Monitoring and Assessment of the Pulmonary Function in Ventilated Infants and Children

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Introduction

Respiratory monitoring is standard of care of ventilated children with respiratory failure. This by itself may be an indication for admission to a Pediatric Intensive Care Unit (PICU) equipped with modern technology since continuous monitoring has the potential for alerting the clinician for sudden deteriorations and thus allow for timely intervention.

The major goals of respiratory measurements and monitoring are:
1) to measure, continuously, ventilatory indices that enhance our understanding of the underlying pathophysiology, aid in diagnosis, and guide management;
2) to provide alarms that alert caregivers to a significant change in the patient's condition; and
3) to provide trends that assist in the assessment of the severity of the disease and the therapeutic response and prognosis. Hence, all patients with moderate to severe respiratory failure should be monitored for gas exchange and preferably also for respiratory mechanics.

Two main difficulties arise when assessing pulmonary functions in infants and small children:
a) Lack of co-operation: co-operation is required to perform many "adult-type" pulmonary function tests and can be achieved in children only after 6–7 years of age;
b) Small size of young patients: The latter is evident as small volumes and flow rates in absolute terms which necessitate the use of complex equipment and technique.

On the other hand, unique physiological and anatomical characteristics of the infant and the small child make certain methods of evaluation of the respiratory system possible mainly and almost exclusively in this age group (e.g. transcutaneous blood gas measurement, maximal expiratory flow rates, thoracoabdominal asynchrony in some clinical situations).

Therefore, monitoring of pediatric patients requires an individual and careful approach based on physical examination, non-invasive techniques and selective application of invasive measures.

D. Tibboel et al. (eds.), *Intensive Care in Childhood*

Clinical assessment of cyanosis and alveolar ventilation, and hence arterial oxygen and carbon dioxide tensions, is unreliable [1, 2]. Thus, precise assessment of ventilatory adequacy must be based on both clinical and laboratory studies, and much emphasis has had to be placed on arterial blood gases (or their indirect measurement) for help with both the diagnosis and management of respiratory failure. Recently, the incorporation of high speed microprocessors and personal computers has enabled the application of old, and the development of new, pulmonary function tests suitable for those unable to cooperate (e.g. infants, young children and patients who are under neuromuscular blockade and/or heavily sedated). This has allowed those involved in the care of such patients to make novel measurements of physiologic variables and reach new perspectives in both the assessment and management of respiratory failure.

This chapter reviews the options available today for the clinician in monitoring and evaluation of the function of the respiratory system in ventilated infants and children. Some of the methods, such as continuous non-invasive assessment of oxygen saturation, are standard of care while other techniques might be indicated only for specific patients because they are time consuming and require expensive equipment and skill. We believe that any intervention which provides more understanding of disease processes is expedient and justified, providing there is little or no deleterious effect on the patient.

Assessment of the Respiratory System

Monitoring and evaluation of the respiratory system is based on three major themes:

1) physical examination;
2) invasive monitoring;
3) non-invasive monitoring.

Much effort has been devoted to develop new non-invasive techniques which would replace invasive methods. We emphasize that "invasiveness" is a relative term and that non-invasive techniques may also harm the patient. For example, procedures such as flow-volume loops originated by forced chest compression and chest radiography are not considered invasive; nevertheless, repeated and frequent assessment may harm the patient.

Physical Examination Monitoring

- Respiratory rate
- Breathing pattern
- Breath sounds
- Skin color
- Pulsus paradoxus
- Cerebral function

Respiratory rate is an easy variable to monitor in non-ventilated infants and children. This variable is reliable primarily during sleep and may vary significantly in awake situation. Breathing rate changes significantly with age so normal values for age should be referenced. Breathing pattern, chest retractions and breathing asynchrony may all characterize respiratory status, nevertheless, they are applicable almost exclusively to non-ventilated patients (or those on low ventilator rate and CPAP). Clinical scoring systems based on skin color, breathing pattern, breath sounds and cerebral function have been developed for common acute respiratory failure situations in infants and children including acute asthmatic attack and acute upper airway obstruction (UAO) [3, 4,5]. However, at least for acute UAO these were found to be unreliable, when compared to objective measurements [5].

Invasive Respiratory Monitoring

- Arterial blood gases
- Mixed venous oxygen tension

Arterial Blood Gases

The interpretation of arterial blood gases is beyond the scope of this paper, but comprehensive reviews of the types of arterial blood gas and acid-base disturbances observed in respiratory failure are available [1].

Invasive respiratory monitoring of patients in respiratory failure is based on arterial blood sampling for arterial blood gas (ABG) analysis. Intermittent arterial blood gas analysis is still regarded as the standard diagnostic tool for accurate assessment of pulmonary gas exchange and ventilator management. This is either a painful procedure or requires indwelling arterial catheters which may produce complications. Another major disadvantage is that ABG analysis provides only intermittent data and may miss sudden changes. Oxygenation indices based on arterial pO_2 levels have been used in clinical practice. These include: (A-a)DO_2, PaO_2/PAO_2 (alveolar-arterial pO_2 difference and ratio respectively) and PaO_2/FiO_2.

Recently, *continuous invasive ABG monitoring* has become available for pediatric patients. This allows continuous analysis of pH as well as PaO_2 and $PaCO_2$ by means of an intra-arterial fiberoptic sensor and the results are displayed on a bedside monitor [1]. Clinical studies are still required to prove its usefulness, applicability, reliability and cost effectiveness in infants and children. Potential applications include all clinical conditions with a high probability for cardiorespiratory instability requiring frequent ABG sampling, including intra- and post-operative management of patients undergoing cardiothoracic surgery, weaning from ECMO and HFOV, and ARDS.

Another problem is that ABG is affected also by patient's crying or altered ventilation just prior to ABG sampling. In the sedated ventilated child with

indwelling arterial lines, this should not occur. In some more severe situations, mixed venous (pulmonary artery) SvO_2 is also used. This is, however, much less commonly performed in children as it requires pulmonary artery catheterization, a technique seen as being less applicable in children compared with adults.

Technologic advances made noninvasive devices available for continuous monitoring of oxygen (O_2) and carbon dioxide (CO_2). These include end-tidal CO_2, transcutaneous CO_2 and O_2 and pulse oximetry (*vide infra*). If the caregiver is aware of their limitations, they allow a quick feedback on rapidly changing conditions and are helpful in the continuous supervision of respiratory therapy. Detailed descriptions of their operation and limitations are available in recent reviews [8, 9]. Noninvasive blood gas monitoring has the potential to reduce significantly the frequency of ABG sampling (e.g. at the Children's Hospital of Los Angeles a 50% decrease in ABG sampling was recorded during the first three years that pulse oximetry, transcutaneous and end-tidal CO_2 were introduced into the PICU, with similar numbers of patients admitted each year).

Non-Invasive Respiratory Monitoring

- Chest radiography
- Ventilation
- Oxygenation
- Respiratory mechanics
- Lung volumes
- Metabolic Gas Exchange
- Respiratory muscle function

Chest Radiography

Although not unanimously agreed, it appears appropriate to do routine daily chest radiographs in intubated mechanically ventilated children. Out of 538 routine daily chest radiographs in one series of 74 adult ICU patients [10], major findings, defined as those requiring immediate diagnostic or therapeutic intervention, were detected in 13 patients (17.6%). However, the fraction of new major findings determined solely by the chest films as a percentage of total films was small (18/538 or 3.4%). Endotracheal tube (ETT) malposition counted as the most common major finding followed by central venous line malpositioning, pneumothorax and pleural effusion. The clinical value of routine chest radiographs in a pediatric ICU has also been demonstrated [11]. It is reasonable to assume that tube malposition will be encountered more frequently in infants and small children than in adults because of the ETT mobility with head position and thus has less room for error in this age group [12].

Ventilation

Arterial carbon dioxide level is the measurement of alveolar ventilation. Non-invasive techniques for $PaCO_2$ measurement include *capnography* and *transcutaneous CO_2* monitoring.

End-Tidal Carbon Dioxide

End-tidal carbon dioxide (E_TCO_2) is usually measured and monitored by respiratory mass spectrometry or by non-dispersive infrared absorption spectrophotometry. Two techniques are available: side-stream in which gas from the proximal end of the ETT is continuously aspirated and main-stream in which an inline CO_2 sensor is directly connected to the ETT and is thus advantageous in ventilated patients. This allows a continuous display of a breath-by-breath waveform of CO_2 concentration changes during respiration. End-tidal CO_2 pressure ($PetCO_2$), measured as the plateau value of an exhaled CO_2 display, closely approximates the $PaCO_2$ in normal lungs and may be used to measure $PaCO_2$ non–invasively and continuously. Although end-tidal CO_2 monitoring by capnography is routinely used for healthy infants and children in sleep laboratories, its use to assess $PaCO_2$ is limited to following trends in children requiring assisted ventilation for cardiorespiratory diseases that affect gas exchange and ventilation-perfusion (/) matching [13]. In patients with extreme / mismatches such as with ARDS or obstructive lung diseases large alveolar-arterial CO_2 gradients can be observed and E_TCO_2 underestimates $PaCO_2$. It has been shown that E_TCO_2 can be used for $PaCO_2$ estimation in ventilated children with mild to moderate lung disease, but can be used only for detecting trends in children with severe pulmonary impairment and / mismatching [1]. This may explain why capnography has not been so widely used in the pediatric ICU. Several investigators have suggested that $PetCO_2$ is not applicable to children with severe / mismatching and that correction factors should be employed [15]. The gap between $PaCO_2$ and $PetCO_2$ is partly caused by uneven ventilation and nonhomogeneous pulmonary capillary blood distribution. An error in recording may also result from the lack of alveolar plateau (which is necessary for end-tidal recording). The lack of the plateau phase is more likely to occur in small children who breath at relatively high rates and small V_T. In a study of 134 mechanically ventilated infants and children where only end-tidal CO_2 values were used, it was possible to define the limitations of the technique [14]. $PetCO_2$ was found to be a reliable and accurate method for $PaCO_2$ assessment as long as the PaO_2/PAO_2 ratio was greater than 0.3. In ventilated children with PaO_2/PAO_2 less than 0.3, $PetCO_2$ could still be used but only for detecting trends in $PaCO_2$ changes. However, capnography is very useful in the guidance of hyperventilation for intracranial hypertension, detection of endotracheal tube accidents (disconnection, obstruction, accidental extubation, esophageal intubation) and the determination of the patient's progress during weaning from ventilatory support [16–21]. When a sudden drop in $PetCO_2$ occurs and $PaCO_2$ is unchanged one should suspect increased dead space ventilation. This is typical for pulmonary vascular disease or pulmonary embolism. In

this situation, there are alveoli which are not perfused so their $PaCO_2$ stays low resulting in low end-tidal CO_2 levels. During cardiac arrest, circulation ceases and $PetCO_2$ gradually falls (while $PaCO_2$ rises) reappearing as an elevated $PetCO_2$ only when pulmonary circulation is restored by effective resuscitation. Hence, $PetCO_2$ monitoring can be used to assess the extent to which resuscitative measures maintain pulmonary perfusion.

Transcutaneous CO_2 Monitoring

Transcutaneous CO_2 ($P_{tc}CO_2$) monitoring devices measure the CO_2 tension at the surface of the epidermis. Because of the high CO_2 tissue solubility this allows an accurate estimation of $PaCO_2$ in conditions with normal skin perfusion [16, 1,2]. This is especially true for neonates where a thin skin improves the degree of accuracy of $P_{tc}CO_2$ monitoring [24, 25]. However, it is important to emphasize that $P_{tc}CO_2$ is higher than the corresponding $PaCO_2$. This difference is influenced by the higher temperature at which the electrodes operate (43–44°C), local metabolic CO_2 production, capillary blood flow and cardiac output [1]. This leads to an unpredictable overestimation of $PaCO_2$ in conditions with significantly reduced skin perfusion [15]. In a study of 134 children receiving mechanical ventilation, skin perfusion at the site of the transcutaneous electrode was found to significantly influence $TcPCO_2$ accuracy [14]. In infants and children with normal skin perfusion (capillary refill time less than 3 seconds), the mean difference between $TcPCO_2$ and $PaCO_2$ was only 0.2 mmhg (SD = 5.4) compared to 4.1 (SD = 9.9) in patients with decreased skin perfusion. Hence, this technique may not be satisfactory and applicable in patients with low skin perfusion. Further, the long response and lag times of the electrode limit the use to a select group of hemodynamically stable patients [23]. Despite its limitations, $P_{tc}CO_2$ is accurate in neonatal patients and adds valuable information (at the least as a trend monitor) in older infants and children.

Oxygenation

Pulse Oximetry

Pulse oximetry is based on the fact that oxygenated and reduced hemoglobin can be distinguished by their differential absorption of two wavelengths of light. It allows an easy and continuous way to measure and assess oxygen saturation (SaO_2). In addition to the ECG and respiration, most ventilated infants and children are monitored for SaO_2 by pulse oximetry (SpO_2). One concern about pulse oximetry in pediatric ICU patients is the decreased accuracy at low saturation levels resulting in significantly overestimation or underestimation of true SaO_2 when O_2 saturation falls below 75–80% [1, 2]. Pulse oximetry is quite accurate at SaO_2 levels above 85% with 95% confidence limits of approximately + 4% (4). However, because of the shape of the oxygen dissociation curve with its characteristic flat section at PaO_2 levels above 60 mmHg, large discrepant oxygen tensions may be related to a single level of pulse oximetry reading. This may be even more pronounced when the hemoglobin dissociation curve is

shifted to the right or left as a result of changes in pH, temperature and 2,3 DPG or from the presence of fetal hemoglobin in small infants. When 14 pulse oximeters were evaluated and their SpO_2 was compared to SaO_2 measured simultaneously with drawn blood samples, it was found that both the error in accuracy (mean $SpO_2 - SaO_2$), and the error in precision (SD of the differences) remained below 3% for $SaO_2 > 83\%$, but were increased to 8% and 5% respectively for deeper hypoxia [1]. Inaccuracies may also occur in the presence of jaundice, elevated carboxyhemoglobin and skin pigmentation [30, 31] and during the loss of a reliable waveform in low perfusion states. The latter may be partially overcome with the new combined pulse oximeters which also simultaneously monitor pulse rate from chest electrodes. This pulse oximeter disregards measurements when peripheral and central pulse rates are not in agreement. Although there is little in the literature, there appears to be only a marginal influence on accuracy due to the presence of fetal rather than adult hemoglobin in neonates and infants in the first 2–3 months of life. Another disadvantage of the pulse oximeter is that it does not alert for hyperoxygenation – a situation which may be dangerous in preterm infants. Thus, infants of this age group need to be monitored by the transcutaneous PO_2 technique which has been found reliable for preterm neonates whose skin is very thin [27]. Despite these limitations, pulse oximetry is very useful in monitoring oxygenation, the detection of hypoxemia and the guidance of cardiorespiratory therapy.

Respiratory Mechanics

The mechanic properties of the lungs are best described by flow-volume loops.

Tidal Breathing Flow-Volume Loops

Tidal breathing flow-volume or pressure-volume loops (TBFV or TBPV loops) are increasingly used in continuous or intermittent monitoring of mechanical ventilation in both Neonatal and Pediatric ICU's. They can be measured on special "stand-alone" equipment, or are increasingly incorporated into modern ventilators. These allow the measurement of tidal volume (V_T), tidal flows and pressures generated during mechanical and spontaneous breaths. Thus, impacts of alteration in ventilator settings or lung physiology on these parameters can be readily detected [32, 33]. Spontaneous tidal volume breaths and ventilator breaths can be compared (especially along the expiratory flow limb where flow-limitation may be readily seen) which enables an estimate of the ventilatory reserve provided by mechanical ventilation (Figures 1 and 2).

Nevertheless, experience showing the usefulness of this variable in clinical practice is scarce. Spontaneous breaths may differ significantly, hence, the TBFV loops vary so that no significant clinical information can be obtained. Ventilator breaths are much more consistent so are the TBFV loops derived. One possible use of TBFV curves is when flow limitation already occurs during

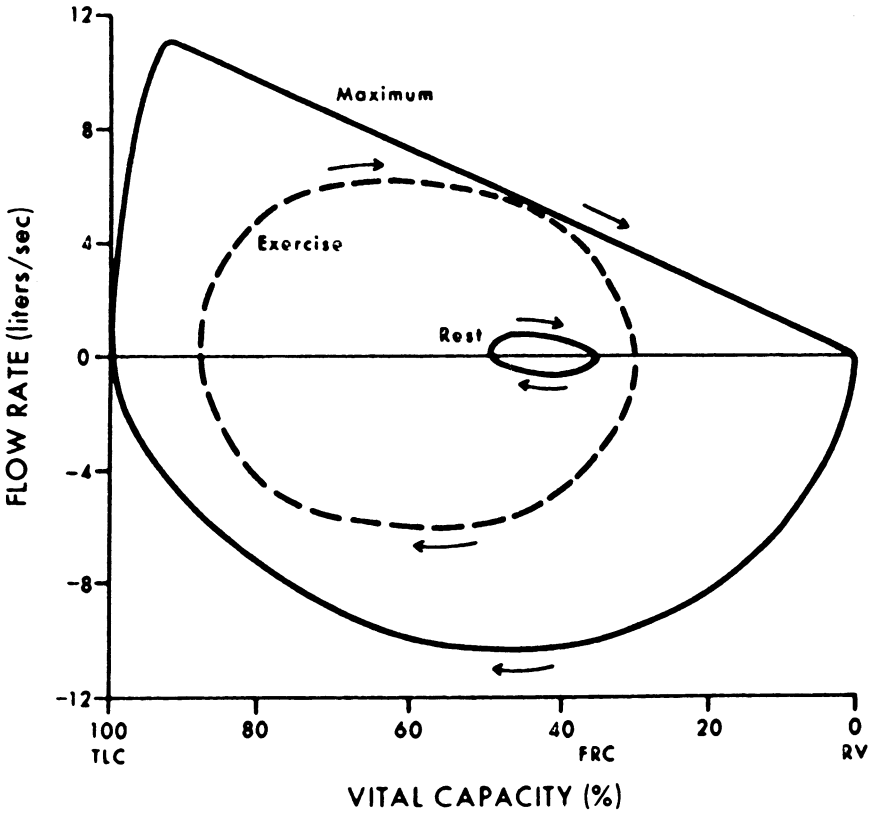


Fig. 1. Superimposed FV-loops demonstrating the concept of flow limitation. Three FV-loops from a tidal breath, a tidal breath during exercise and from a voluntary maximal expiratory maneuver demonstrate that flow limitation can be partly reached during exercise.

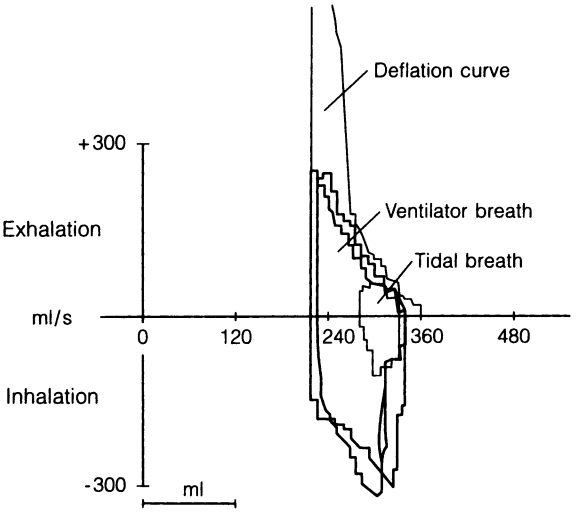


Fig. 2. Superimposed tidal breath, ventilator breath and forced deflation FV-loops of a 9.5 month old infant with BPD illustrate the lack of ventilatory reserve. In this patient airway obstruction is so severe that flow limitation (proven by forced deflation) occurs even during tidal breathing (Reproduced with permission from Hammer J and Newth CJL. Intensive Care Med (1995) 21:744)

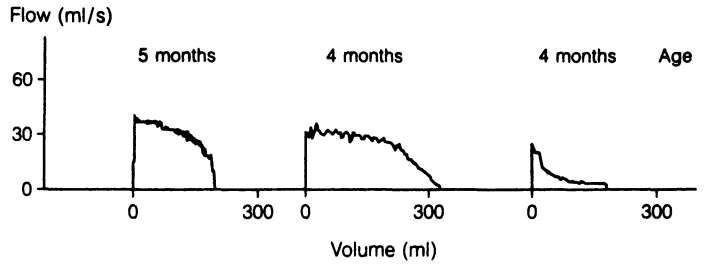
tidal breathing indicating lack of respiratory reserve (Figure 2). However, this still requires forced expiratory flow-volume loops for comparison and reference. The shape of the loop may be useful to detect various types of airway pathology or partially obstructed endotracheal tubes [34].

Forced Expiratory Flow-Volume Loops

The measurement of maximal expiratory flows (MEF) is a sensitive test of abnormalities in the tracheobronchial tree and contributes greatly to the diagnosis and treatment of lung disease. Two different techniques have been developed to allow examination of forced expiratory flow-volume loops (FEFV loops) in small children who are unable to generate a voluntary maximal expiratory maneuver: the forced deflation (FD) technique and the rapid thoracoabdominal compression (RTC) technique [1, 2]. These methods are also used to measure maximal flow rate at FRC and flow limitation [36–38]. It is important that techniques measuring MEF rates reach flow limitation for precise interpretation of the acquired data. Unless it is certain that flow is limited (effort independent) at a particular lung volume, changes in flow rates after a therapeutic maneuver (e.g. bronchodilator) may still be attributed to factors other than a simple response to therapy. It has recently been shown that the FD and the RTC techniques are capable of producing forced expiratory flows at flow limitation in intubated animals and infants with normal and obstructed airways [37,38,1]. Nevertheless, it should be noted that the RTC method may be difficult and cumbersome to perform in ventilated infants and small children because it requires wrapping the patient's chest and abdomen interfering with tubes and sensors applied to the trunk which also may prevent satisfactory contact of the jacket onto the body. While RTC can be performed in non-ventilated spontaneously breathing children, the deflation method was developed specifically for intubated infants and children, may be advantageous in this population and may be regarded as the "gold standard" to measure vital capacity (VC) and MEF in intubated or tracheotomized infants and children.

For the FD test procedure, the lungs are inflated by squeezing a breathing bag filled from a continuous compressed O_2 supply to +40 cm H_2O inflation pressure, defined as total lung capacity (TLC). Inflation pressures are held static for at least 3 seconds, after which a sliding valve is activated to expose the airways to a 100-L capacity, constant negative pressure source of –40 cm H_2O deflation pressure. The lungs are deflated until expiratory flow ceases at residual volume (RV) or for at least 3 seconds. VC and MEF at various subdivisions are measured by an interposed pneumotachograph. Throughout the procedure the individual is usually under neuromuscular blockade and/or heavy sedation.

Normal values for VC and MEF at the various subdivisions still need to be defined, but in our laboratory lie in the range of 55–70 $ml \cdot kg^{-1}$ for VC and 24–38 $ml \cdot kg^{-1} \cdot sec^{-1}$ for MEF_{25} and 6–15 $ml \cdot kg^{-1} \cdot sec^{-1}$ for MEF_{10}. Since it has become standard of care to use inhaled bronchodilators on intubated and ventilated patients in a variety of diseases, their effectiveness can easily be documented by the FD technique [1]. Obstructive airways and restrictive lung dis-



	ARDS (restrictive)	Normal	Bronchiolitis (obstructive)
VC (ml/kg)	30	68	23
MEF_{25} (ml/kg/s)	48	45	3

Fig. 3. Typical forced deflation FV-curves from TLC (+40 cm H_2O) to RV (−40 cm H_2O). Each curve generated from a child with cuffed 3.5 mm I.D. ETT under neuromuscular blockade (Reproduced with permission from Hammer J and Newth CJL. Intensive Care Med (1995) 21:744)

eases produce very characteristic patterns (Figure 3) which are helpful in assessing the underlying pathophysiology (e.g. RSV infection causing bronchiolitis, airway disease in BPD, ARDS or pneumonia).

Serial VC and MEF assessments are helpful in a variety of lung diseases like BPD and ARDS requiring long term mechanical ventilation and document the resolution or progression of the disease process [41]. These measurements are helpful in the evaluation of the response to therapy in a wide range of clinical situations: e.g. the response of a ventilated child with bronchiolitis, viral pneumonia or BPD to aerosolized bronchodilators and the response of patients with cardiogenic pulmonary edema, ARDS, diffuse pneumonia to diuretics.

Resistance and Compliance

Compliance and resistance reflect the mechanical properties of the respiratory system and require the measurement of flow, volume and pressure. Compliance (C) is defined as the change in volume per unit change in pressure:

$$C = \frac{\Delta\text{volume}}{\Delta\text{pressure}} = \frac{\text{ml}}{\text{cm } H_2O}$$

Monitoring of respiratory compliance and resistance as well as of lung volumes can assist the clinician to: a) obtain better understanding of the physiology of the disease b) indicate the course of the disease; c) optimize ventilator settings; d) assess the effectiveness of treatments modalities and medications. It must be emphasized that compliance reflects the mechanical properties of the respiratory system only if measured value is corrected for the absolute vo-

lume of gas in the lungs (*specific compliance*). In other words, the value obtained is different at various lung volumes, dependent on the shape of the pressure-volume curve, which in turn depends on the amount of lung disease and therapeutic maneuvers such as PEEP or surfactant administration. Sudden changes in compliance often reflect the opening and closing of individual lung units rather than changes in lung tissue and surface tension characteristics [42]. Thus, ideally compliance should be corrected for total lung capacity (TLC) and body weight [43].

Resistance (R) is calculated from the equation:

$$R = \frac{\text{pressure}}{\text{flow}} = \frac{\text{cm } H_2O}{\text{ml/sec}}$$

and represents the resistive properties of the airways, lung tissue and chest wall.

Obtaining pulmonary functions in ventilated children has been previously considered experimental and safely and reproducibly accomplished only in a few laboratories. With the incorporation of microprocessors and electronic sensors and the availability of automated systems, this area has developed to the stage of clinical bedside practice. Several methods have been designed to measure compliance and resistance in ventilated infants which has led to a confusing nomenclature for the practitioner. Compliance is referred to as either dynamic compliance (C*dyn*) when it is measured when ventilation is in motion, or as static (passive) compliance (C*rs*) when respiratory muscles are inactive during the test procedure. The same applies to the resistance of the respiratory system, which is referred to as either dynamic (Re) or total respiratory system resistance (R*rs*). C*dyn* can be simply calculated by dividing tidal volume (V_T) by the total change in pressure necessary to deliver that volume. These numbers can be easily extracted from mechanical ventilation. However, it is understood that C*dyn* is related to both elastic and flow resistive characteristics according to the equation of motion of the single compartment model of the respiratory system:

$$P = \frac{V}{C} + RF$$

where P = transpulmonary pressure, V = tidal volume and F = tidal flow. Thus, C*dyn* changes with alteration of mechanical ventilation settings including respiratory frequency, inspiratory and end-expiratory pressure [1].

The respiratory dynamic compliance (C*dyn*) of the lungs and chest wall can be measured using an esophageal balloon and a pneumotachograph placed at the proximal end of the ETT. This allows for pressure-volume curves to be displayed for calculations of C*dyn* and for differentiation of C*dyn* into its components of lung compliance (C_L) and chest wall compliance (C_{CW}). However,

C_{CW} is usually very high in infants and its contribution to total respiratory compliance (C_{TOT}) can often be neglected [45, 46], since C_L and C_{CW} are related as follows:

$$\frac{1}{C_{TOT}} = \frac{1}{C_L} + \frac{1}{C_{CW}}$$

This technique has several limitations [43]. Average pleural pressure necessary for calculations is not always possible to obtain, the technique is highly dependent on accurate placement of the esophageal catheter, compliance results are affected by the respiratory rate and the accuracy of such measurements in intubated infants and children is controversial [1, 2]. Therefore, methods which measure static compliance (C*rs*) and resistance (R*rs*) based on relaxation of both inspiratory and expiratory muscles during brief airway occlusions during exhalation have become more popular, especially in ventilated infants and children.

The most widely used methods are the passive deflation and the multiple occlusion techniques [49–51]. The following discussion concentrates on the passive deflation technique. The reader is referred to recent literature for the other methods [52].

If one measures alveolar pressure at a known lung volume at which no flow occurs, static C*rs* can be determined. If one measures alveolar pressure at a known lung volume at which no flow occurs, static C*rs* can be determined (*Δvolume/Δpressure*). Alveolar pressure can be obtained by measuring pressure at the proximal end of the ETT during relaxation of the respiratory muscles against an occluded ETT (zero gas flow). The concept uses the Hering-Breuer reflex in infants but is easily performed also in older ventilated patients by occluding the expiratory port long enough to allow the airway pressure to reach a constant value and equilibration of alveolar with the proximal ETT pressure. This technique may be especially applicable to infants and children ventilated for acute respiratory failure because they are usually heavily sedated or paralyzed so that their respiratory muscles are not activated and end inspiratory relaxation is easily achieved. Fitting a straight line to the passive expiratory flow-volume curve obtained following release of an expiratory occlusion and measuring the slope, C*rs*, R*rs* and time constant (T*rs*) can be obtained from a single occlusion procedure (slope = time constant) [53, 54]. The expiratory time constant or emptying time of the respiratory system will be entirely dependent on the mechanical properties of the lungs and can be described as follows:

$$Trs = Crs \times Rrs$$

Hence, both C*rs* and R*rs* can be obtained from a single breath. The technique is highly reproducible and requires only transient disruptions of mechanical ventilation [43]. The determination of T*rs* gives some idea of how rapidly the lung empties following a mechanical breath. A single time constant is defined

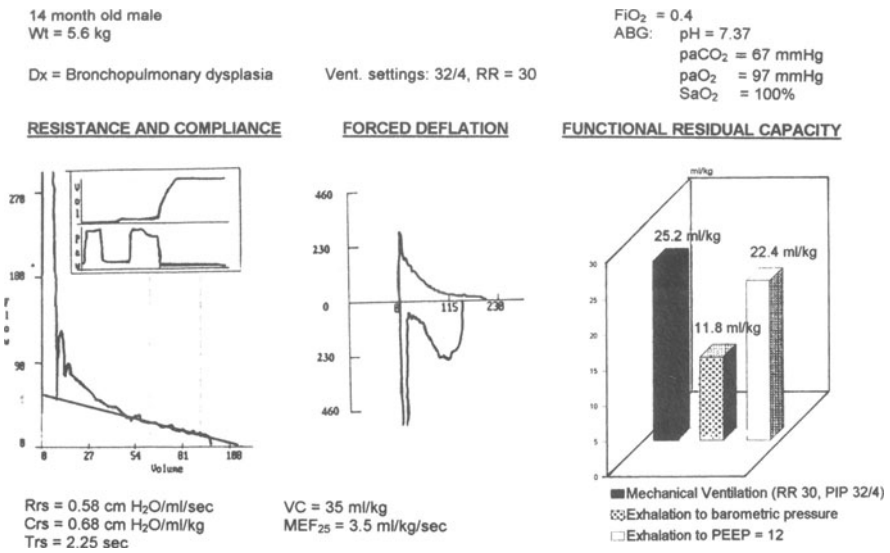


Fig. 4. Passive FV-loop, forced deflation FV-loop and FRC measurements in a 14 month old male with severe BPD demonstrate severe obstructive and restrictive lung disease. There is generation of inadvertent PEEP during mechanical ventilation at a rate of 30 min^{-1} and ventilator pressures of 40/4 cm H_2O comparable to a real PEEP of about 12 cm H_2O.

as the time required to exhale 63% of the tidal volume. Three time constants are needed to exhale 95% of the delivered tidal volume. This permits the determination of respiratory rates allowing complete exhalation or the detection of rate settings which lead to inadvertent PEEP (Figure 4).

The passive deflation technique relies on the assumption that the respiratory system can be regarded as a single compartment model with a linear flow-volume curve (single T*rs*). This occurs only if C*rs* and R*rs* are constant (or changing reciprocally which is unlikely). This is valid in most healthy infants especially over the tidal volume range. However, in the presence of lung disease, the lung may be nonuniform in terms of regional T*rs* so that the respiratory system will not always behave like a single compartment model and a single time constant (single slope) will not adequately describe all the respiratory mechanics [55, 56]. Infants with restrictive lung diseases such as acute ARDS or pulmonary edema or with severe obstructive airway disease may exhibit multiple time constants [57]. In all these circumstances C*rs* and R*rs* are best measured over the longest linear fit of the passive expiratory FV-curve. However, calculation of time constants at different intercepts may give additional information and better describe the respiratory mechanics over the whole expiration phase [58]. Pattern recognition adds valuable information to the interpretation of results obtained by measuring respiratory mechanics. While obstructive lung disease is characterized by a concave slope of the passive expiratory FV curve. Restrictive lung disease often results in convex curve patterns. It is important to note that in the case of intubated patients, C*rs* and

R*rs* measurements include the physical properties of the ETT which may distort the flow-volume relationships. The resistance of the ETT is flow dependent and is related to the internal diameter and length of the tube [59]. The effect of the ETT becomes negligible with ETT sizes of 5.0 mm internal diameter or higher. Therefore, the resistance of the ETT over a range of flow rates should be taken into consideration. Nevertheless, even with small ETTs, the technique can be used to follow disease progress and response to therapy. Unfortunately, there is still a great lack of normal values for C*rs* and R*rs* in intubated infants and children with normal lungs. According to our studies, such normal data lie in the range of 0.8–1.2 $ml \cdot cm\ H_2O^{-1} \cdot kg^{-1}$ for C*rs* and 0.4–0.8 $ml \cdot cm\ H_2O^{-1} \cdot sec$ (up to 1.0 with ETT <3.5mm I.D.) for Rrs (see Table 1).

Alternatively, accurate measurements of volume and flow for a precise numeric characterization of the severity and type of the disease process are easily obtained by the rapid thoracic compression technique or, preferably in intubated patients, the forced deflation technique, because these techniques do not rely upon a single compartment model.

Lung Volumes

Although the most fundamental interest in lung volume measurements in infancy and childhood relates to the assessment of normal and abnormal lung growth, the determination of lung volumes is an important part of the respiratory management of infants and children [1]. Lung volume measurements can help in diagnosing respiratory disorders, in evaluating responses to therapy,

Table 1. Normal values for pulmonary function variables for ventilated infants

	Los Angeles[a]	Lund[d]	Pittsburgh[e]
N	10	20	16
Age (mon)	6.8	8.4	2.9
Weight (kg)	6.5	7.5	5.6
C_{RS} ($ml/cmH_2O/kg$)	0.96		
R_{RS} ($cmH_2O/ml/s$)	0.06		
MEF_{25} (ml/kg/s)	41.1		27.3/39.2[f]
TLC (ml/kg)	68.9	60.6	
FVC (ml/kg)	57.2		41.8
FRC (ml/kg)	24.4/17.1–25.2[b]	18.5	
RV (ml/kg)	11.7		
FRC/TLC	0.35	0.31	
RV/TLC	0.17		
Extrathoracic V_D (ml/kg)	1.75–2.5[c] Age-dependent		
Intrathoracic V_D (ml/kg)	1.03[c] Not age-dependent		

[a] Hammer et al. [76]; [b] Sivan et al. [63]; [c] Numa A, Newth CJL [1]; [d] Thorsteinsson et al. [65]; [e] Mallory et al. [40]; [f] Mallory et al. [1]

and in finding suitable ventilator settings with respect to rate and ventilating pressures [61–63]. Lung volume is also an important variable when lung mechanics are measured [1] because *specific compliance* and *specific resistance* are normalized by lung volume, i.e., the functional residual capacity (FRC), as are maximal expiratory flow rates in partial FV-loop maneuvers performed using the RTC compression technique.

While in non-intubated infants and small children the only lung volumes that can be accurately, repeatedly, and reliably measured are the FRC and tidal volume (V_T), in intubated patients other lung volumes such as total lung capacity (TLC), vital capacity (VC) and residual volume (RV) can also be obtained.

FRC can be measured by three techniques: plethysmographic (infant body box), helium (He) dilution (a closed-circuit method), and nitrogen (N_2) washout (in its modern form, an open-circuit method). Sulphahexafluoride has recently been used in a promising washin – washout technique [1], but as yet, has been validated only in an animal laboratory [1]. In contrast to the gas dilution techniques which measure only gas volume that is in connection with the mouth and which can be diluted or washed out, the infant body plethysmography measures the thoracic gas volume (TGV) i.e. it measures all gas spaces including lung areas which are not in communication with the airway. At present, this technique is relatively impractical in ventilated infants and children although continuing efforts are being made to apply this technique also to the PICU environment [1, 2].

Helium (He) Dilution

The closed-circuit He dilution method is based on the principle of gas equilibration. Gas which contains a known concentration of He as a marker is equilibrated between an unknown lung volume, V_L (FRC or any other volume to be measured) and a closed system which has a reservoir of known volume (V_{gas}) in line, by rebreathing. After equilibration is achieved, the He concentration is the same in all parts of the system including the reservoir. The total volume of the gas distribution ($V_L + V_{gas}$) can thus be calculated from the initial concentration and volume of distribution of the He and its final concentration. Substructing apparatus volume from total volume gives lung volume. That is, if C_1 = He concentration at start of experiment, and C_2 = the concentration when gas mixing is complete, then:

$$V_{gas} \cdot C_1 = (V_{gas} + V_1) \cdot C_2$$

and

$$V_L = \frac{V_{gas}(C_1 - C_2)}{C_2}$$

The initial He concentration can range between 6% and 15%, although concentrations as low as 3% have been used. Therefore, the He dilution technique can be used on patients with lung disease requiring very high inspired oxygen concentrations ($FiO_2 = 0.97$).

Time of equilibration in healthy infants and young children is usually between 40–60s, but may be considerably longer, and even 3–5 minutes, in the presence of airway disease.

The closed-circuit He dilution method has been adapted to measure FRC on ventilated patients by Heldt et al. [69]. The patient is connected via the ETT and a sliding valve to both a bag (which is situated inside a transparent plexiglass box) and to the ventilator (Figure 5).

In normal pre-test position the patient is ventilated directly by the ventilator through the valve. The bag, which contains a known amount of gas with known He concentration (and thus a known amount of Helium) is sealed and is not connected to the patient. At end-exhalation the valve is switched so that the patient is directly connected only to the He-containing bag while the ventilator ventilates the box surrounding the bag and compresses the bag accordingly. The patient is thus ventilated by the bag which is externally compressed by the ventilator cycle. After several breaths, equilibration of He concentration between the lungs and the bag is achieved and FRC can be calculated in the same way as in non-ventilated subjects.

Lung volume measurement by He dilution is a bedside procedure, but still requires considerable operator training and many technical issues have to be considered. Size and volume of the spirometric system as well as of the circuit

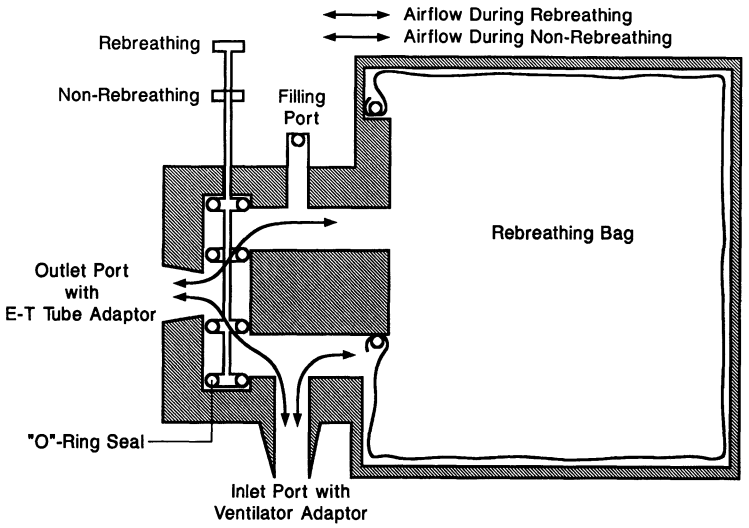


Fig. 5. Schematic diagram for ventilation circuit for FRC measurement in ventilated patients by the He dilution technique (Reproduced with permission from Heldt GP and Peters RM. Chest (1978) 74:492).

need to be adjusted for patient's size. A rapid and accurate He analyzer should be used and its linearity and calibration over a wide range of FiO_2 levels should be carefully evaluated. Moreover, calibration depends on the O_2/He mixture ratio and should be repeated each time. The system must include a CO_2 scrubber and a water absorption system. Because the system is a closed one, during measurements, O_2 must be added at exactly the same rate as CO_2 is absorbed in order to keep the volume of the circuit constant. This can prove to be a technically demanding procedure requiring complex valving which may affect the reliability of the technique.

Leak-free connections in intubated infants are more difficult to achieve in this age group, where cuffed tubes are rarely used. If the leak is minimal, it may be eliminated by gentle tracheal pressure during the recording period. Although a method for correcting leaks during FRC_{He} measurements has been described [1] and is currently incorporated into some automated systems, this has not been fully evaluated nor validated and may result in significant errors.

Nitrogen (N_2) Washout

The technique is based on washing out the N_2 from the lungs by giving the subject 100% O_2 to breathe. If the amount of N_2 washed out is measured and the initial alveolar N_2 concentration is known, then the lung volume from which point the washout started can be derived. Hence, when washout starts at FRC:

$$FRC = \frac{VN_2}{\text{initial lung } [N_2]}$$

In this open circuit method, the patient is switched to breathing 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.

$$VN_2 = \int \dot{V}\,[N_2] \cdot dt$$

In 1985, Gerhardt and co-workers [71] devised an open washout system to which a constant background O_2 flow was delivered. The patient inhaled from and exhaled to that circuit with background flow. Although the instantaneous flow rate of the washout circuit changes continuously as the subject breathes, the average flow leaving the system over time remains unchanged because the volume of gas subtracted during inspiration is added back to the system during exhalation (this is true as long as the temperature and humidity of the inhaled and exhaled gas are equal – a condition which is easy to meet by using a humidifier). Hence, if flow is a constant value the equation can be simplified. This holds for both test and calibration procedures:

$$VN_{2\,test} = \dot{V}_{test} \int [N_2]_{test} \cdot dt$$

and the volume of the washed out N_2 is obtained from dividing these equations to provide

$$VN_{2\,cal} = \dot{V}_{cal} \int [N_2]_{cal} \cdot dt$$

the basic equation for the nitrogen washout technique.

$$VN_{2\,test} = \frac{\dot{V}_{test}}{\dot{V}_{cal}} X \frac{VN_{2\,cal}}{\int [N_2]_{cal} \cdot dt} X \int [N_2]_{test} \cdot dt$$

If the constant flow is kept unchanged during both calibration and test procedures ($\dot{V}_{cal} = \dot{V}_{test}$), the equation can be simplified:

$$VN_{2\,test} = \frac{VN_{2\,cal}}{\int [N_2]_{cal} \cdot dt} X \int [N_2]_{test} \cdot dt$$

The integrated N_2 concentration (measured during the test) is related to N_2 volume by the calibration factor: $VN_{2\,cal}/\int [N_2]_{cal}\,dt$ which is defined during calibration procedure ($VN_{2\,cal}$ is the preset calibration volume and $\int [N_2]_{cal}\,dt$ is measured during calibration).

Calibration is performed by washing out a preset amount of room air from a precision syringe connected to the washout circuit and the piston is pushed back and forth analogous to breathing.

Because the method ignored the instantaneous change in flow and used only the average constant flow for calculation, it was essential that sampling of N_2 for concentration measurements would "see" a continuous decrease of N_2 concentration as the washout proceeds, without the effect of the respiratory phase (Figure 6).

This was achieved by incorporating a mixing chamber in the exhalation circuit before the sampling port from which mixed expired gas was sampled for N_2 analysis (Figure 7).

The technique developed by Gerhardt et al for spontaneously breathing infants and children [72] is not immediately applicable to ventilated children

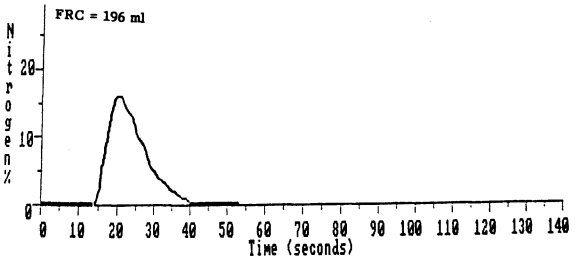


Fig. 6. N_2 washout curve during lung volume measurement by the N_2 washout technique.

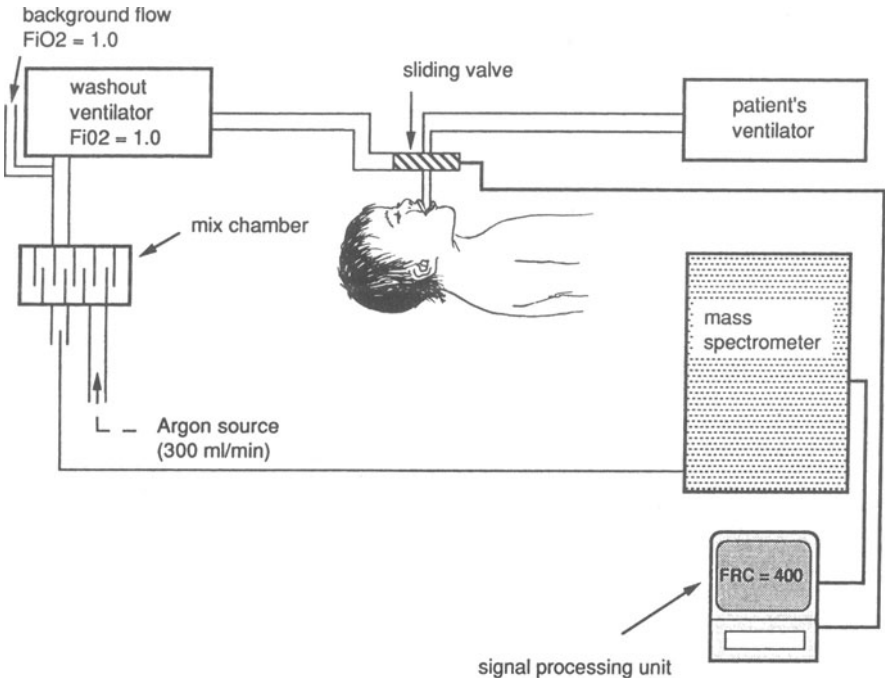


Fig. 7. Schematic diagram for the N_2 washout system for lung volume determinati on in ventilated patients (Reproduced with permission from Sivan Y, Deakers TW and Newth CJL. Pediatri Res (1990) 28:446).

mainly because the gas flow during calibration does not equal the flow during the test so the simplified equation is not valid. In order to overcome this difficulty, we used the respiratory mass spectrometer already "in-line" for measuring the instantaneous N_2 concentration [73], to record the minute ventilation (flow per time) by the argon dilution technique [74]. This is performed during both calibration and test and their ratio ($\dot{V}_{test}/\dot{V}_{cal}$) is calculated for use in the basic equation. At FRC the patient is switched to a second ventilator delivering 100% O_2 (washout ventilator) and washout starts.

This N_2 washout technique (which unlike the He dilution method is limited to patients at $FiO_2 < 0.65$) in our PICU allows accurate determination of FRC during mechanical ventilation and correlates well with those values produced using the Douglas bag technique [73]. In other studies of patients with restrictive lung disease, including a group with ARDS [57], FRC measured at clinically chosen levels of PEEP (4–10 cm H_2O) was 45% below predicted FRC for nonintubated normal children and 60% below that of ventilated children with normal lungs at physiological levels of PEEP (2–4 cm H_2O). The use of progressively greater levels of PEEP produced increases in FRC towards predicted normal values [63]. However, these observations suggest that in ARDS at least, normalization of FRC would require sufficient PEEP to contribute to barotrau-

ma or to compromise of cardiac output and systemic oxygen transport. In spontaneously breathing infants and children, FRC is the same whether determined by He dilution or N_2 washout methods [75], and is in the range of 17.1–25.2 $ml.kg^{-1}$ (mean = 20.4 $ml \cdot kg^{-1}$). Only limited data has been reported for FRC in ventilated infants and children with normal lungs [63] [76]. Sivan et al [63] showed values which were up to 50% more than the normal values for spontaneously breathing children on PEEP's of 2–4 cm H_2O. (See Table I).

As already mentioned, measurement of FRC is required for calculation of *specific compliance* and for V_{max}FRC during forced deflation procedures. The N_2 washout technique has also been shown to measure also lung volumes above FRC accurately [77].

The measurement of oxygen consumption, carbon dioxide production and minute ventilation ($\dot{V}_E$, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$) can be done by a number of techniques. A relatively easy method is performed by respiratory mass spectrometry alone [74]. The principle is that a known mass flow of a marker gas of known concentration is injected into the patient's expirate upstream of a mixing box, and the resulting gas composition downstream is used to deduce the mass flows of all its components. A major problem with this technique is that it requires a very stable O_2 concentration with variation of no more than 0.2%. This may necessitate very accurate and stable O_2 supply systems other than the ICU wall. This problem becomes greater when the FiO_2 is increased. Nonetheless, these measurements can be performed reproducibly at $FiO_2 < 0.8$, without difficulty.

Respiratory Muscle Function

The evaluation of the performance of the respiratory muscles is divided into the measurement of two components:

a) *muscle strength* which is a function of muscle bulk is assessed by the instantaneous development of pressure during a contraction and is clinically represented by diaphragmatic weakness – failure of the diaphragm to generate force; and
b) *muscle endurance* which is defined as the ability of the diaphragm to sustain a previously targeted force output during repetitive contraction. Muscle endurance is a function of muscle fiber type, integrity of contractile elements, number of muscle mitochondria, oxidative enzymes and capillary blood supply. Diaphragmatic fatigue represents a failure of this ability to sustain force output and is reversible with rest [78].

Inspiratory and expiratory *muscle strength* can be evaluated by monitoring maximum respiratory pressures: maximum inspiratory pressure (Pi_{max}) and maximum expiratory pressure (Pe_{max}) obtained during inspiratory or expiratory maneuvers against an occluded airway. Proper performance of these exercises requires patient cooperation. In ventilated children Pi_{max} or its more common term NIF (negative inspiratory force) may be used in the evaluation of patient ability to be weaned from assisted ventilation where values of NIF

more negative than 30 cm H_2O usually predict successful weaning. Pi_{max} is measured after exhalation to residual volume and Pe_{max} is measured from total lung capacity. Inspiratory muscle strength can also be assessed by measuring the pressure across the diaphragm (transdiaphragmatic pressure; Pdi). This is obtained by inserting a balloon catheter into the esophagus and the stomach simultaneously to measure pleural and abdominal pressures respectively. Pdi is the difference *abdominal pressure – esophageal pressure* measured during a maximal inspiratory effort against closed airways.

Another test for evaluation of respiratory muscle strength is the measurement of vital capacity (VC). VC greater than 10–15 mL/kg has been suggested to predict successful weaning.

The major problem with all these tests is that they are effort dependent and therefore are applicable mainly to older cooperative children. Serial measurements of these indices in children with neuromuscular disorders such as Guillain-Barré syndrome and other causes of diaphragmatic failure are useful in the assessment of disease progress.

Respiratory *muscle endurance* is quantified by relating the level of ventilation to the time it can be sustained. This may be assessed by measuring Pdi response to phrenic nerve stimulation, electromyography of the diaphragm, relaxation rate of respiratory pressures and maximum sustained ventilation [1]. These tests are of limited clinical value because they are invasive, require patient cooperation and they have not been proven useful in clinical practice. A relative simple and non-invasive way to assess diaphragmatic fatigue is by measuring the paradoxical inward motion of the diaphragm on inspiration. This may be quantitated by measuring the chest wall to abdominal asynchrony which easily done by the phase angle technique (the abdomen lags behind the chest motion). Although breathing asynchrony on CPAP prior to extubation has been showed to predict successful weaning in adults, preliminary results in infants and children are not promising [1]. More studies are needed to see whether this technique may be used to follow progression and response to therapy.

Although breathing asynchrony in increasingly used in infants and children with a variety of respiratory disorders including in the PICU environment [1], its use in ventilated patients is limited because chest wall-abdominal asynchrony may be observed only on spontaneous patient breaths.

Summary

Today, modern technology allows for bedside assessment of many physiologic variables of the respiratory system in infants and children requiring assisted ventilation. Miniaturization of equipment and the application of technology based on the personal computer with rapid data acquisition and processing has made the evaluation of the respiratory status in ventilated patients possible. Moreover, it has allowed for monitoring and assessment of the respiratory sys-

tem even in ventilated, uncooperative infants and small children in whom some of the variables measured are very small in absolute terms to make any measurement difficult. Hence, these developments open up new possibilities for monitoring changes in disease processes affecting the respiratory system, and improved medical management of infants and children with lung and heart diseases in particular.

The challenges of measuring resistance, compliance, forced expiratory flows, diffusion, functional residual capacity, metabolic gas exchange and thoracoabdominal asynchrony has led recently to the development of a number of ingenious techniques.

However, all of these techniques are limited by implicit assumptions, by the physiology of the respiratory system they intend to assess, and to differing degrees by the invasiveness required for measurement. It is most important to be aware of the limitations of each of the techniques and to use each method within its limitations. For example lung volume measurement by the N_2 washout technique is limited to $FiO_2 \leq 0.70$. Any measurement of lung volume in an infant or child ventilated at a higher FiO_2 requires the use of another method (e.g. helium dilution) or decreasing the FiO_2 momentarily for the test period (if clinically possible). Several techniques (measurement of lung volumes, R*rs*, C*rs*, forced deflation, rapid thoracic compression, O_2 consumption and CO_2 production) require that there be no leak around the endotracheal tube. Therefore, they are applicable only to infants and children with cuffed endotracheal tubes or with uncuffed tubes with pharyngeal packing, where leaks of gas (or pressure) can be prevented. Cuffed ETT are not recommended for use in children under the age of 8 years [1], but in a recent prospective study involving 250 infants and children, using cuffed ETT one-half size smaller than the calculated uncuffed ETT for age, no greater incidence of complications either short-term (post-extubation stridor) or long-term (tracheostomy) were observed [83].

Some techniques such as measurement of thoracoabdominal asynchrony by the phase angle technique and transcutaneous O_2 and CO_2 measurements are age limited. Other are limited by the respiratory disease itself, e.g. pulse oximetry and CO_2 assessment by capnography. RTC, FD, R*rs*, C*rs*, lung volumes by gas dilution techniques and metabolic gas exchange measurements are not possible in the presence of a draining pneumothorax. Arterial CO_2 assessment by capnography is inaccurate in the presence of severe $\dot{V}/\dot{Q}$ mismatch and transcutaneous O_2 and CO_2 measurements are severely affected by low skin perfusion. Flow-volume relationships may be distorted in the presence of a small ETT and this effect should be corrected for, and assessment of respiratory mechanics from passive deflation flow-volume curves assumes a single-compartment model which is not always true, e.g. severe restrictive and obstructive diseases.

In this review, only the basic concepts of the various techniques are presented. For a more detailed description of the technical aspects of the pulmonary function measurements and for a step-by-step "how to do it" guide the reader is referred to the new textbook of Infant Pulmonary Function Testing – A Prac-

tical Guide [84] where the limitations and reference normal values for each technique are also presented.

Nevertheless, when applied with meticulous care and within these limitations, these novel techniques bring new insights and awareness, but also new responsibilities in the management of infants and children with respiratory compromise. Not all of these techniques need to be applied to all infants in the ICU. Not all the assumptions upon which some of these techniques we have described are based will prove true. Any such methods which do not withstand solid scientific testing must be quickly discarded and replaced with better and (hopefully) easier methods.

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