment has been produced, wherein deadspace has been further reduced. The most recent estimates using such equipment suggest that, in contrast to previous comparisons[161], very similar estimates of FRC are achieved in healthy infants, irrespective of whether plethysmography or gas dilution is used [321] Further work is currently being undertaken to confirm these findings, but in the meantime considerable caution is required when using published reference values for infant plethysmography as

these may over-estimate expected values, and result in failure to identify hyper-inflation in infants with airway disease.

10.2 Reference Values for Pre-School Children

Reference values for preschool children (2-5 years) are even more limited than those in infants, with widely discrepant predicted values at any given length or height. Individual data collected in three different laboratories from 191 young Caucasian children was combined and used to develop the following equation for infants and children of both sexes from birth to 7 years of age and 125 cm height [2] :

$FRC_{He} = 0.0031 \ H^{2.56} \ k$ (RSD=0.169, 95% CI 72-139%)

where FRC is in mL, H is height in cm, and k is a term used to account for differences between data collected in different labs. k = 1.18 for data reported by Taussig et al.[118] and Greenough et al. [218], and 1.40 for more recent data from Greenough et al. [219]

Comment: In the interest of having a single equation that can be used and tested for the consensus document, it was suggested that we eliminate the multiple k factors and instead substitute a single values that would be most likely to be representative for most labs. However, this was not agreed upon. Whether the differences between laboratories are due to differences in methodology, equipment, or population has not yet been determined. Additional data are needed to resolve this controversy.

A compilation of representative predicted values for FRC_{He} for young children of various standing heights [2] from published studies [218;220] is presented in Table 3.

Table 3 - Representative values of FRC_{He} in young children at arbitrarily chosen heights.

Height (cm)	90	100	110	120
FRC_{He} (mL)	368	482	615	769

10.3 Reference values in Children and Adolescents

Details of reference populations and regression equations for children and adolescents have been summarized in a report [221], where it can be seen that equations have frequently been derived from relatively small populations (<200 children) over a 6-12 year age range, when growth and developmental changes are extremely rapid. Relatively few of the published studies have taken puberty or age into account. It is also important to interpret results with respect to longitudinal rather than cross-sectional data if the effects of growth and temporal changes are to be properly accounted for.[222-225] Most commonly used in the past in North America are the equations published by Polgar and Promadhat[226], Weng and Levison [227] or Cook and Hamann [228]. Until more studies are available using modern techniques, the prediction equations of Cook and Hamann [228] are suggested for use in the age range 5-18 year for gas dilution methods, and those of Zapletal[229] for plethysmographic data.

The following comments must be noted:

1. More work is needed to establish appropriate reference values from newborns to the elderly, especially in infants and children.

2. Most prediction equations were derived from Caucasian populations. Differences secondary to ethnicity are not well defined; until better information is available, correction factors for black and oriental children should be the same as those recommended for adults.[2]
3. Utilizing the currently available equations, at the start of adulthood there are discontinuities at the interfaces between predictions for children and adults.
4. Prediction equation models using standing height alone may not be as reliable as models based on age or age and height.

Cogswell et al.[230] compared plethysmographic and He dilution measurements in 225 healthy children between 5-15 years of age and found that FRC_{pleth} exceeded FRC_{He} by between 130-320 mL (mean 206 mL) for every height group. By contrast Kraemer et al.[153] found no significant differences between measurements of FRC using plethysmography, N_2 washout, and He dilution in 54 children, ages 7-17 years. Reliable reference values for lung volumes in infants and children have yet to be established from radiographic or other imaging techniques.

10.4 Reference Values for Adults

Prediction equations from data derived in ample numbers of healthy subjects of each sex and ethnic group evenly distributed by age and height using adequately described measurement techniques are not currently available.[231] Data from earlier studies may not fit present day populations due to cohort effects.

Accordingly, a working party of the European Community for Steel and Coal derived summary equations using the technique previously applied by Polgar and Promadhat.[226] This process of developing prediction equations is not ideal because they were derived from published regression equations which may be suboptimal characterizations of the original data which was no longer available and because they included data from smokers and ex-smokers. These "composite" prediction equations are summarized in Table 4. Because all smokers and ex-smokers could not be excluded in the derivation of prediction equations, the value for RV in healthy nonsmokers may be smaller. In healthy adults most studies have shown that results from plethysmographic and gas dilution methods are comparable [164;232;233] so that reference values for FRC_{He} and FRC_{Pleth} are the same.

Table 4 - Reference values for lung volumes in adults.

Volume		Equation	95%CI¶	90%CI¶	RSD
Males					
TLC	L	7.99 H-7.08	±1.37	±1.15	0.70
RV	L	1.31 H+0.022 A-1.23	±0.67	±0.80	0.41
FRC	L	2.34 H+0.01 A-1.09	±0.99	±1.18	0.60
FRC/TLC	%	43.8+0.21 A	±13.2	±11.1	6.74
RV/TLC	%	14.0+0.39 A	±10.7	±9.0	5.46
Females					
TLC	L	6.60 H-5.79	±1.18	±0.99	0.60
RV	L	1.81 H+0.016 A-2.00	±0.58	±0.69	0.35
FRC	L	2.24 H+0.001 A-1.00	±0.82	±0.98	0.50
FRC/TLC	%	45.1+0.16 A	±11.6	±9.8	5.93
RV/TLC	%	19.0+0.34 A	±11.4	±9.6	5.83

¶ Based on lower and upper 2½ and 97½, or 5 and 95 percentiles. Percentiles are obtained from predicted ± value shown. A= age in years, H = stature in meters.

The equations (Table 4) apply to a height range of 1.55-1.95 m in men, and 1.45-1.80 m in women between ages 18-70 years. For subjects between 18 and 25 years of age, an age of 25 should be substituted in the equations to account for the transitional plateau phase between lung growth and the subsequent increase in RV associated with aging. For purposes of internal consistency in reports, it is recommended that the predicted value for RV be derived by subtracting the predicted value for VC from the predicted value for TLC.

Similarly, it is recommended that for reporting predicted values for ratios (e.g., RV/TLC), that these ratios be derived from the ratios of the predicted values for RV and TLC rather than from independent prediction equations of the ratios.

Differences in absolute lung volumes attributable to ethnicity[234;235] are not well defined. These differences may in part be explained by differences in trunk length relative to standing height, but also to differences in fat free mass, chest dimensions and the power of respiratory muscles. Prediction values for RV, VC, and TLC are, on average, 12% lower in blacks than in whites[236]; this difference may be smaller in elderly persons than in young adults.[237] Predictive values for absolute lung volumes for adults of Asian ethnicity are generally considered to be lower than those for Caucasians, but the magnitude of the differences is not well defined; the difference may be less in Asians raised on "Western" diets during childhood.[8]

10.5 Selection of Prediction Equations

As is the case with prediction values for most pulmonary function tests[231;238], the following factors must be considered when selecting predictive values for absolute lung volumes:

1. The characteristics of the reference population should match those of your patient or study group with respect to age and body size, sex, racial, and ethnic mix, and, if possible, nutritional and socioeconomic background and environmental exposures (e.g., pollution, altitude, etc.).

2. Avoid any extrapolation of regression equations beyond the size and age range of subjects actually studied.

3. Longitudinal studies analyzed by appropriate statistical models are necessary to describe properly the growth of an individual and the functional changes associated with aging.

4. Similar equipment, techniques, measurement conditions and analytical approaches should have been used in the selected reference population as will be used on your patients or subjects.

5. Assumptions underlying the statistical model used for calculating the prediction equation should be valid and biologically meaningful. In the pediatric age range, linear regression of untransformed values of lung volume on height is not justified: first the relationship is not linear, and secondly the scatter is not normally distributed around the predicted, but increases in proportion (heteroscedastic) to the predicted value[2]. In adults the scatter (RSD) around the predicted lung volume appears to be independent of the volume (homoscedastic).

After one or more prediction equations are selected, they should be tested by making measurements of absolute lung volumes on 10-20 healthy subjects of ages and ethnicity similar to your patient or study population. While 10-20 healthy subjects may be too small of a sample for statistical validity, it will provide some evidence confirming or disproving the reference value selection. Mean residuals (i.e., [measured-predicted]/RSD) in adults, or mean values (expressed as a percent of predicted in children and adolescents) significantly different from 100% of predicted suggests that

either there are problems with the measurements or that the predictive equations are not appropriate for your patient or study population.

10.6 Reporting of Measurements of Lung Volumes

It is recommended that, with the exception of the neonatal period, lung volumes in infants and children should be expressed with respect to prediction equations based on body length or height as the major determinant. The usefulness of additional factors such as age/developmental stage or age-height interaction is not yet established.
In healthy children and infants, both height and weight may be equally good predictors but, beyond the neonatal period, length or height is preferable provided it can be measured accurately since it is less dependent on the relative undernourishment that may accompany many disease states such as cystic fibrosis. [2] Length may be difficult to measure accurately in newborn infants. Consequently, both weight and length should be measured whenever possible, so that either may be used as predictors during the neonatal period. In young infants, lung volumes can be expressed per kg body weight, but this is not recommended beyond the first month of life. Lung volumes should never be expressed per cm body length.[2]

Assessing limits of normality from results expressed as a percent predicted is not valid in adults because the scatter around the predicted value is approximately constant, irrespective of the subject's height or age. However, the procedure is valid in children and adolescents for whom the scatter is proportional to the mean.[2]

Recommendation:

In adults, it is recommended that the expression of lung volumes as "percent predicted" be replaced or supplemented by the use of standardized residuals or percentiles. The standardized residual (also called standard deviation score) is the difference between observed and predicted value, divided by the standard deviation of the prediction (RSD in Table 4), leading to a dimensionless number. In a healthy population, the 90% confidence interval of the standardized residual is 1.64 (corresponding with the 95th percentile) and -1.64 (corresponding with the 5th percentile).[2] The standardized residual is thus indicative of how far the observed value is removed from the predicted, and also the likelihood that such a value would be observed in a healthy population.[239] Standardized methods of measuring stature must be employed. In infants, this requires the use of a calibrated stadiometer and two trained adults. Repeat measurements should be within 0.5 cm of each other. In the case of spinal abnormalities, arm span may be used instead of standing height. [2]

10.7 Challenges for the Future

The prediction equations which represent data integrated from equations published by different investigators (e.g., Tables 1-4) have a number of disadvantages, including an inability to define accurately the variance for calculations of standardized residuals and percentiles. These equations are therefore viewed as interim solutions. A recent joint initiative by the ERS and ATS to standardize infant lung function testing[109] and the current recommendations for lung volume measurements in adults may resolve some of the previous limitations in data and permit prospective collection of data measured under more standardized conditions. Therefore, investigators who have collected data

according to defined methodology are invited to submit their data to the ERS for inclusion in their data bank. This data bank will be available for research purposes; in addition, in the future, it will enable us to establish whether cohort effects affect ventilatory function.

A number of factors makes it difficult to define "normal" reference values for FRC measured in patients on mechanical ventilation including the need to adjust many predictive equations for the 25-30% differences expected because the patients are in the supine rather than sitting posture, and variable impact on FRC of different types of sedation and/or anesthesia commonly used in ventilated patients. There are few reports available on expected values for FRC during mechanical ventilation in children (or adults).

There is a need for well-designed longitudinal studies on lung volumes in infants and children, with special emphasis on the transition from infancy into childhood, during puberty and from adolescence into adulthood (18-25 years). The effects of sexual maturity on lung function must be taken into account accompanied by correlations with ethnicity and nutrition. In addition, the secular trend for successive cohorts to grow taller appears to be associated with a changing ratio of leg to trunk length [2;108], so that the relationship between stature and lung volumes is likely to be changing.
Future studies also need to consider more carefully other descriptors of subjects' health which may affect lung function (e.g., family history of asthma, maternal cigarette use

during pregnancy, passive tobacco smoke exposure, and mild lower respiratory infections in infancy and childhood).

11. REPRODUCIBILITY OF LUNG VOLUME MEASUREMENTS

It is important to know the variability or reproducibility of clinical measurements for a number of reasons. A knowledge and understanding of test variability can enhance the interpretation of the results.[5] Test reproducibility can also be a useful indicator of the quality of a laboratory's measurements and procedures when compared with results from other laboratories or historical data from biologic control subjects. Changes in procedures are occasionally associated with significant reductions[240] or increases in test variability; a trend towards an increasing variability may indicate an equipment malfunction or procedural problems. Because the sensitivity of a test can be improved with reductions in test variability, attempts should be made to regularly monitor and minimize test variability.

Method of expressing variability:

The within subject variability for lung volumes, as with spirometry, is not the same for all types of subjects.[5] Subjects with obstructive airways disease can create special problems with gas dilution/washout and plethysmographic techniques not seen in healthy subjects with resultant inaccuracies and/or higher variability of repeat measurements. In addition, differences in variabilities of lung volume measurements from patients with increased volumes may be partially explained from expressing these variabilities as percentages of the observed values rather than in absolute terms. At least for FVC and FEV_1, it has been shown that reproducibility should be expressed in

absolute terms [240] rather than as a percentage. Additional data is needed for each lung volume parameter in order to conclude whether or not this is the case for measurements of lung volumes as well.

Most previous reports of variability, however, have described variability as coefficients of variation (CV). As presented in detail in the background paper[5], CVs for He dilution and N_2 washout measurements of FRC in infants range from 3.6 - 6.6% with one study of infants less than 2 months of age reporting a CV of 12%. For plethysmographic measurements in infants, the range of reported CVs is 2.5% to 11%.[5] For children, reported CVs for FRC range from 3.3 to 7% for He dilution and plethysmographic techniques.[2] In adults, for both [5] He dilution and plethysmographic techniques, reported CVs range from 2.4 to 14% for RV, 3.9 to 10% for FRC, and 1.5 to 4% for TLC.[5]

12. INFECTIOUS DISEASE PRECAUTIONS

For more detailed literature citations for this section, the reader is referred to the background paper. [4]

Although the devastating consequences of the acquired immunodeficiency syndrome (AIDS) have clearly been responsible for the current anxiety regarding the transmission of communicable diseases from pulmonary function testing, there are a number of other diseases with substantial clinical impact which could also potentially be transmitted as a result of pulmonary function testing (e.g., hepatitis B, tuberculosis, varicella [chicken pox]), especially in immunologically compromised patients.

As of 1980, the Center for Communicable Disease had received no reports of nosocomial transmission of disease from pulmonary function testing.[241] Nevertheless, it is possible that such transmission could occur. One case of skin test conversion attributed to spirometric testing on an instrument previously used on a patient with active tuberculosis was reported.[242] One report of bacterial contamination of PF equipment noted 92% bacterial contamination on mouthpieces, 50% bacterial contamination on proximal tubing, but no culture positivity from samples taken within the volume displacement spirometer. [243]

There is no epidemiologic evidence that HIV is transmitted from saliva or expired gases.[244] The very few reported cases of transmission of HIV between dentists,

paradental personnel, and patients are most likely secondary to blood transmission. However, fragments of HIV virus have been isolated from human saliva[245] so the possibility of transmission via saliva cannot be excluded with 100% certainty.

The mortality rate for all forms of acute viral hepatitis (A,B,C,D) is approximately 1%; the prevalence of secondary chronic active hepatitis and cirrhosis is 3-60% and 0-20% respectively. The prevalence of asymptomatic hepatitis B virus carriers is about 0.2%, much lower than for hepatitis C (~3%) but 20-30 times higher prevalence than carriers of HIV. It has been estimated that currently in the U.S. there are at least 30 times more deaths annually from occupationally acquired hepatitis B than AIDS in health care workers.

Though transmission of hepatitis B is usually via exchange of blood, hepatitis B antigen has been identified in saliva and this is considered as a possible route of transmission as saliva from patients with hepatitis B virus has been shown to cause disease in animals when injected percutaneously. Oral ingestion of the virus can cause hepatitis but only with high doses of virus. There is, however, no epidemiologic or clinical evidence that hepatitis B is transmitted from respiratory expirates.

The transmission of influenza virus is generally[246], but not always [247], considered to be via deposition of the virus on surfaces during respiratory maneuvers such as sneezing or coughing, rather than transmission to the recipient by inadvertent hand-to-nose maneuvers. However, occasional reports of significant number of passengers (e.g., 30-

40%) being infected with specific influenza organisms traceable to a single passenger on one airline flight strongly suggest that transmission by inhalation can occur from inhalation of finely dispersed droplets recirculated in closed loop ventilation systems.[4]

Other pathogenic viruses which may be excreted in respiratory tract secretions and which may cause disease when exposed to the respiratory tract mucosa of potential recipients include respiratory syncytial virus [248], varicella zoster (chicken pox), and measles.[249] Tuberculosis is clearly infectious via transmission of organisms suspended in droplets such as may be generated during coughing [249], or, possibly during forced expiratory maneuvers in patients with tuberculous infections of the lung.[242]

Suspensions of droplets containing tuberculous bacillus can remain infectious for hours if the droplets are of sufficiently small size and the dose inhaled exceeds the critical dose required to cause disease. [250] Bacteria which may reside in respiratory tract secretions more commonly (e.g., staphylococcus, pseudomonas) may also be of concern, especially if transmitted to immunosuppressed patients.

The efficacy of droplet barriers in preventing transmission of tuberculosis (or presumably other bacterial infections) are considered adequate only when the efficacy of the barriers is high (e.g., 99.97% efficiency for droplet sizes down to 0.3 micrometers, as in high efficiency particle air [HEPA] filters). The feasibility of using filters located distal to mouthpieces in pulmonary function testing equipment is limited by the difficulty in finding filters which will entrap particles of viral size (e.g., 0.017 micrometers

diameter) without increasing the resistance and/ or the dead space of the testing circuit to levels which will interfere with testing. Although increases in resistance and dead space can theoretically be corrected for mathematically, these changes may cause physiologic changes in respiration which may invalidate the results or require that we redefine the limits of normality and disease severity. Filters with "tolerable" resistance for PF testing must be viewed primarily as highly efficient barriers for small airborne droplets which may contain infectious agents and remain suspended in air after testing rather than as filters for the viruses themselves. Guimond and Gibson [251] noted resistances ranging from 0.026 to 0.54 kPa L^{-1} s (0.22 to 5.35 cmH_2O L^{-1} $s^{-1)}$ at flow of 8 LPS when 6 filters were compared. When moistened from 10 minutes of rebreathing, introduction of these filters reduced PEF by 1-21% and FEV_1 by 1-13%. Johns et al., in testing the effects of a disposable barrier filter in patients as well as healthy subjects, noted no significant effect on plethysmographic or single breath He dilution measurements of absolute lung volumes; statistically significant reductions were noted for FEV_1 and PEF but the reductions were small and not clinically significant.[252] Primarily because of heightened anxiety regarding equipment hygiene associated with the AIDS epidemic and the perceived need to quell patient anxieties regarding testing apparatus used on other patients, many labs have adopted stringent measures of infection control which have included the in-line placement of filters between mouthpieces or tubing and test apparatus. It should be recognized that the primary goal of these filters is to prevent either the transmission of droplets of respiratory tract secretions to surfaces on more distal equipment, or prevent the re-aerosolization of droplets during inspiratory efforts by patients tested subsequently on the same system.[4]

This would be in accord with practices using ventilators Although disposable bag-in-a-box systems have been described [253] which provide effective control of cross-contamination from pulmonary testing, such approaches involve significant changes in testing technology and may require new predictive values.

12.1 Recommendations

Because of the paucity of credible reports of transmission of communicable disease from pulmonary function testing, and uncertainties about the efficacy of filters placed between the patient and the equipment, the workshop concluded that the use of filters could not be mandated.

If a "viral filter" or droplet barrier is used to prevent inhalation of potentially infectious fluids or aerosolized droplets by either lab personnel or patients subsequently undergoing testing on the same apparatus, its effects on all parameters measured must be known and corrected for. Such barriers can also be an integral part of disposable flow-measuring pneumotachometer devices although issues of cost and calibration need attention. Mouthpieces, tubing, valves, and other equipment on the patient side of a droplet barrier should be physically cleaned and sterilized (or disposed of and replaced with clean components) between each subject.

Alternatives include disinfecting, after each patient, surfaces of all equipment (e.g., mouthpieces, tubing, valves) exposed to expired gases which could potentially infect

subsequent patients. Disinfection recommendations [250;254;255] must be followed meticulously.

As is the case for spirometry and other aspects of pulmonary function testing, updated guidelines for prevention of infectious disease should be followed including "Universal Precautions", handwashing between patients, and other standard measures. Because maximal expiratory efforts to RV often stimulate coughing in subjects with lung disease, subatmospheric pressure ventilation for pulmonary function laboratories is recommended.

13. CLINICAL USEFULNESS OF LUNG VOLUME MEASUREMENTS

13.1 Introduction:

In assessing the clinical usefulness of lung volume measurements, we considered the contributions of volume measurements to assessments of diagnosis, functional severity, functional disability, course of disease, and response to treatment and whether the measurements provided clinically useful information not available from less expensive and/or less invasive tests or procedures. We also defined usefulness primarily as it relates to the clinical care of individual patients rather than the usefulness of these measurements in research where conclusions are usually based on analyses from groups of patients. We attempted to identify when conclusions were based on data derived from measurements made by highly expert investigators as compared with those obtained under more typical clinical environments.

We based decisions on clinical usefulness as much as possible on "evidence-based" data such as prospective studies specifically designed to assess clinical usefulness using clinically meaningful outcomes (i.e., improved outcomes of mortality, morbidity, quality of life, or lower costs of medical care). Retrospective studies were a second choice. When we only had clinical experience which favored, or did not favor, the clinical usefulness of a test, the support had to be identified as anecdotal, with the recognition that such "anecdotal" support is the foundation for many clinical practices which most clinicians believe would be "proven" to be clinically useful if objectively assessed. Absence of proof of clinical usefulness does not mean the absence of clinical usefulness. For a number of diagnostic procedures and therapies, which are accepted as standards of practice, definitive studies which confirm improved clinical outcome are currently often not available; (e.g., chronic bronchodilator therapy for patients with stable COPD; use of pulse oximeters to monitor patients during surgery).[256] It is also important to recognize that a specific test (or method of measuring lung volumes) may be clinically useful for the assessment or management of patients only within defined levels of disease severity.

13.2 Infants and Children

There are a number of unresolved controversies regarding measurements of lung volumes in infants, which include measurement conditions, equipment characteristics, measurement techniques, presentation of results and the use of reference values. In addition, the relative limitations and advantages of plethysmographic versus gas dilution

techniques and recommendations regarding "the" test to use in specific clinical or research situations have yet to be clearly defined. And there is a paucity of well designed studies for evaluating the clinical usefulness of these measurements. All of these factors impair efforts to define clinical usefulness.

In infants, recognition of a significant decrease in FRC can lead to a diagnosis of lung hypoplasia. FRC measurements can also be helpful in assessing the response to primary closure of abdominal wall defects[257] and in the neonatal surgical repair of diaphragmatic defects.[258]

During the early stages of respiratory distress syndrome (RDS) in infants, FRC measurements may be helpful for assessing the severity of disease [156] and for assessing improvement of RDS during the diuretic phase [259] or after exogenous surfactant [260] or for determining optimal PEEP. [261;262] Such FRC measurements are most helpful when made in association with compliance and gas exchange measurements. Comparative measurements of FRC by the He dilution technique and body plethysmography have suggested gas trapping in pre-term infants suffering from persistent or recurrent wheezing and/or cough [263] although controversies regarding the magnitude of these differences in healthy infants limits the applicability of these conclusions. Elevation of FRC_{pleth} is often the first sign of respiratory dysfunction in infants with cystic fibrosis.[264;265]

Because forced expiratory maneuvers are not feasible, the assessment of bronchodilator responsiveness in infants with cystic fibrosis, acute bronchiolitis, asthma, and other disease processes should include FRC measurements [266] as they are less invasive and more specific than arterial blood gases for defining responses to bronchodilators, less invasive than measurements of work of breathing, and helpful for interpreting changes in airways resistance or forced expiratory flows that may occur during such interventions.[109;178;267] During acute respiratory bronchiolitis, FRC measurements by plethysmography have demonstrated hyperinflation which decreased with recovery [268;269] though the inherent variability of FRC measurements may limit the clinical usefulness of these measurements in individual cases. Studies have suggested that FRC measurements in infants with congenital heart disease can be useful in evaluating severity of cardiorespiratory functional limitation preoperatively.

In older children, measurements of lung volumes in survivors of RDS, with or without subsequent BPD, indicate that RV/TLC ratios are often increased and FVC is decreased. [270-273] This carries over to adult survivors of BPD who on average have mild obstructive airways disease with an increased RV/TLC ratio, reduced maximal expiratory flows, but a normal TLC. [274] There is not, however, concordance between impairment expressed by values of spirometry compared with the degree of hyperinflation. We currently do not have enough data from longitudinal studies to use such information for the prediction of morbidity and mortality.

In children with cystic fibrosis, serial assessments of the severity of hyperinflation helps to assess progression of the disease and responses to treatment, and also facilitate interpretation of volume-dependent measurements such as diffusing capacity or airways resistance. In children with interstitial lung diseases, lung volume measurements help to quantify the severity of mechanical restriction of the lung and help evaluate response to therapy, but analyses are not available as to whether simpler measurements of VC from spirometry are of equivalent usefulness.

Recent measurements of lung volumes at the bedside have documented their usefulness for the diagnosis and management of acute respiratory failure. [141;275-277] In children with neuromuscular disease, static lung volumes can be used to follow progression of disease and help anticipate the need for ventilatory support. [278-280] In children with alpha-1 antitrypsin deficiency, more research is needed comparing spirometry and measurements of hyperinflation and elastic recoil [281;282] as a guide to therapy (e.g., if spirometric flows are normal but volumes show hyperinflation or lung recoils are diminished, is treatment indicated?). In adults, Lindmark et al. noted that in heterozygote 1-antitrypsin deficient adults, RV was significantly elevated but spirometry did not indicate obstruction as compared with controls.[283]

One study has shown the usefulness of lung volume measurements to test the response to therapy in children with thalassemia major. [284]

13.3 Adults

A retrospective study of PFTs in 4,774 patients with obstructive lung disease concluded that RV and FRC measured by plethysmography were elevated in proportion to the degree of airflow obstruction but that the degree of hyperinflation as indicated by plethysmographic measurements of RV, FRC, and TLC was not clinically useful for separating self-reported diagnoses of asthma, emphysema, or chronic bronchitis. [285] In a study of 311 subjects with COPD [286], it was noted that subjects with severe hypercapnia had the largest FRC/TLC ratios; it has not been shown, however, that this knowledge translates into meaningful improvements of clinical outcome (although such evidence may evolve from upcoming studies on optimal selection of individuals for lung volume reduction surgery). In evaluating responses to therapy, Chrystyn et al.[287] noted that oral theophylline reduced dyspnea and the trapped gas volume (in proportion to the theophylline plasma level), whereas the improvement in FEV_1 was borderline. Whether or not baseline measurements of trapped gas volume will serve as useful predictors of beneficial responses to theophylline remains to be defined in a prospective study.

Schwartz et al.[288] found a significantly larger RV (mean =114% predicted) in 7 current smokers with idiopathic pulmonary fibrosis than in 21 never smokers (mean RV =82% of predicted) or in 44 former smokers (mean RV =82% predicted) whereas no differences were found among groups in FVC, FEV_1, or D_LCO. Currently, however, there is no evidence that the early recognition of lung dysfunction associated with smoking will lead to improved clinical outcome. Such recognition, however, may be useful for research and possibly have defined clinical usefulness in the future.

Isolated reductions in RV (RV < 65% of predicted measured by both plethysmography and N_2 washout, despite normal VC, FEV_1/FVC, and D_LCO) have been related to disease processes involving either the lung parenchyma or chest wall in 92% of the patients with these findings; follow up studies indicated an increase in the mean RV in the group of patients who clinically improved and a decrease in the group that worsened. [289] As is typical of most retrospective studies available for assessing the clinical usefulness of measurements of lung volumes, because of the study design, it is not possible to identify the frequency with which isolated reductions in RV would lead to the recognition of disease not already obvious from other more commonly available procedures (e.g., physical exam, chest radiograph).

Dalavanga et al.[290] found the average TLC to be significantly lower (86% predicted) in 12 patients with primary Sjogren's syndrome and active alveolitis when compared to 10 patients with Sjogren's syndrome without alveolitis (mean TLC =106% predicted); TLC measurements provided better discrimination than either spirometric or D_LCO measurements. Similar conclusions were found by Chinet et al.[291] in subjects with chronic fibrosing alveolitis when TLC and VC measurements were related to the degree of fibrosis and cellular infiltration on lung biopsies. Currently the clinical usefulness of TLC measurements in Sjogren's syndrome or fibrosing alveolitis will depend on the outcome of studies regarding the efficacy of treatment of active alveolitis. Johnson et al. noted that in subjects with idiopathic pulmonary fibrosis, measurements of TLC were better than VC for predicting mortality or response to cyclophosphamide.[292] In contrast

with the potential suggested by the above studies, others have concluded [293;294] that TLC measurements were insensitive for detecting interstitial lung disease.

There is anecdotal evidence that measurement of TLC is useful for recognizing when a restrictive process is superimposed with obstructive airway disease (situations in which reduced VC are frequently erroneously attributed to obstructive airway disease. [295] It is unlikely that making TLC measurements in *all* individuals with obstructive airways diseases would prove to be cost-effective for detecting otherwise unrecognized individuals with superimposed restrictive diseases. More appropriate would be studies which look at the impact on clinical outcome of making TLC measurements in those patients with COPD and clinical presentations which raise the possibility of restrictive disease (e.g., those whose dyspnea is out of line with the degree of obstruction or is interfering with daily activities despite optimal therapy of obstructive disease) not recognized from standard clinical exams including chest radiographs. In a 10 year follow up of 13 subjects with early emphysema, a significant increase in RV was noted which contrasted with the non-significant small decrease in VC. [296] In asthmatics, RV increases during naturally occurring exacerbations or induced bronchoconstruction and decreases after bronchodilation[20] and can remain somewhat elevated after normalization of FEV_1.[297] How such data will translate into clinical impact remains to be defined.

It has been claimed that comparisons of TLC by plethysmography and gas washout or dilution techniques can provide information about air trapping not otherwise available[298]

, particularly in respect to a cyst or bulla being considered for surgical intervention.[299] Conversely, measuring the slowly ventilated space as defined by Emannuel might provide similar information.[121] However, since these studies were done more than twenty years ago, the conclusions need to be reassessed after comparing the physiologic methods with currently available technology such as CT scans.

13.4 FRC During Exercise

Abnormal changes in end-expiratory lung volumes and associated flow limitations of tidal flows during exercise may identify mild expiratory flow limitations as a specific cause for dyspnea on exertion [78], conclusions which would not otherwise be made from standard exercise or PFT studies. However, detection of these flow limitations are generally made using spirometric measurements of inspiratory capacity with the assumption that TLC does not change during exercise, therefore measurements of absolute lung volumes are not essential for such studies. Similarly, although increases in FRC in patients on ventilators have been demonstrated to be better predictors of barotrauma than peak airway pressures or tidal volumes, these measurements are generally made from spirometric measurements of volumes expired from the FRC during sedation and paralysis[86] and do not necessitate measurements of absolute volumes.

13.5 Use of Absolute Lung Volumes for Interpreting Other Physiologic Tests

TLC coupled with measurements of elastic recoil of the lung can be useful in assessing the source of restrictive lung disease when chest radiographs do not show evidence of

parenchymal lung disease. A low TLC with a normal or low lung recoil at TLC suggests chest wall restriction, muscle weakness, or obesity. A low TLC with high lung elastic recoil at TLC is consistent with a stiff lung or atelectasis. However, reductions in lung compliance are seen after chest strapping of normal lungs [42] and in patients with restriction secondary to neuromuscular disease [51] which diminishes the specificity of such patterns.

Many consider that knowledge of the lung volume is essential to the interpretation of D_LCO, since D_LCO is volume dependent.[300] The volume dependence of $D_{L,}CO$ can be taken into account by use of the term $D_{L,}CO/V_A$.[301-303] An otherwise not explained progressive decline in single breath TLC (or alveolar volume, V_A) obtained as part of the D_LCO measurement suggests the need for a measurement of TLC by plethysmographic or radiographic methods to assess the significance of the decline in V_A, (i.e., to distinguish between a true decline in TLC vs worsening of intrapulmonary gas mixing). Similarly, since D_LCO/V_A as well as D_LCO rises if measurements are made using progressively larger single-breath inspirations, if a follow-up D_LCO shows a decrease but the corresponding D_L/V_A rises, it suggests that the decrease in D_LCO may be spurious, reflecting an inadequate inspiration.

As in the case of diffusing capacity, airways resistance and conductance are volume dependent and changes in airways resistance and conductance during serial measurements may be better interpreted knowing concomitant changes in lung volume and elastic recoil.[304-306] Others, however, have concluded that volume adjustment of lung mechanic studies and D_LCO has no clinical relevance.[307]

13.6 Radiographic Measurements of Absolute Lung Volumes

Though the quantitative assessments are very approximate, the most frequently performed assessments of TLC are obtained from routine chest radiographs. Qualitative estimates of lung volumes are done (often unconsciously) every time a chest x-ray is viewed. More quantitative measurements of TLC can readily be obtained from standard PA and lateral chest radiographs as discussed in the section on volumes calculated from imaging techniques. However, the inaccuracies of radiographic measurements of TLC in individual patients (95% confidence intervals of approximately +/- 15%) limits the clinical usefulness of such measurements. Serial measurements in the same patient should be more sensitive for detecting changes, but the clinical usefulness of such serial measurements has not been assessed. These techniques may play a particularly useful role in epidemiologic studies which have chest radiographs available for other purposes, thereby obviating the need for separate measurements of absolute lung volumes.

13.7 Conclusions

In infants and children too young to cooperate with spirometry, measurements of FRC may be useful for characterizing the cause of respiratory dysfunction, assessing severity, and evaluating responses to therapy. Technical challenges associated with such measurements, however, often limit their usefulness in non-research clinical environments.

In children as well as adults, there is some evidence that elevations of RV or TLC may provide evidence of obstructive lung disease in patients whose maximal expiratory flows are within normal limits; how often such information will translate into beneficial changes in therapy of such patients remains to be defined. In those with moderate to severe obstructive disease, measurements of TLC by plethysmographic or radiographic methods may be useful for recognition of superimposed restrictive disease not recognized from routine chest radiographs or physical exam. Assessing the severity of hyperinflation may be particularly useful for selecting optimal candidates for lung volume reduction surgery and assessing responses to this surgery.

In children and adults with restrictive processes without evidence of obstructive airway disease on spirometry, measurements of TLC are unlikely to provide clinically useful information not already available from spirometry. In cases with both obstructive and restrictive processes, measurements of TLC can be more useful clinically than relying on spirometry alone.

Because of the paucity of appropriate studies of the clinical usefulness and/or cost effectiveness of physiologic measurements, many of the conclusions cited above are by necessity drawn from the experience of some workshop participants. Well designed, prospective studies of the cost-effectiveness and clinical usefulness of measurements of absolute lung volumes are clearly needed to define their clinical roles more conclusively in the future.

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14. Reference List

1. Clausen, J. L., A. L. Coates, and P. H. Quanjer. 1997. Measurement of lung volumes in humans: review and recommendations from an ATS/ERS workshop. Eur Respir J 1997; 10: 1205-6. *Eur.Respir.J.* 10:1205-1206.

2. Stocks, J. and P. H. Quanjer. 1995. Reference values for residual volume, functional residual capacity and total lung capacity. *Eur.Respir.J.* 8:492-506.

3. Clausen, J. L. 1997. Measurement of absolute lung volumes by imaging techniques. *Eur.Respir.J.* 10:2427-2431.

4. Clausen, J. L. 1997. Lung volume equipment and infection control. *Eur.Respir.J.* 10:1928-1932.

5. Hankinson, J. L., J. Stocks, and R. Peslin. 1997. Reproducibility of lung volume measurements. *Eur.Respir.J.* 11:787-790.

6. Bancalari, E. and J. L. Clausen. 1998. Pathophysiology of changes in absolute lung volumes. *Eur.Respir.J.* 12:248-258.

7. Brown, R., P. Enright, and D. Leith. 1998. Multiple-breath helium dilution measurements of lung volumes in adults. *Eur.Respir.J.* 11:246-255.

8. Gaultier, C. and R. O. Crapo. 1997. Effects of nutrition, growth hormone disturbances, training, altitude, and sleep on lung volumes. *Eur.Respir.J.* 10:2913-2919.

9. Coates, A. L., R. Peslin, D. Rodenstein, and J. Stocks. 1997. Measurement of lung volumes by plethysmography. *Eur.Respir.J.* 10:1415-1427.

10. Newth, C. J., P. Enright, and R. L. Johnson, Jr. 1997. Multiple breath nitrogen washout techniques: including measurements with patients on ventilators. *Eur.Respir.J.* 10:2174-2185.

11. Leith, D. E. and R. Brown. 1999. Human lung volumes and the mechanisms that set them. *Eur.Respir.J.* 11:468-472.

12. Johnson, R. L., Jr., S. S. Cassidy, R. Grover, M. Ramanathan, A. Estrera, R. C. Reynolds, R. Epstein, and J. Schutte. 1991. Effect of pneumonectomy on the remaining lung in dogs. *J.Appl.Physiol.* 70:849-858.

13. anonymous. 1975. Pulmonary terms and symbols. Report of the ACCP-ATS Joint Committee. *Chest* 67:583-593.

14. Bartels, H., P. Dejours, R. H. Kellogg, and J. Mead. 1973. International Union of Physiological Sciences Committee on Nomenclature; Glossary on respiration and gas exchange. *J.Appl.Physiol.* 34:549-558.

15. Quanjer, P. H., G. J. Tammeling, J. E. Cotes, M. Fabbri, H. Matthyus, and O. F. Pedersen. 1993. Symbols, abbreviations and units. *Eur.Respir.J.* 6:85-100.

16. Quanjer, P. H. and J. Stocks. 1995. Respiratory function measurements in infants: Symbols, abbreviations, and units. *Am J Respir Crit Care Med* 151:2041-2057.

17. Quanjer, P. H., P. D. Sly, and J. Stocks. 1997. Uniform symbols, abbreviations, and units in pediatric pulmonary function testing. Pediatr Pulmonol. *Pediatr Pulmonology* 24:2-11.

18. Degroodt, E. G., P. H. Quanjer, and M. E. Wise. 1983. Influence of external resistance and minor flow variations on single breath nitrogen test and residual volume. *Bull.Eur.Physiopathol.Respir.* 19:267-272.

19. Skloot, G., S. Permutt, and A. Togias. 1995. Airway hyperresponsiveness in asthma; a problem of limited smooth muscle relaxation with inspiration. *J Clin.Invest.* 96:2393-2403.

20. Pellegrino, R., B. Violante, R. Selleri, and V. Brusasco. 1994. Changes in residual volume during induced bronchoconstriction in healthy and asthmatic subjects. *Am J Respir Crit Care Med* 150:363-368.

21. Leith, D. E. and R. Brown.1999.. Human lung volumes and the mechanisms that set them. *Eur Respir J.* 13: 468-72.

22. Petty, T. L., G. W. Silvers, and R. E. Stanford. 1987. Mild emphysema is associated with reduced elastic recoil and increased lung size but not with air-flow limitation. *Am Res Respir Dis.* 136:867-871.

23. Christensson, P., M. J. Arborelius, and R. Kautto. 1981. Volume of trapped gas in lungs of healthy humans. *J.Appl.Physiol.* 51:172-175.

24. Chan, K. N., C. M. Noble-Jamieson, A. A. M. Wllman, E. M. Bryan, and M. Silverman. 1989. Lung function in children of low birth weight. *Arch.Dis.Child* 64:1284-1293.

25. Raven, P. B., S. Taguchi, B. Drinkwater, M. Kaneko, S. Horvath, and H. Matsui. 1974. Anthropometric, spirometric, and physiologic comparisons of migrant Japanese. *Hum.Biol.* 46:483-494.

26. Jain, B. P., J. S. Brody, and A. G. Fischer. 1973. The small lung of hypopituitarism. *Am.Rev.Respir.Dis.* 108:49-55.

27. Schorr-Lesnick, B., A. S. Tierstein, L. K. Brown, and A. Miller. 1985. Pulmonary function in singers and wind-instrument players. *Chest* 88:201-205.

28. Leith, D. E. and M. Bradley. 1976. Ventilatory muscle strength and endurance training. *J.Appl.Physiol.* 41:508-516.

29. Fanta, C. H., D. E. Leith, and R. Brown. 1983. Maximal shortening of inspiratory muscles: effect of training. *J.Appl.Physiol.* 54:1618-1623.

30. Lahiri, S., R. G. DeLaney, J. S. Brody, M. Simpser, T. Velasquez, E. K. Motoyama, and C. Polgar. 1976. Relative role of environmental and genetic factors in respiratory adaptation to high altitude. *Nature* 261:133-135.

31. DeGraff, A. C. J., R. F. Grover, R. L. Johnson, Jr., J. W. J. Hammond, and J. M. Miller. 1970. Diffusing capacity of the lung in Caucasians native to 3,100 m. *J.Appl.Physiol.* 29:71-76.

32. Johnson, R. L., Jr., S. S. Cassidy, R. F. Grover, J. E. Schutte, and R. H. Epstein. 1985. Functional capacities of lungs and thorax in beagles after prolonged residence at 3,100 m. *J.Appl.Physiol.* 59:1773-1782.

33. Cunningham, E. L., J. S. Brody, and B. P. Jain. 1974. Lung growth induced by hypoxia. *J.Lab.Physiol.* 37:362-366.

34. Demedts, M. 1990. Mechanisms and consequences of hyperinflation. *Eur.Respir.J.* 3:617-618.

35. Macklem, P. T. 1984. Hyperinflation. *Am.Rev.Respir.Dis.* 129:1-2.

36. Stark, A. R., B. A. Cohlan, T. B. Waggener, I. D. Frantz, and P. C. Kosch. 1987. Regulation of end-expiratory lung volume during sleep in premature infants. *J.Lab.Physiol.* 62:1117-1123.

37. Bryan, A. C. and S. J. England. 1984. Maintenance of an elevated FRC in the newborn. *Am.Rev.Respir.Dis.* 129:209-210.

38. Taussig, L. M. and P. J. Helms 1996. Basic physiology. In J. Stocks, P. D. Sly, R. S. Tepper, and W. J. Morgan, editors Infant Respiratory Function Testing John Wiley and Sons, New York.

39. Young, S. L., D. F. Tierney, and J. A. Clements. 1970. Mechanism of compliance change in excised rat lungs at low transpulmonary pressure. *J.Appl.Physiol.* 29:780-785.

40. Haber, P. S., H. J. Colebatch, C. K. Ng, and L. A. Greaves. 1983. Alveolar size as a determinant of pulmonary distensibility in mammalian lungs. *J.Appl.Physiol.* 54: 837-845

41. Bachofen, H., S. Schurch, M. Urbginelli, and E. R. Weibel. 1987. Relations among alveolar surface tension, surface area, volume, and recoil pressure. *J.Appl.Physiol.* 62:1878-1887.

42. Caro, C. G., J. Butler, and A. B. DuBois. 1960. Some effects of restriction of chest cage expansion on pulmonary function in man: an experimental study. *J.Clin.Invest.* 39:573-583.

43. Estenne, M., P. A. Gevenois, W. Kinnear, P. Soudon, A. Heilporn, and A. DeTroyer. 1993. Lung volume restriction in patients with chronic respiratory muscle weakness: the role of microatelectasis. *Thorax* 48:698-701.

44. Sato, S., K. Takada, H. Nakamura, S. Yasui, and K. Takahashi. 1993. Elastic recoil pressure arising from surface tension in hamster lungs treated with intrathracheal bleomycin. *Tohoku J.Exp.Med.* 152:325-331.

45. Burkhardt, A. 1989. Alveolitis and collapse in the pathogenesis of pulmonary fibrosis. *Am.Rev.Respir.Dis.* 140:513-524.

46. Smith, J. C. and W. Mitzner. 1983. Elastic characteristics of the lung perivascular interstitial space. *J.Appl.Physiol.* 54:1717-1725.

47. West, J. B., K. Tsukimoto, O. Mathieu-Costello, and R. Prediletto. 1991. Stress failure in pulmonary capillaries. *J.Appl.Physiol.* 70:1731-1742.

48. Jackson, J. C., A. P. MacKenzie, E. Y. Chi, T. A. Standaert, W. E. Truog, and W. A. Hodson. 1990. Mechanisms for reduced total lung capacity at birth and during hyaline membrane disease in premature newborn monkeys. *Am.Rev.Respir.Dis.* 142:413-419.

49. Bradvik, I., P. Wollmer, B. Simonsson, U. Albrechtsson, K. Lyttkens, and B. Jonson. 1989. Lung mechanics and their relationship to lung volumes in pulmonary sarcoidosis. *Eur.Respir.J.* 2:643-651.

50. De Troyer, A. and S. Borenstein. 1980. Acute changes in respiratory mechanics after pyridostigmine injection in patients with myasthenia gravis. *Am.Rev.Respir.Dis.* 121:629-638.

51. Gibson, G. L., N. B. Pride, J. Newsom-Davis, and L. C. Loh. 1977. Pulmonary mechanics in patients with respiratory muscle weakness. *Am.Rev.Respir.Dis.* 115:389-395.

52. Demedts, M., J. Beckers, F. Rochette, and J. Bulcke. 1982. Pulmonary function in moderate neuromuscular disease without respiratory complaints. *Eur.J.Respir.Dis.* 63:62-67.

53. Allen, S. M., B. Hunt, and M. Green. 1985. Fall in vital capacity with posture. *Br.J.Dis.Chest* 79:267-271.

54. Estenne, M. and A. DeTroyer. 1987. Mechanism of the postural dependence of vital capacity in tetraplegic subjects. *Am.Rev.Respir.Dis.* 135:367-371.

55. Mier-Jedrze-Jowiez, A., B. Conor, J. Moxham, and M. Green. 1988. Assessment of diaphragm weakness. *Am.Rev.Respir.Dis.* 137:677-683.

56. Enright, P. L., R. A. Kronmal, M. Higgens, M. Schenker, and E. F. Haponik. 1993. Spirometry reference values for women and men 65-85 years of age. *Am.Rev.Respir.Dis.* 147:125-133.

57. Lopata, M. and E. Onal. 1982. Mass loading, sleep apnea, and the pathogenesis of obesity. *Am.Rev.Respir.Dis.* 126:640-645.

58. Rochester, D. F. and Y. Enson. 1974. Current concepts in the pathogenesis of the obesity-hypoventilation syndrome. *Am.J.Med.* 57:402-420.

59. Beardsmore, C. S., J. Stocks, and M. Silverman. 1982. Problems in measurement of thoracic gas volume in infancy. *J.Appl.Physiol.* 52:995-999.

60. Rodenstein, D. O. and D. C. Stanescu. 1982. Reassessment of lung volume measurement by helium dilution and by body plethysmography in chronic air-flow obstruction. *Am.Rev.Respir.Dis.* 126:1040-1044.

61. Brown, R. and A. S. Slutsky. 1984. Frequency dependence of plethysmographic measurement of thoracic gas volume. *J.Appl.Physiol.* 57:1865-1871.

62. Greaves, L. A. and H. J. H. Colebatch. 1985. Large lungs after childhood asthma: a consequence of enlarged airspaces. *Aust.N.Z.J.Med.* 15:427-434.

63. Hsia, C. C. W., F. Fryder-Doffey, V. Stalder-Navarro, R. L. Jr. Johnson, R. C. Reynolds, and E. R. Weibel. 1993. Structural changes underlying compensatory increase in diffusing capacity after left pneumonectomy in adult dogs. *J.Clin.Invest.* 92:758-764.

64. Merkus, P. J. F. M., E. E. van Essen-Zandvliet, J. M. Kouwenberg, E. J. Duiverman, H. C. Van Houwelingen, and K. F. e. a. Kerrebijn. 1993. Large lungs after childhood asthma: a case-control study. *Am.Rev.Respir.Dis.* 148:1484-1489.

65. Rothstein, M. S., M. N. Zelefsky, P. Q. Eichacker, D. J. Rudolph, and M. H. J. Williams. 1989. Radiographic measurement of total lung capacity in acute asthma. *Thorax* 44:510-512.

66. Blackie, S. P., S. al Majed, C. A. Staples, C. Hilliam, and P. D. Pare. 1990. Changes in total lung capacity during acute spontaneous asthma. *Am.Rev.Respir.Dis.* 142:79-83.

67. Lindroth, M., B. D. Johnson, H. Ahlstrom, and N. W. Svenningsen. 1981. Pulmonary mechanics in early infancy. Subclinical grunting in low-birth-weight infants. *Pediatr.Res.* 15:979-984.

68. Harrison, V. C., H. V. Heese, and M. Klein. 1968. The significance of grunting in hyaline membrane disease. *Pediatrics* 41:549-559.

69. Gibson, G. L. 1996. Pulmonary hyperinflation a clinical overview. *Eur.Respir.J.* 9:2640-2649.

70. Pellegrino, R. and V. Brusasco. 1997. Lung hyperinflation and flow limitation in chronic airway obstruction. *Eur.Respir.J.* 10:543-549.

71. De Troyer, A. 1997. Effect of hyperinflation on the diaphragm. *Eur.Respir.J.* 10:708-713.

72. Lougheed, M. D., M. Lam, L. Forkert, K. A. Webb, and D. E. O'Donnell. 1993. Breathlessness during acute bronchoconstriction in asthma. *Am.Rev.Respir.Dis.* 148:1452-1459.

73. Agostoni, E. and G. Torri. 1962. Diaphragm contraction as a limiting factor to maximum expiration. *J.Appl.Physiol.* 17:427-428.

74. D'Angelo, E., E. Pranki, L. Marazzini, and J. Milic-Emili. 1994. Dependence of maximal flow-volume curves on time course of preceding inspiration in patients with chronic obstructive pulmonary disease. *Am.J.Respir.Crit.Care Med.* 150:1581-1586.

75. Stubbing, D. G., L. D. Pengelly, J. L. C. Morse, and N. L. Jones. 1980. Pulmonary mechanics during exercise in normal males. *J.Appl.Physiol.* 49:506-510.

76. Babb, T. G. and J. R. Rodarte. 1991. Lung volumes during low-intensity steady-state cycling. *J.Lab.Physiol.* 70:934-937.

77. Stubbing, D. G., L. D. Pengelly, J. L. C. Morse, and N. L. Jones. 1980. Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. *J.Appl.Physiol.* 49:511-515.

78. Johnson, B. D., W. G. Reddan, D. F. Pegelow, K. C. Seow, and J. A. Dempsey. 1991. Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am.Rev.Respir.Dis.* 143:960-967.

79. Babb, T. G., R. Viggiano, B. Hurley, B. A. Staats, and J. R. Rodarte. 1991. Effect of mild-to-moderate airflow limitation on exercise capacity. *J.Appl.Physiol.* 70:223-230.

80. Paintal, A. S. 1995. Sensations from J receptors. . *News in Physiological Sciences* 10:238-243.

81. O'Donnell, D. E. 2002. Breathlessness in patients with chronic airflow limitation; mechanisms and management. *Chest* 106:904-912.

82. O'Donnell, D. E. and K. A. Webb. 1993. Exertional breathlessness in patients with chronic airflow limitation; the role of lung hyperinflation. *Am.Rev.Respir.Dis.* 148:1351-1357.

83. Belman, M. J., W. C. Botnick, and J. W. Shin. 1996. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 153:967-975.

84. Henderson Smart, D. J. and D. J. Read. 1979. Reduced lung volume during behavioral active sleep in the newborn. *J.Appl.Physiol.* 46:1081-1085.

85. Poets, C. F., G. A. Rau, K. Neuber, M. Gappa, and J. Seidenberg. 1997. Determinants of lung volume in spontaneously breathing preterm infants. *Am J Respir Crit Care Med* 155:649-653.

86. Williams, T. J., D. V. Tuxen, C. D. Scheinkestel, D. Czarny, and G. Bowes. 1992. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. *Am.Rev.Respir.Dis.* 146:607-615.

87. Gelb, A. W., P. Southorn, and K. Rehder. 1981. Effect of general anaesthesia on respiratory function. *Lung* 159:187-198.

88. Damia, G., D. Mascheroni, M. Croci, and L. Tarenzi. 1988. Perioperative changes in functional residual capacity in morbidly obese patients. *Br.J Anaesth* 60:574-578.

89. Ploysongsang, V. and S. A. Schonfeld. 1982. Mechanism of production of crackles after atelectasis during low-volume breathing. *Am.Rev.Respir.Dis.* 126:413-415.

90. Garfinkel, F. and R. S. Fitzgerald. 1978. The effect of hyperoxia, hypoxia and hypercapnia on FRC and occlusion pressure in human subjects. *Respir.Physiol.* 33:241-250.

91. Geubelle, F., M. Francotte, M. Beyer, I. Louis, and M. M. Logvinoff. 1977. Functional residual capacity and thoracic gas volume in normoxic and hyperoxic new born infants. *Acta Paediatr.Belg.* 30:221-225.

92. De los Santos, R., J. J. Seidenfeld, A. Ansueto, and et.al. 1987. One hundred percent oxygen lung injury in adult baboons. *Am.Rev.Respir.Dis.* 136:657-661.

93. Quanjer, P. H., G. J. Tammeling, J. E. Cotes, O. F. Pedersen, R. Peslin, and J. C. Yernault. 1993. Lung volumes and ventilatory flows. Report Working Party

"Standardization of Lung Function Tests", European Community for Steel and Coal and European Respiratory Society. *Eur.Respir.J.* 1993; 6, Suppl. 16, 5-40.

94. Corbeel, L. J. 1969. International Symposium on Body Plethysmography, Comparison Between Measurements of Functional Residual Capacity and Thoracic Gas Volume in Chronic Obstructive Polmonary Disease. *Prog.Resp.Res.* 4:194-204.

95. Cordain, L., A. Tucker, D. Moon, and J. M. Stager. 1990. Lung volumes and maximal respiratory pressures in collegiate swimmers and runners. *Res Q.Exerc.Sport.* 61:70-74.

96. Meneely, G. R. and N. L. Kaltreider. 1948. The Volume of the Lung Determined by Helium Dilution. Description of the Method and Comparison with other Procedures. *J.Clin.Invest.*129-139.

97. Quanjer, P. H., L. H. Anderson, and G. J. Tammeling. 1983. Standardized lung function test, Chapter 2, Static lung volumes and capacities. *Bull.Eur.Physiopathol.Respir.* Suppl.5:11-21.

98. Desmond, K. J., A. Coates, J. G. Martin, and P. H. Beaudry. 1986. Trapped gas and airflow limitation in children with cystic fibrosis and asthma. *Pediatr Pulmonology* 2:128-134.

99. Krumpe, P. E., H. J. MacDannald, T. N. Finley, H. E. Schear, J. Hall, and D. Cribbs. 1981. Use of an acoustic helium analyzer for measuring lung volumes. *J.Lab.Physiol.* 50:203-209.

100. Kauppinen Walin, K., A. R. Sovijarvi, A. Muittari, and A. UUsitalo. 1980. Determination of functional residual capacity with 133-xenon radiospirometry. Comparison with body plethysmography and helium spirometry. Effect of body position. *Scand.J Clin.Lab.Invest.* 40:347-354.

101. Larsson, A., D. Linnarsson, C. Jonmarker, B. Jonson, H. Larsson, and O. Werner. 1987. Measurement of lung volume by sulfur hexafluoride washout during spontaneous and controlled ventilation: further development of a method. *Anesthesiology* 67:543-550.

102. Yamamura, T., A. Okamura, N. Kikuchi, M. Fukuda, and O. Kemmotsu. 1992. [Measurement of functional residual capacity by sulfur hexafluoride washout]. *Masui.* 41:925-931.

103. Hathirat, S., M. Mitchell, and A. D. J. Renzetti. 1970. Measurement of the total lung capacity by helium dilution in a constant volume system. *Am.Rev.Respir.Dis.* 102:760-770.

104. Gardner, R. M., J. L. Clausen, R. O. Crapo, G. R. Epler, J. L. Hankinson, J. L. J. Johnson, and A. L. Plummer. 1986. Quality assurance in pulmonary function laboratories. *Am.Rev.Respir.Dis.* 134:625-627.

105. Ferris, B. G. 1978. Comparison of 5 Methods for Determination of FRC and TLC in 100 Persons. *Am.Rev.Respir.Dis.* 118(6):92-111.

106. Ljungberg H, Hulskamp G, Hoo A-F, Pillow JJ, Lum S, Gustafsson P, nd Stocks J. 2002. Estimates of plethysmographic FRC exceed those by gas dilution in infants with cystic fibrosis (CF) but not in healthy controls. Thorax. Supp III, iii23.

107. Merkus, P. J., S. Verver, E. E. Essen-Zandvliet, E. J. Duiverman, K. F. Kerrebijn, and P. H. Quanjer. 1992. Lung volumes measured by the forced rebreathing technique in children with airways obstruction. *Eur.Respir.J.* 5:879-886.

108. American Thoracic Society/European Respiratory Society. 1993. Respiratory mechanics in infants; physiologic evaluation in health and disease. *Am.Rev.Respir.Dis.* 147:474-496.

109. Tepper, R. S., I. T. Merth, C. J. Newth, and T. Gerhardt 1996. Measurements of Functional Residual Capacity in Infants. In J. Stocks, P. D. Sly, R. S. Tepper, and W. J. Morgan, editors Infant Respiratory Function Testing John Wiley and Sons, Inc., New York. 165-190.

110. Merth, I. T., G. J. Verschragen, I. C. W. Olievier, P. J. de Winter, and P. H. Quanjer. 1993. Water-sealed spirometer for measurements in newborns and infants. *J.Appl.Physiol.* 74:470-475.

111. Bar-Yishay, E. and K. S. McCoy. 1991. Functional residual capacity, FRC, as measured by helium dilution technique in CF infants is not affected by the application of CPAP. *Am.Rev.Respir.Dis.* 143:A129.

112. Berglund, G. and P. Karlberg. 1956. Determination of the functional residual capacity in newborn infants. *Acta Paediatr.Belg.* 45:541-544.

113. Cook, C. D., J. M. Suterland, S. Segal, R. B. Cherry, J. Mead, M. B. McIlroy, and C. A. Smith. 1957. Studies of respiratory physiology in the newborn infant. III. Measurements of mechanics of respiration. *J.Clin.Invest.* 36:440-448.

114. Gaultier, C. I. 1989. Lung volumes in neonates and infants. *Eur.J.Respir.Dis.Suppl.* 4:130S-134S.

115. Gaultier, C., M. Boule, Y. Allaire, A. Clement, and F. Girard. 1979. Growth of lung volumes during the first three years of life. *Bull.Eur.Physiopathol.Respir.* 15:1103-1116.

116. Hanrahan, J. P., I. B. Tager, R. G. Castile, M. R. Segal, S. T. Weiss, and F. E. Speizer. 1990. Pulmonary function measures in healthy infants. Variability and size correction. *Am.Rev.Respir.Dis.* 141:1127-1135.

117. Moriette, G., M. Chaussain, M. F. Radvanyi Bouvet, H. Walti, N. Pajot, and J. P. Relier. 1983. Functional residual capacity and sleep states in the premature newborn. *Biol.Neonate* 43:125-133.

118. Taussig, L. M., T. R. Harris, and M. D. Lebowitz. 1977. Lung function in infants and young children: functional residual capacity, tidal volume, and respiratory rats. *Am.Rev.Respir.Dis.* 116:233-239.

119. Tepper, R. S., W. J. Morgan, K. Cota, A. Wright, and L. M. Taussig. 1986. Physiologic growth and development of the lung during the first year of life. *Am.Rev.Respir.Dis.* 134:513-519.

120. Walti, H., G. Moriette, M. F. Radvanyi Bouvet, M. Chaussain, F. Morel Kahn, N. Pajot, and J. P. Relier. 1986. Influence of breathing pattern on functional residual capacity in sleeping newborn infants. *J Dev.Physiol* 8:167-172.

121. Emmanuel, G., W. A. Briscoe, and A. Cournand. 1960. A Method for the Determination of the Volume of Air in the Lungs: Measurements in Chronic Pulmonary Emphysema. *J.Clin.Invest.*329-337.

122. Suter, P. M., H. B. Fairley, and R. M. Schlobohm. 1975. Shunt, lung volume and perfusion during short periods of ventilation with oxygen. *Anesthesiology* 43:617-627.

123. Yuksel, B., A. Greenough, N. Chan, and R. Russell. 1993. Comparison of helium dilution and nitrogen washout measurements of functional residual capacity in premature infants. *Pediatr Pulmonology* 16:197-200.

124. Poets, C. F., G. A. Rau, M. Gappa, and J. Seidenberg. 1996. Comparison of heliox and oxygen as washing gases for the nitrogen washout technique in preterm infants. *Pediatr.Res.* 39:1099-1102.

125. McCoy KS, Castile RG, Allen ED, Filbrun DA, Flucke RL, Bar-Yishay E. 1995. Functional residual capacity (FRC) measurements by plethysmography and helium dilution in normal infants. Pediatr Pulmonol.19:282-290.

126. Tepper, R. S. and S. Asdell. 1992. Comparison of helium dilution and nitrogen washout measurements of functional residual capacity in infants and very young children. *Pediatr.Pulmonol.* 13:250-254.

127. Gaultier, C. L. 1989. Lung volumes in neonates and infants. *Eur.J.Respir.Dis.Suppl.* 4:130S-134S.

128. Gaultier, C. I., M. Boule, Y. Allaire, A. Clement, and F. Girard. 1979. Growth of lung volumes during the first three years of life. *Bull.Eur.Physiopathol.Respir.* 15:1103-1116.

129. De Muth, G. R. and W. F. Howatt. 1965. The growth of lung function: I lung volume. *Pediatrics* 35:162-176.

130. Krauss, A. N. and P. A. Auld. 1971. Pulmonary gas trapping in premature infants. *Pediatr.Res.* 5:10-16.

131. DuBois, A. B., S. Y. Botelho, and J. H. Comroe, Jr. 1955. A New Method for Measuring Airway Resistance in Man using a Body Plethysmograph: Values in Normal Subjects and in Patients with Respiratory Disease. *J.Clin.Invest.*327-335.

132. Roy, C. H., R. J. Barnes, M. F. Heath, and P. L. Sensky. 1992. A modified helium dilution technique for measuring small lung gas volumes. *J Dev.Physiol* 17:87-92.

133. Heldt, G. P. and R. M. Peters. 1978. A simplified method to determine functional residual capacity during mechanical ventilation. *Chest* 74:492-496.

134. Schulze, A., P. Schaller, A. Topfer, and H. Kirpalani. 1994. Measurement of functional residual capacity by sulfur hexafluoride in small-volume lungs during spontaneous breathing and mechanical ventilation. *Pediatr.Res.* 35:494-499.

135. Huygen, P. E., B. W. Feenstra, E. Hoorn, J. R. Jansen, and A. Zwart. 1991. PDPS: a pulmonary data processing system for assessment of gas exchange properties by multiple gas wash-out. *Comput.Methods Programs Biomed.* 36:223-235.

136. Fowler, W. W., E. R. Cornish, Jr., and S. S. Kety. 1952. VIII. Analysis of alveolar ventilation by pulmonary N2 clearance curves. *J Clin.Invest.* 31:40-50.

137. Bouhuys, A. 1963. Pulmonary nitrogen clearance in relation to age in healthy males. *J.Appl.Physiol.* 18:297-300.

138. Huygen, P. E., I. Gultuna, C. Ince, A. Zwart, J. M. Bogaard, B. W. Feenstra, and H. A. Bruining. 1993. A new ventilation inhomogeneity index from multiple breath. *Crit Care Med.* 21:1149-1158.

139. Cournand, A., R. C. Darling, J. S. Mansfield, and D. W. J. Richards. 1940. Studies on the intrapulmonary mixture of gases. II. Analysis of the rebreathing method (closed circuit) for measuring residual air. *J.Clin.Invest.* 19:599-608.

140. Gothard, J. W., C. M. Busst, M. A. Branthwaite, N. J. H. Davies, and D. M. Denison. 1980. Applications of respiratory mass spectrometry to intensive care. *Anaesthesia* 35:890-895.

141. Sivan, Y., T. W. Deakers, and C. J. Newth. 1990. Functional residual capacity in ventilated infants and children. *Pediatr.Res.* 28:451-454.

142. Shinozaki, T., J. C. J. Abajian, B. S. Tabakin, and J. S. Hanson. 1966. Theory and clinical application of a digital nitrogen washout computer. *J.Appl.Physiol.* 21:202-208.

143. Brunner, J. X., G. Wolff, G. Cumming, and H. Langenstein. 1985. Accurate measurement of N2 volumes during N2 washout requires dynamic adjustment of delay time. *J.Lab.Physiol.* 59:1008-1012.

144. Robertson, J. S., W. E. Siri, and H. B. Jones. 1950. Lung ventilation patterns determined by analysis of nitrogen elimination: use of mass spectrometer as a continuous gas analyzer. *J.Clin.Invest.* 29:577-590.

145. Kety, S. S. 1951. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol.Rev.* 3:1-41.

146. Darling, R. C., A. Cournand, J. S. Mansfield, and D. W. J. Richards. 1940. Studies on the intrapulmonary mixture of gases. I. Nitrogen elimination from blood and body tissues during high oxygen breathing. *J.Clin.Invest.* 19:591-597.

147. Cournand, A., E. D. Baldwin, R. C. Darling, and D. W. J. Richards. 1941. Studies on intrapulmonary mixture of gases. IV. the significance of the pulmonary emptying rate and a simpliefied open circuit measurements of residual air. *J.Clin.Invest.*-681.

148. 2002. Wissentschaftliche Tabellen, Documenta Geigy, 7th ed. Geigy, Basel. 246.

149. 1962. U.S. Standard Atmosphere US Government Printing Office, Washington D.C.

150. Sjoqvist, B. A., K. Sandberg, O. Hjalmarson, and T. Olsson. 1984. Calculation of lung volume in newborn infants by means of a computer-assisted nitrogen washout method. *Pediatr.Res.* 18:1160-1164.

151. Gerhardt, T., D. Hehre, E. Bancalari, and H. Watson. 1985. A simple method for measuring functional residual capacity by N2 washout in small animals and newborn infants. *Pediatr.Res.* 19:1165-1169.

152. Sivan, Y., T. W. Deakers, and C. J. Newth. 1990. An automated bedside method for measuring functional residual capacity by N2 washout in mechanically ventilated children. *Pediatr.Res.* 28:446-450.

153. Kraemer, R., M. Zehnder, and B. Meister. 1986. Intrapulmonary gas distribution in healthy children. *Respir.Physiol.* 65:127-137.

154. Ibanez, J., J. M. Raurich, and S. G. Moris. 1982. A simple method for measuring the effect of PEEP on functional residual capacity during mechanical ventilation. *Crit.Care Med.* 10:332-334.

155. Paloski, W. H., J. C. Newell, D. G. Gisser, H. H. Stratton, S. J. Annest, M. E. Gottlieb, and D. M. Shah. 1981. A system to measure functional residual capacity in critically ill patients. *Crit.Care Med.* 9:342-346.

156. Richardson, P., M. L. Wyman, and A. L. Jung. 1980. Functional residual capacity and severity of respiratory distress syndrome in infants. *Crit.Care Med.* 8:637-640.

157. Schoene, R. B., D. J. Pierson, and J. Butler. 1981. Constancy of functional residual capacity in the supine position during hypoxia and hyperoxic hypercapnia. *Am.Rev.Respir.Dis.* 124:508-510.

158. Nunn, J. F., E. J. M. Campbell, and B. W. Peckett. 1959. Anatomical subdivisions of the volume of respiratory dead space and effect of position of the jaw. *J.Appl.Physiol.* 14:174-176.

159. Numa, A. H. and C. J. Newth. 1996. Anatomic dead space in infants and children. *J.Appl.Physiol.* 80:1485-1489.

160. Gerhardt, T., L. Reifenberg, D. Hehre, R. Feller, and E. Bancalari. 1986. Functional residual capacity in normal neonates and children up to 5 years of age determined by a N2 washout method. *Pediatr.Res.* 20:668-671.

161. Gappa, M., M. E. Fletcher, C. A. Dezateux, and J. Stocks. 1993. Comparison of nitrogen washout and plethysmographic measurements of lung volume in healthy infants. *Am.Rev.Respir.Dis.* 148:1496-1501.

162. Mitchell, R. R., R. M. Wilson, L. Holzapfel, A. M. Benis, D. Sierra, and J. J. Osborn. 1982. Oxygen wash-in method for monitoring functional residual capacity. *Crit.Care Med.* 10:529-533.

163. Lanteri, C. J., J. M. Raven, and P. D. Sly. 1990. Should TGV be measured from end-inspiratory occlusions rather than end-expiratory occlusions in wheezy infants? *Pediatr.Pulmonol.* 9:214-219.

164. DuBois, A. B., S. Y. Botelho, G. N. Bedell, R. Marshall, and J. H. Comroe, Jr. 1955. A Rapid Plethysmographic Method for Measuring Thoracic Gas Volume: A Comparison with a Nitrogen Washout Method for Measuring Functional Residual Capacity in Normal Subjects. *J.Clin.Invest.*322-326.

165. Desmond, K. J., D. L. Demizio, P. D. Allen, P. H. Beaudry, and A. L. Coates. 1988. An alternate method for the determination of functional residual capacity in a plethysmograph. *Am.Rev.Respir.Dis.* 137:273-276.

166. Coates, A. L., K. J. Desmond, and D. L. Demizio. 1995. The simplified version of Boyle's Law leads to errors in the measurement of thoracic gas volume. *Am.J Respir.Crit Care Med.* 152:942-946.

167. Stanescu, D. C., D. Rodenstein, M. Cauberghs, and K. P. Van de Woestijne. 1982. Failure of body plethysmography in bronchial asthma. *J.Appl.Physiol.* 52:939-948.

168. Rodenstein, D. O., D. C. Stanescu, and C. Francis. 1982. Demonstration of failure of body plethysmography in airway obstruction. *J.Appl.Physiol.* 52:949-954.

169. Shore, S. A., O. Huk, S. Mannix, and J. G. Martin. 1983. Effect of panting frequency on the plethysmographic determination of thoracic gas volume in chronic obstructive pulmonary disease. *Am.Rev.Respir.Dis.* 128:54-59.

170. Rodenstein, D. O. and D. C. Stanescu. 1983. Frequency dependence of plethysmographic volume in healthy and asthmatic subjects. *J.Appl.Physiol.* 54:159-165.

171. Godfrey, S., C. S. Beardsmore, C. Maayan, and E. Bar Yishay. 1986. Can thoracic gas volume be measured in infants with airways obstruction? *Am.Rev.Respir.Dis.* 133:245-251.

172. Helms, P. 1982. Problems with plethysmographic estimation of lung volume in infants and young children. *J.Appl.Physiol.* 53:698-702.

173. Rodenstein, D. O., C. Francis, and D. C. Stanescu. 1983. Airway closure in humans does not result in overestimation of plethysmographic lung volume. *J.Appl.Physiol.* 55:1784-1789.

174. LeSouef, P. N., J. M. Lopes, S. J. England, M. H. Bryan, and A. C. Bryan. 1983. Influence of chest wall distortion on esophageal pressure. *J.Appl.Physiol.* 55:353-358.

175. Coates, A. L., G. M. Davis, P. Vallinis, and E. W. Outerbridge. 1989. Liquid-filled esophageal catheter for measuring pleural pressure in preterm neonates. *J.Appl.Physiol.* 67:889-893.

176. Castile, R. G. and R. Brown. 1986. More problems with Boyle's Law - or, "Vtg or not Vtg, that is the question". *Am.Rev.Respir.Dis.* 133:184-185.

177. Mead, J. 1960. Volume displacement body plethysmography for respiratory measurements in human subjects. *J.Appl.Physiol.* 15:736-740.

178. Stocks, J., F. Marchal, R. Kraemer, P. Gutkowski, E. Bar-Yishay, and S. Godfrey 1996. Plethysmographic assessment of functional residual capacity and airway resistance. In J. Stocks, P. D. Sly, R. S. Tepper, and W. J. Morgan, editors Infant Respiratory Function Testing John Wiley and Sons, New York. 190-240.

179. Stocks, J. and M. E. Fletcher. 1991. On the effect of the thermodynamics of an infant plethysmograph on the measurement of thoracic gas volume [letter; comment]. *Pediatr.Pulmonol.* 10:63-64.

180. Peslin, R. 1984. Body plethysmography. Techniques in the Life Sciences, Respiratory Physiology,414 ed. Elsevier Scientific Publishers, County Clare Ireland. 1-26.

181. Bates, J. H. 1989. Correcting for the thermodynamic characteristics of a body plethysmograph. *Ann.Biomed.Eng.* 17:647-655.

182. Coates, A. L., K. J. Desmond, D. Demizio, P. D. Allen, and P. H. Beaudry. 1988. Sources of error in flow-volume curves. Effect of expired volume measured at the mouth vs that measured in a body plethysmograph. *Chest* 94:976-982.

183. Peslin, R., C. Gallina, and M. Rotger. 1987. Methodological factors in the variability of lung volume and specific airway resistance measured by body plethysmography. *Bull.Eur.Physiopathol.Respir.* 23:323-327.

184. Zarins, L. P. and J. L. Clausen 1982. Body Plethysmography. In J. L. Clausen, editor Pulmonary Function Testing Guidelines and Controversies. Equipment, methods, and normal values,1 ed. Academic Press, New York. 141-153.

185. Clausen, J. L. and L. Powell Zarins 1982. Estimation of Lung Volumes from Chest Radiographs. In J. L. Clausen, editor Pulmonary Function Testing Guideline and Controversies, Equipment, Methods, and Normal Values,1 ed. Academic Press,Inc., New York. 155-163.

186. Stocks, J., N. M. Levy, and S. Godfrey. 1977. A new apparatus for the accurate measurement of airway resistance in infancy. *J.Appl.Physiol.* 43:155-159.

187. Marchal, F., C. Duvivier, R. Peslin, P. Haouzi, and J. P. Crance. 1991. Thoracic gas volume at functional residual capacity measured with an integrated-flow plethysmograph in infants and young children. *Eur.Respir.J.* 4:180-187.

188. Stocks, J. and S. Godfrey. 1977. Specific airway conductance in relation to postconceptional age during infancy. *J.Appl.Physiol.* 43:144-154.

189. Sly, P. D., C. J. Lanteri, and J. H. Bates. 1990. Effect of the thermodynamics of an infant plethysmograph on the measurement of thoracic gas volume. *Pediatr.Pulmonol.* 8:203-208.

190. Stocks, J., U. Nothen, P. Sutherland, D. J. Hatch, and P. Helms. 1987 Improved accuracy of the occlusion technique for assessing total respiratory compliance in infants. *Pediatr.Pulmonol.* 3:71-77.

191. Dezateux, C., Stocks J, A. M. Wade, I. Dundas, and M. E. Fletcher. 2001 Airway function at one year: association with premorbid airway function, wheezing and maternal smoking. *Thorax.* 56:680-686

192. Prechtl, H. F. 1974. The behavioural states of the newborn infant (a review). *Brain Res* 76:185-212.

193. Mallol, J., M. E. Hibbert, C. F. Robertson, A. Olinsky, P. D. Phelan, and P. D. Sly. 1988. Inherent variability of pulmonary function tests in infants with bronchiolitis. *Pediatr.Pulmonol.* 5:152-157.

194. Beardsmore, C. S., U. M. MacFadyen, S. S. Moosavi, S. P. Wimpress, J. Thompson, and H. Simpson. 1989. Measurement of lung volumes during active and quiet sleep in infants. *Pediatr.Pulmonol.* 7:71-77.

195. Barnhard, H. J., J. A. Pierce, J. W. Joyce, and J. H. Bates. 1960. Roentgenographic Determination of Total Lung Capacity, A New Method Evaluated in Health, Emphysema and Congestive Heart Failure. *Amer.J Med.* 28:51-60.

196. Loyd, H. M., T. String, and A. B. DuBois. 1966. Radiographic and Plethysmographic Determination of Total Lung Capacity. *Radiology* 86:7-14.

197. Pratt, P. C. and G. A. Klugh. 1967. A Method for the Determination of Total Lung Capacity from Posteroanterior and Lateral chest Roentgenograms. *Am.Rev.Respir.Dis.* 96:548-552.

198. Harris, T. R., P. C. Pratt, and K. H. Kilburn. 1971. Total lung capacity measured by roentgenograms. *Am.J Med.* 50:756-763.

199. Pierce, R. J., D. J. Brown, M. Holmes, G. Cumming, and D. M. Denison. 1979. Estimation of lung volumes from chest radiographs using shape information. *Thorax* 34:726-734.

200. Bush, A. and D. M. Denison. 1986. Use of different magnification factors to calculate radiological lung volumes. *Thorax* 41:158-159.

201. Rodenstein, D. O., T. Sopwith, D. M. Denison, and D. C. Stanescu. 1985. Reevaluation of the radiographic method for measurement of total lung capacity. *Bull.Eur.Physiopathol.Respir.* 21:521-525.

202. Ries, A. L., J. L. Clausen, and P. J. Friedman. 1979. Measurement of lung volumes from supine portable chest radiographs. *J.Appl.Physiol.* 47:1332-1335.

203. Block, A. J., C. M. Bush, C. White, P. G. Boysen, J. W. Wynne, and V. C. Taasan. 1981. A radiographic method for measuring steady-state functional residual capacity in the supine patient. A method suitable for sleep studies. *Am.Rev.Respir.Dis.* 124:330-332.

204. Fumey, M. H., B. G. Nickerson, M. Birch, R. McCrea, and L. C. Kao. 1992. A radiographic method for estimating lung volumes in sick infants. *Pediatr.Pulmonol.* 13:42-47.

205. Salam, H. and W. J. Warwick. 1978. Measurement of total lung capacity by a roentgenography- planimetry method in children 4-16 years of age. *Respiration* 36:177-182.

206. Cann, C. E. 1987. Quantitative CT applications: comparison of current scanners [published erratum appears in Radiology 1987 Sep;164(3):879]. *Radiology* 162:257-261.

207. Crapo, R. O., T. Montague, and J. D. Armstrong. 1979. Inspiratory lung volume achieved on routine chest films. *Invest.Radiol.* 14:137-140.

208. Kilburn, K. H., R. H. Warshaw, J. C. Thornton, K. Thornton, and A. Miller. 1992. Predictive equations for total lung capacity and residual volume calculated from radiographs in a random sample of the Michigan population. *Thorax* 47:519-523.

209. Barret, W. A., P. D. Clayton, and G. R. Lambson. 1976. Computerized roentgenographic determination of total lung capacity. *Am.Rev.Respir.Dis.* 113:239-244.

210. Gaultier, C., M. E. Fletcher, C. Beardsmore, E. Motoyama, and J. Stocks 1996. Measurement conditions. In J. Stocks, P. D. Sly, R. S. Tepper, and W. J. Morgan, editors Infant Respiratory Function Testing John Wiley and Sons, New York. 29-44.

211. Degroodt, E. G., P. H. Quanjer, M. E. Wise, and B. C. Van Zomeren. 1986. Changing relationships between stature and lung volumes during puberty. *Respir.Physiol.* 65:139-153.

212. Borsboom, G. J., W. van Pelt, and P. H. Quanjer. 1993. Pubertal growth curves of ventilatory function: relationship with childhood respiratory symptoms. *Am.Rev.Respir.Dis.* 147:372-378.

213. Nelson, N. M., L. S. Prod'Hom, R. B. Cherry, P. J. Lipsitz, and C. A. Smith. 1963. Pulmonary Function in the newborn infant, V. Trapped gas in the normal infant's lung. *J.Clin.Invest.* 42:1850-1857.

214. Doershuk, C. F. and L. W. Matthews. 1969. Airway resistance and lung volume in newborn infants. *Pediatr.Res.* 3:128-134.

215. Doershuk, C. F., T. D. Downs, L. W. Matthews, and M. D. Lough. 1970. A method for ventilatory measurements in subjects 1 month--5 years of age: Normal results and observations in disease. *Pediatr.Res.* 4:165-174.

216. Hatch, D. J. and B. W. Taylor. 1976. Thoracic gas volume in early childhood. *Arch.Dis.Child* 51:859-864.

217. Phelan, J. A. and H. E. Williams. 1969. Ventilatory studies in healthy infants. *Pediatr.Res.* 3:425-432.

218. Greenough, A., J. Stocks, U. Nothen, and P. Helms. 1986. Total respiratory compliance and functional residual capacity in young children. *Pediatr.Pulmonol.* 2:321-326.

219. Greenough, A., M. F. Hird, L. Everett, and J. F. Price. 1991. Importance of using lung function regression equations appropriate for ethnic origin. *Pediatr Pulmonol.* 11:207-211.

220. Taussig, L. M., V. Chernick, R. Wood, P. A. Farrell, and R. B. Mellins. 1980. Standardization of lung function testing in children. Proceedings and Recommendations of the GAP Conference Committee, Cystic Fibrosis Foundation. *J Pediatr.* 97:668-676.

221. Quanjer, P. H., J. Stocks, G. Polgar, M. Wise, J. Karlberg, and G. J. Borsboom. 1989. Compilation of reference values for lung function measurements in children. *Eur.J.Respir.Dis.Suppl.* 2:184S-261S.

222. Hibbert, M. E., A. Lannigan, L. I. Landau, and P. D. Phelan. 1989. Lung function values from a longitudinal study of healthy children and adolescents [published erratum appears in Pediatr Pulmonol 1990;8(1):68]. *Pediatr.Pulmonol.* 7:101-109.

223. Hopper, J. L., M. E. Hibbert, G. T. Macaskill, P. D. Phelan, and L. I. Landau. 1991. Longitudinal analysis of lung function growth in healthy children and adolescents. *J.Appl.Physiol.* 70:770-777.

224. Pattishall, E. N., R. W. Helms, and G. L. Strope. 1989. Noncomparability of cross-sectional and longitudinal estimates of lung growth in children. *Pediatr.Pulmonol.* 7:22-28.

225. Sherrill, D. L., M. Lebowitz, R. Knudson, and B. Burrows. 1992. Continuous longitudinal regression equations for pulmonary function measures. *Eur.Respir.J.* 5:452-462.

226. Polgar, G. and V. Promadhat. 1971. Pulmonary function testing in children: Techniques and standards W.B.Saunders Co.

227. Weng, T. R. and H. Levison. 1969. Standards of pulmonary function in children. *Am.Rev.Respir.Dis.* 99:879-894.

228. Cook, C. D. and J. F. Hamann. 1961. Relation of lung volumes to height in healthy persons between the ages of 5 and 38 years. *J Pediatr.* 59:710-714.

229. Zapletal, A., T. Paul, and M. Samanek. 1977. [Significance of contemporary methods of lung function testing for the detection of airway obstruction in children and adolescents (author's transl)]. *Z.Erkr.Atmungsorgane.* 149:343-371.

230. Cogswell, J. J., D. Hull, A. D. Milner, A. P. Norman, and B. Taylor. 1975. Lung function in childhood. 2. Thoracic gas volumes and helium functional residual capacity measurements in healthy children. *Br.J Dis.Chest* 69:118-124.

231. Quanjer, P. H. 1983. Standardized lung function testing. Report Working Party Standardization of Lung Function Tests. *Bull.Eur.Physiopathol.Respir.* 19, Suppl.5:1-95.

232. Tierney, D. F. and J. A. Nadel. 1962. Concurrent measurements of functional residual capacity by three methods. *J.Appl.Physiol.* 17(6):871-873.

233. Woitowitz, H. J., F. W. Buchheim, and R. Woitowitz. 1967. On the theory and praxis of total body plethysmography in the lung function analysis. *Prax.Pneumol.* 8:449-471.

234. Cotes, J. E. 1993. Lung function. In J. E. Cotes, editor Lung function: Assessment and application in medicine,5th ed. Blackwell Scientific Publications, Oxford.

235. Yang, T. S., J. Peat, V. Keena, P. M. Donnelly, W. Unger, and A. Woolcock. 1991. A review of the racial differences in the lung function of normal Caucasian, Chinese and Indian subjects. *Eur.Respir.J.* 4:872-880.

236. Lapp, N. L., H. E. Amandus, R. Hall, and W. K. Morgan. 1974. Lung volumes and flow rates in black and white subjects. *Thorax* 29:185-188.

237. Lanese, R. R., M. D. Keller, M. F. Foley, and E. H. Underwood. 1978. Differences in pulmonary function tests among whites, blacks, and American Indians in a textile company. *J Occup.Med.* 20:39-44.

238. American Thoracic Society. 1991. Lung function testing: selection of reference values and interpretative strategies. *Am.Rev.Respir Dis.* 144:1202-1218.

239. Robience, Y., J. C. Yernault, P. Libert, M. Denaut, J. L. Halloy, and M. Richez. 1978. [Regional lung function in coal workers (author's transl)]. *Bull.Eur.Physiopathol.Respir.* 14:23-30.

.

240. Hankinson, J. L. and K. M. Bang. 1991. Acceptability and reproducibility criteria of the American Thoracic Society as observed in a sample of the general population. *Am.Rev.Respir Dis.* 143:516-521.

241. Gold, P. M. and D. W. Schwesinger 1980. Pulmonary laboratory infection control and safety. In J. Clausen, editor Pulmonary Function Testing, Guidelines and Controversies, Acedemic Press, New York, NY. 15.

242. Hazaleus, R. F., J. Cole, and M. Berdischewsky. 1980. Tuberculine skin testing conversion from exposure to contaminated pulmonary function testing apparatus. *Respiratory Care* 26:53-55.

243. Rutala, D. R., W. A. Rutala, D. J. Weber, and C. A. Thomann. 1991. Infection risks associated with spirometry. *Infect.Control Hosp.Epidemiol.* 12:89-92.

244. Friedland, G. H. and R. S. Klein. 1987. Transmission of the human immunodeficiency virus. *N.Engl.J Med.* 317:1125-1135.

245. Groopman, J. E., S. Z. Salahuddin, M. G. Sarngadharan, P. D. Markham, M. Gonda, A. Sliski, and R. C. Gallo. 1984. HTLV-III in saliva of people with AIDS-related complex and healthy homosexual men at risk for AIDS. *Science* 226:447-449.

246. Hendley, J. O., R. P. Wenzel, and J. M. J. Gwaltneyu. 1971. Transmission of rhinovirus colds by self-inoculation. *N.Engl.J Med.* 288:1361-1364.

247. Dick, E. C., L. C. Jennings, K. A. Mink, C. D. Wartgow, and S. L. Inhorn. 1987. Aerosol transmission of rhinovirus colds. *J Infect.Dis.* 156:442-448.

248. Hall, C. B. and R. G. J. Douglas. 1981. Modes of transmission of respiratory syncytial virus. *J Pediatr.* 99:100-103.

249. Remington, P. L., W. N. Hall, I. H. Davis, A. Herald, and R. A. Gunn. 1985. Airborne transmission of measles in a physician's office. *JAMA* 253:1574-1577.

250. Menzies, D., A. Fanning, L. Yuan, and M. Fitzgerald. 1995. Tuberculosis among health care workers. *N.Engl.J Med.* 332:92-98.

251. Guimond, V. J. and N. N. Gibson. 1990. Effect of inline filters on spirometry. *Canadian Journal of Respiratory Therapy* 26:9-11.

252. Johns, D. P., C. Ingram, H. Booth, T. J. Williams, and E. H. Walters. 1995. Effect of a microaerosol barrier filter on the measurement of lung function. *Chest* 107:1045-1048.

253. Denison, D. M., D. S. Cramer, and P. J. Hanson. 1989. Lung function testing and AIDS. *Respir Med.* 83:133-138.

254. 1987. Recommended infection-control practices for dentistry. Dental Disease Prevention Activity, Center for Prevention Svcs, Hospital Infections Program, Center for Infectious Diseases, CDC. *N.Y.J Dent.* 57:170-3, 197.

255. Spach, D. H., F. E. Silverstein, and W. E. Stamm. 1993. Transmission of infection by gastrointestinal endoscopy and bronchoscopy. *Ann.Intern.Med.* 118:117-128.

256. Moller, J. T., T. Pedersen, L. S. Rasmussen, P. F. Jensen, B. D. Pedersen, O. Ravlo, N. H. Rasmussen, K. Espersen, N. W. Johannessen, J. B. Cooper, et al. 1993. Randomized evaluation of pulse oximetry in 20,802 patients: I. Design, demography, pulse oximetry failure rate, and overall complication rate. *Anesthesiology* 78:436-444.

257. Nakayama, D. K., R. Mutich, and E. K. Motoyama. 1992. Pulmonary dysfunction after primary closure of an abdominal wall defect and its improvement with bronchodilators. *Pediatr.Pulmonol.* 12:174-180.

258. Nakayama, D. K., E. K. Motoyama, and E. M. Tagge. 1991. Effect of preoperative stabilization on respiratory system compliance and outcome in newborn infants with congenital diaphragmatic hernia. *J Pediatr.* 118:793-799.

259. Heaf, D. P., J. Belik, A. R. Spitzer, M. H. Gewitz, and W. W. Fox. 1982. Changes in pulmonary function during the diuretic phase of respiratory distress syndrome. *J Pediatr.* 101:103-107.

260. Goldsmith, L. S., J. S. Greenspan, S. D. Rubenstein, M. R. Wolfson, and T. H. Shaffer. 1991. Immediate improvement in lung volume after exogenous surfactant: alveolar recruitment versus increased distention. *J Pediatr.* 119:424-428.

261. Richardson, P., C. L. Bose, and J. R. Carlstrom. 1986. The functional residual capacity of infants with respiratory distress syndrome. *Acta Paediatr.Scand.* 75:267-271.

262. Richardson, C. P. and A. L. Jung. 1978. Effects of continuous positive airway pressure on pulmonary function and blood gases of infants with respiratory distress syndrome. *Pediatr.Res.* 12:771-774.

263. Yuksel, B. and A. Greenough. 1991. Relationship of symptoms to lung function abnormalities in preterm infants at follow-up. *Pediatr.Pulmonol.* 11:202-206.

264. Kraemer, R. 1989. Early detection of lung function abnormalities in infants with cystic fibrosis. *J R.Soc.Med.* 82 Suppl 16:21-25.

265. Kraemer, R. 1993. Whole-body plethysmography in the clinical assessment of infants with bronchopulmonary diseases. *Respiration* 60:1-8.

266. Hiatt, P. W., H. Eigen, P. Yu, and R. S. Tepper. 1988. Bronchodilator responsiveness in infants and young children with cystic fibrosis. *Am.Rev.Respir.Dis.* 137:119-122.

267. LeSouef, P. N., R. Castile, E. Motoyama, D. Turner, and W. Morgan 1996. Forced Expiratory Maneuvers. In J. Stocks, P. D. Sly, R. S. Tepper, and W. J. Morgan, editors Infant Respiratory Function Testing John Wiley and Sons, New York. 379-410.

268. Henry, R. L., A. D. Milner, G. M. Stokes, I. G. Hodges, and R. C. Groggins. 1983. Lung function after acute bronchiolitis. *Arch.Dis.Child* 58:60-63.

269. Seidenberg, J., I. B. Masters, I. Hudson, A. Olinsky, and P. D. Phelan. 1989. Disturbance in respiratory mechanics in infants with bronchiolitis. *Thorax* 44:660-667.

270. Andreasson, B., M. Lindroth, W. Mortensson, N. W. Svenningsen, and B. Jonson. 1989. Lung function eight years after neonatal ventilation. *Arch.Dis.Child* 64:108-113.

271. Coates, A. L., H. Bergsteinsson, K. J. Desmond, E. W. Outerbridge, and P. H. Beaudry. 1977. Long-term pulmonary sequelae of premature birth with and without idiopathic respiratory distress syndrome. *J Pediatr.* 90:611-616.

272. Mansell, A. L., J. M. Driscoll, and L. S. James. 1987. Pulmonary follow-up of moderately low birth weight infants with and without respiratory distress syndrome. *J Pediatr.* 110:111-115.

273. Smyth, J. A., E. Tabachnik, W. J. Duncan, B. J. Reilly, and H. Levison. 1981. Pulmonary function and bronchial hyperreactivity in long-term survivors of bronchopulmonary dysplasia. *Pediatrics* 68:336-340.

274. Northway, W. H. J., R. B. Moss, K. B. Carlisle, B. R. Parker, R. L. Popp, P. T. Pitlick, I. Eichler, R. L. Lamm, and B. W. J. Brown. 1990. Late pulmonary sequelae of bronchopulmonary dysplasia [see comments]. *N.Engl.J Med.* 323:1793-1799.

275. Newth, C. J., M. Stretton, T. W. Deakers, and J. Hammer. 1997. Assessment of pulmonary function in the early phase of ARDS in pediatric patients. *Pediatr Pulmonol.* 23:169-175.

276. Ross, L. A., W. H. Mason, J. Lanson, T. W. Deakers, and C. J. Newth. 1992. Laryngotracheobronchitis as a complication of measles during an urban epidemic. *J Pediatr* 121:511-515.

277. Greenough A, Everett L, Pool J, Price JF. 1991 A 2-year longitudinal study of lung hyperinflation in young asthmatics. Respir Med. 85: 379-382.

278. Begin, R., M. A. Bureau, L. Lupien, and B. Lemieux. 1980. Control and modulation of respiration in Steinert's myotonic dystrophy. *Am.Rev.Respir.Dis.* 121:281-289.

279. Gilgoff, I. S., E. Kahlstrom, E. MacLaughlin, and T. G. Keens. 1989. Long-term ventilatory support in spinal muscular atrophy. *J Pediatr.* 115:904-909.

280. Smith, P. E., P. M. Calverley, and R. H. Edwards. 1988. Hypoxemia during sleep in Duchenne muscular dystrophy. *Am.Rev.Respir.Dis.* 137:884-888.

281. Buist, A. S., B. E. Adams, A. H. Azzam, and G. J. Sexton. 1980. Pulmonary function in young children with alpha 1-antitrypsin deficiency: comparison with matched control subjects. *Am.Rev.Respir.Dis.* 122:817-822.

282. Hird, M. F., A. Greenough, G. Mieli-Vergani, and A. P. Mowat. 1991. Hyperinflation in children with liver disease due to alpha-1- antitrypsin deficiency. *Pediatr.Pulmonol.* 11:212-216.

283. Lindmark, B. E., M. J. Arborelius, and S. G. Eriksson. 1990. Pulmonary function in middle-aged women with heterozygous deficiency of the serine protease inhibitor alpha 1- antichymotrypsin. *Am.Rev.Respir.Dis.* 141:884-888.

284. Lands, L. C., S. Woods, C. Katsardis, K. J. Desmond, and A. L. Coates. 1991. The effects of diuresis and transfusion on pulmonary function in children with thalassemia major. *Pediatr.Pulmonol.* 11:340-344.

285. Dykstra BJ, Scalon PD, Kester MM, Beck KC, Enright PL. 1999 Lung volumes in 4,774 patients with obstructive lung disease.Chest. 115: 68-74.

286. Begin, P. and A. Grassino. 1991. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease [see comments]. *Am.Rev.Respir.Dis.* 143:905-912.

287. Chrystyn, H., B. A. Mulley, and M. D. Peake. 1988. Dose response relation to oral theophylline in severe chronic obstructive airways disease. *BMJ.* 297:1506-1510.

288. Schwartz, D. A., R. K. Merchant, R. A. Helmers, S. R. Gilbert, C. S. Dayton, and G. W. Hunninghake. 1991. The influence of cigarette smoking on lung function in patients with idiopathic pulmonary fibrosis. *Am.Rev.Respir.Dis.* 144:504-506.

289. Owens, M. W., G. T. Kinasewitz, and W. M. Anderson. 1987. Clinical significance of an isolated reduction in residual volume. *Am.Rev.Respir Dis.* 136:1377-1380.

290. Dalavanga, Y. A., S. H. Constantopoulos, V. Galanopoulou, L. Zerva, and H. M. Moutsopoulos. 1991. Alveolitis correlates with clinical pulmonary involvement in primary Sjogren's syndrome. *Chest* 99:1394-1397.

291. Chinet, T., F. Jaubert, D. Dusser, C. Danel, J. Chretien, and G. J. Huchon. 1990. Effects of inflammation and fibrosis on pulmonary function in diffuse lung fibrosis. *Thorax* 45:675-678.

292. Johnson, M. A., S. Kwan, N. J. Snell, A. J. Nunn, J. H. Darbyshire, and M. Turner-Warwick. 1989. Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. *Thorax* 44:280-288.

293. Ferris, B. G. 1978. Recommended Standardized Procedures for Pulmonary Function Testing. *Am.Rev.Respir.Dis.* 118(6):55-88.

294. Epler, G. R., T. C. McLoud, E. A. Gaensler, J. P. Mikus, and C. B. Carrington. 1978. Normal chest roentgenograms in chronic diffuse infiltrative lung disease. *N.Engl.J Med.* 298:934-939.

295. Kaminsky, D. A. and C. G. Irvin. 1993. Anatomic correlates of reversible restrictive lung disease. *Chest* 103:928-931.

296. Demedts, M. and J. Aumann. 1988. Early emphysema. Ten years' evolution. *Chest* 94:337-342.

297. McFadden, E. R. J. 1975. Exertional dyspnea and cough as preludes to acute attacks of bronchial asthma. *N.Engl.J Med.* 292:555-559.

298. Bedell, G. N., R. Marshall, A. B. DuBois, and J. H. Comroe, Jr. 1956. Plethysmographic determination of gas trapped in the lungs. *J.Clin.Invest.* 35:664-670.

299. Pride, N. B., C. E. Barter, and P. Hugh-Jones. 1973. The ventilation of bullae and the effect of their removal on thoracic gas volumes and tests of over-all pulmonary function. *Am.Rev.Respir.Dis.* 107:83-98.

300. Miller, J. M. and R. L. Johnson, Jr. 1966. Effect of lung inflation on pulmonary diffusing capacity at rest and exercise. *J.Clin.Invest.* 45:493-500.

301. Stam, H., B. A. van den, K. Grunberg, T. Stijnen, H. A. Tiddens, and A. Versprille. 1996. Pulmonary diffusing capacity at reduced alveolar volumes in children. *Pediatr Pulmonol.* 21:84-89.

302. Stam, H., V. Hrachovina, T. Stijnen, and A. Versprille. 1994. Diffusing capacity dependent on lung volume and age in normal subjects. *J Appl.Physiol* 76:2356-2363.

303. Quanjer, P. H. 1996. A step forward in clinically evaluating gas transfer in the lung. *Pediatr Pulmonol.* 21:75-76.

304. Briscoe, W. A. and A. B. DuBois. 1958. The relationship between airway resistance, airway conductance and lung volume in subjects of different age and body size. *J.Clin.Invest.* 98:812-815.

305. Butler, J., C. G. Caro, Alcala, and A. B. DuBois. 1959. Physiological factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease. *J.Clin.Invest.* 29(4):584-591.

306. Smith, H. R., C. G. Irvin, and R. M. Cherniack. 1992. The utility of spirometry in the diagnosis of reversible airways obstruction. *Chest* 101:1577-1581.

307. Kanengiser, L. C., D. M. Rapoport, H. Epstein, and R. M. Goldring. 1989. Volume adjustment of mechanics and diffusion in interstitial lung disease. Lack of clinical relevance. *Chest* 96:1036-1042.

308. Morris MG, Gustafsson P, Tepper R, Gappa M, Stocks J. 2001 Standards for infant respiratory function testing: The bias flow nitrogen washout technique for measuring the functional residual capacity. *Eur Respir J*.17:529-36.

309. Frey, U., Reinmann, B., and Stocks, J.1999. A standardized mechanical infant lung model to test infant lung function equipment. Am J Respir Crit Care Med 159, A478.

310. Frey U, Stocks J, Coates A, Sly P, Bates J. Standards for infant respiratory function testing: Specifications for equipment used for infant pulmonary function testing. *Eur Respir J* 2000;16:731-40.

311. Frey U, Stocks J, Sly P, Bates J. 2000. Specifications for signal processing and data handling used for infant pulmonary function testing. *Eur Respir J*. 16:1016-22.

312. Frey U, Reinmann B, Stocks J. 2001. Standards for infant respiratory lung function testing: The infant lung function model, a mechanical analog to test infant lung function equipment. *Eur Respir J*. 17:755-64.

313. Reinmann B, Stocks J, Frey U. 2001. Assessment of an infant whole-body plethysmograph using an infant lung function model. *Eur Respir J*. 17:765-72.

314. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. Standards for infant respiratory function testing: Plethysmographic measurements of lung volume and airway resistance. *Eur Respir J* 2001;17:302-12.

315. Spence DPS, Kelley YJ, Ahmed J, Calverley PMA, Pearson MG. 1995. Critical evaluation of computerized x ray planimetry for the measurement of lung volumes. Thorax. 50: 383-6.

316. Dimitrious G, Greenough A, Kavvadia V, Shute M, Karani J. A radiographic method for assessing lung area in neonates. The Brit J of Radiology 1999; 72; 335-8.

317. Gierada DS, Yusen RD, Pilgram TK,, Crouch L, Slone RM, Bae K, Lefrak SS, Cooper JD. 2001. Repeatability of quantitative CT indexes of emphysema in patients evaluated for lung volume reduction surgery. Radiology. 220: 448-454.

318. Brown MS, McNitt-Gray MF, Goldin JG, Greaser LE, Hayward UM, Sayre JW, Kamelo M, Aberle DR. 1999. Automated measurement of single and total lung volume from CT. J of Computer Assisted Tomographny. 23: 632-40.

319. Stocks J, Sly P, Morris MG, Frey U. Standards for infant respiratory function testing: What(ever) next? Eur Respir J 2000;16:581-4.

320. Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. 2001. Standards for infant respiratory function testing: Plethysmographic measurements of lung volume and airway resistance. Eur Respir.17:302-12.

321.. Pillow, J. J., Ljungberg, H., Hulskamp, G., Cantarella, A., Gustafsson, P.,Schibler, A., and Stocks, J. 2002. Comparable measurements of FRC in healthy infants using three techniques. Eur Respir J 20[Suppl 38], 20s..