

## Respiratory Function Measurements in Infants: Measurement Conditions

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THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY AND THE EUROPEAN RESPIRATORY SOCIETY WAS ADOPTED BY THE ATS BOARD OF DIRECTORS (FEBRUARY 1995) AND THE ERS EXECUTIVE COMMITTEE (MAY 1994).

Advanced neonatal intensive care and improved survival of prematurely born infants with varying degrees of chronic lung disease have focused attention on the usefulness of pulmonary function testing in infants and young children. Pulmonary function tests (PFTs) are useful in research and clinical practice. Classical PFT techniques have been modified and miniaturized for infants, and innovative methods have been developed. Whatever the PFT used, standardization of measurement conditions is crucial for the infant's safety, accuracy of the test, and reproducibility of the data, especially for longitudinal studies and multicenter trials.

Standardization of measurement conditions must address both laboratory conditions and the infant's state with respect to such factors as feeding, posture, sedation, and sleep state.

### LABORATORY CONDITIONS

Achievement of satisfactory results depends on careful handling and minimal disturbance of the infant. Opportunities for repeating or delaying measurements should technical faults develop during testing are usually very limited, and it is therefore advisable to check all equipment before each test. All equipment should be regularly tested for patient safety.

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### Resuscitation Equipment

Each laboratory or measurement area should have oxygen and resuscitation equipment available, which must be suitable for the infants being tested. A self-inflating resuscitation bag with oxygen, as well as a functioning suction apparatus and suction catheters, should be on-hand. An emergency cart or kit must be immediately available. At least one person must be present who is skilled in airway management and pediatric basic life support. Medical back-up who are skilled in pediatric advanced life support or equivalent should be available during all studies on sedated infants, or whenever measurements on unsedated infants involve equipment (such as a mask or pneumotachograph) at the airway opening. A direct contact line to the pediatric intensive care unit would be advantageous. Trained staff should be in attendance throughout all measurements.

In the intensive or critical care environment a second person must be present to monitor the infant.

Any apparatus that comes into contact with the infant must be thoroughly sterilized or disinfected between tests. Most commercially available equipment currently in use is difficult to dismantle and sterilize. Appropriate facilities and procedures must be established to ensure there is no compromise on cleaning and sterilization of equipment used for infant lung function tests.

To control the influence of environmental temperature on respiratory pattern, room temperature should be maintained between 20-25°C (air-conditioning may be required). Even a small increase in body temperature may induce a change in respiratory frequency and pattern (1, 2). When studying young infants (especially those who are preterm), it is particularly important that the laboratory is maintained at an adequate temperature to prevent body cooling. Whenever possible, the local environment should encourage sleep by use of dimmed lighting and noise reduction. Infants should never be left unattended, and when measurements are to be performed on a bench-top type surface, side rails must be fitted.

### PREPARATION OF THE INFANT

For most purposes, lung function measurements should not be made within 3 wk of an upper respiratory tract infection, unless specifically wishing to study this period. Airway resistance and all related parameters can change significantly due to mucosal swelling and increased secretions (3).

Regardless of which tests are to be performed, the preparation of the infant for lung function tests is generally similar.

Normal values for all respiratory parameters are usually related to body weight, length, or both (4). All infants should therefore be weighed unclothed and their length measured at the time of test, or at the nearest possible time in the case of sick ventilated infants. It is important that this is accurate to within 0.5 cm. A precise infant stadiometer and scales should be available in all centers undertaking such measurements.

Some forms of monitoring, most conveniently a pulse oximeter, should be used during all measurements, since even healthy in-

fants may respond adversely to trigeminal stimulation or airway occlusion (5–7).

The infant's clothing should not restrict respiratory movements in any way and should be loosened or removed as necessary.

#### Crown-heel length

Although it is fundamental to the establishment and use of reference values and to the interpretation of pulmonary function results during disease, measuring of an infant's length is rarely described in detail. An acceptable method (8) is therefore described below.

Small infants tend to be disturbed by being straightened for length measurements and, consequently such measurements are usually performed once all lung function tests are completed. A small cotton sheet is placed on the stadiometer before lying the infant on top, as it is hard and cold. Two adults are needed to measure an infant, who should be placed supine onto the stadiometer. One adult positions the baby's head so that it is touching the top of the stadiometer, in the midline (as indicated by the central black line on most stadiometers), while at the same time ensuring that the baby's trunk is lying flat and not rotated on the bed. When this has been achieved, the other adult gently depresses the infant's knees until the legs are fully extended. The adjustable footplate on the stadiometer should be moved up smoothly until it rests against the soles of the infant's feet, the feet being in the midline (as indicated by the central black line). When this has been achieved, the lever is turned to fix the footplate and the length read off the counter. This measurement should be repeated at least twice, until two recordings within 0.5 cm of each other are obtained. The infant's length is reported to one decimal place. The footplate should always be moved gently to avoid damage to the counter. The calibration of the stadiometer should be checked at least weekly, using a purpose-made steel rod of known length. At the same time, the minimum counter reading should be checked against that specified on each stadiometer.

As clothing varies seasonally and geographically, all weights should be reported as naked weight (8).

#### FEEDING

Tests tend to be more successful if the infant is fed, clean, and dry. Providing the infant is feeding enterally, most workers feel that it is not necessary to fast the infant prior to testing, even when performing esophageal manometry or partial expiratory flow maneuvers. However, due consideration should be given to any relevant underlying pathology, particularly esophageal reflux, with a suitable delay ( $\geq 30$  min) between feeding and measurements in such cases. Although preterm infants with chronic lung disease may be particularly prone to oxygen desaturation following a feeding (9), there is only limited evidence that feeding influences pulmonary function tests in infants (10, 11).

#### POSTURE

Much has been written about the effect of body position on respiratory mechanics, lung volumes, gas exchange, and ventilation in infants.

Although there appears to be little evidence that lung volume is position-dependent in the recumbent infant (12), mechanics and respiratory pattern do appear to be position-dependent, especially in the anesthetized infant or one with respiratory disease (12–18).

In addition, signals from measurement apparatus may be influenced by body position. In particular, esophageal pressure changes may be underestimated in neonates lying prone (19). However, esophageal pressure changes during breathing have been found to be similar in lateral and supine positions (16).

The most important consideration in all situations is that, unless assessing the effect of positioning itself, serial measurements in any one infant should be made with the baby in the same position.

Most reference values have been compiled using data collected from infants in the supine or lateral position, and this must be considered when assessing results from infants measured in different positions. In addition to gross trunk position, neck position may also influence results, and a neutral position should be adopted (avoiding flexion, rotation, or overextension) (20). An exception to this appears to be during the forced expiration maneuver, when higher flows may be obtained by extending the neck, possibly as a result of stabilization of the upper airway (21). In addition, slight alterations in neck position may resolve problems such as glottic closure during forced expiration and airway occlusion procedures.

To avoid confusion and aid comparisons, it is important that body position is recorded at the time of measurement. Although historically most measurements in infants have been undertaken with the infant in the supine or lateral position, there is an increasing tendency to measure intubated neonates in the prone position. Better oxygenation has been found in neonates recovering from respiratory distress syndrome when in the prone position (22, 23). However, there are no normative PFT data for prone infants.

#### SEDATION

Most term or preterm neonates can be studied during natural sleep without sedation. Beyond 1 mo of age, however, it becomes increasingly difficult to do so. Sleep deprivation, even if brief, significantly disrupts sleep patterns and increases central and obstructive apneic episodes (24), and is not recommended.

The use and type of sedation will depend on the age and condition of the infant, the reason for the test, and the type of test being performed. The safety of sedative agents has practical and ethical implications, in that these drugs are commonly used for diagnostic lung function assessments and for establishing reference values in normal infants. Currently, the most commonly used sedative agents for PFT are chloral derivatives. Some centers are using midazolam. For these sedative agents, current knowledge on pharmacokinetics and side effects are reviewed.

#### CHORAL DERIVATIVES

##### Pharmacokinetics

*In vivo*, chloral hydrate is metabolized via aldehyde reductase, alcohol dehydrogenase, and aldehyde dehydrogenase to form trichloroethanol (TCE), the pharmacologically active metabolite. Both chloral hydrate and TCE are sufficiently lipid soluble to enter cells throughout the body. TCE is mainly conjugated with glucuronic acid in the liver and mostly excreted into the urine. If the process of conjugation is limited, TCE is transformed by further oxidation to trichloroacetic acid, which is considered inactive and excreted in urine in that form (25, 26). In Europe, triclofos sodium, the phosphate ester of TCE (to which triclofos sodium is rapidly hydrolyzed) (26), has also been used for sedation (1 g of triclofos is pharmacologically equivalent to 660 mg of chloral hydrate [27]).

Triclofos sodium results in less gastric irritation and has a less unpleasant taste than chloral hydrate, and is therefore more acceptable for oral administration in this age group (27, 28).

In adults, after either chloral hydrate or triclofos administration, the plasma half-life of TCE ranges 4–8 h (28). Pharmacokinetics of chloral hydrate have recently been studied in neonates

and infants (25, 26, 29–31). A study of multiple dosing with chloral hydrate in neonates and infants indicates that TCE is present in blood in significant concentration up to 120 h after the last dose of chloral hydrate (26). The pharmacokinetics of chloral hydrate have been studied after a 50 mg·kg<sup>-1</sup> oral dose of chloral hydrate in critically ill neonates and children (31). The patient population was divided into three groups: group 1—preterm infants (31–37 wk); group 2—full-term infants; and group 3—toddler-child patients. Contrary to what has been reported in adults, chloral hydrate was detectable for many hours after oral administration in all three groups. The plasma half-life for TCE in group 3 (9.67 ± 1.72 h [mean ± SD]) was close to that reported for adults (28), but in the less mature subjects it was approximately three (group 2, 27.8 ± 21.32 h, including one extreme outlier) to four (group 1, 39.8 ± 14.27 h) times greater.

Considerable interindividual variation was reported, especially in less mature subjects. This study indicated that there are major developmental differences in the metabolism and elimination of chloral hydrate. Newborn infants, and especially preterm newborns, cannot clear the metabolites of chloral hydrate as effectively as older individuals.

#### Side Effects

**Toxic doses.** Several recent reports, including one from the American Academy of Pediatrics, have reviewed the potential side effects of sedation in infants and children, with special reference to chloral hydrate (32–35).

Chloral hydrate intoxication has been reported both in children and adults (36). Reported toxicity includes respiratory insufficiency (37, 38), encephalopathy (39), gastric necrosis (40), and cardiac arrhythmia (41–44).

**Hypnotic doses.** The commonly used hypnotic dose is 30–50 mg·kg<sup>-1</sup> chloral hydrate. The dose required for complicated lung function protocols may be greater (up to 100 mg·kg<sup>-1</sup> chloral hydrate, 150 mg·kg<sup>-1</sup> triclofos).

The effects of chloral hydrate or triclofos administration on respiratory control should be examined with due regard to the dose, the age of the subject, and the presence of any known disease at time of testing.

**Newborns at term.** Three studies refer to the neonatal period. Comparing 13 unsedated infants (postconceptional age [PCA] 41.3 ± 4.4 wk, of whom seven were healthy and six prone to apnea), with 31 sedated, apnea-prone infants (PCA 43.0 ± 4.0 wk), Lees and coworkers (45) did not find a significant difference in the ventilatory CO<sub>2</sub> response between natural sleep and sleep induced by one 50 mg·kg<sup>-1</sup> dose of chloral hydrate. However, blunting of the CO<sub>2</sub> response has been reported in two of 22 healthy full-term babies (gestational age [GA] 38 ± 1.3 wk; postnatal age [PNA] 39–101 h) (46). In those two babies, tachypnea and oxygen desaturation occurred. This unpredictable side effect of chloral hydrate in healthy full-term newborns may be related to the large interindividual variation in chloral hydrate pharmacokinetics in the neonatal period (31) and reinforces the need for oxygen saturation monitoring following sedation in all infants.

**Preterm newborn infants.** In ventilated preterm infants, prolonged administration of chloral hydrate has been used in intensive care units (26, 31, 47). Adverse effects have been reported, such as direct hyperbilirubinemia (47) and prolonged neurodepression (30), both of which may be related to the delayed clearance of chloral hydrate metabolites in immature newborns. However, after a single oral dose of 20–50 mg·kg<sup>-1</sup> of chloral hydrate, no significant changes in heart rate and respiratory rate were observed in 11 preterm infants with respiratory distress syndrome (26). Preterm infants who have suffered perinatal cerebral insults

may be especially prone to apnea after doses > 30 mg·kg<sup>-1</sup> and should be sedated with caution during the neonatal period.

**Healthy infants.** A large number of healthy infants have been tested by different investigators with regard to potential respiratory side effects of chloral hydrate or triclofos. The ages ranged from 4 wk to 2 yr of age, with doses of chloral hydrate ranging 50–100 mg·kg<sup>-1</sup>, and triclofos 75–100 mg·kg<sup>-1</sup> (48–50). In all these studies, only one dose was administered. There was a small but significant increase in respiratory rate in one study (48), but Turner and colleagues (50) found no significant change in respiratory rate, despite a small reduction in tidal volume, following sedation. In a group of 10 infants aged 4–19 mo, in whom results from paired measurements were successfully obtained, the changes in respiratory rate (+1.9 breaths·min<sup>-1</sup>), heart rate (+5.5 beats·min<sup>-1</sup>), and arterial oxygen saturation (SaO<sub>2</sub>) (–0.68%) were not considered to be of clinical importance (48). The strength of the Hering-Breuer inflation reflex was not influenced by sedation with triclofos sodium at a dose of 75 mg·kg<sup>-1</sup> (49). Measurements of functional residual capacity (FRC) and maximal (forced) expiratory flow at FRC (VmaxFRC) were not significantly affected by sedation (50).

**Wheezy infants.** A 70–100 mg·kg<sup>-1</sup> dose of chloral hydrate caused a fall in SaO<sub>2</sub> and a decrease in clinical score of infants recovering from acute viral bronchiolitis, but not in infants with clinically stable cystic fibrosis (51).

**Infants who have suffered an apparent life-threatening event (ALTE).** When using chloral hydrate at a dose of 100 mg·kg<sup>-1</sup>, Southall and coworkers (unpublished data) noticed that a significant proportion of infants showed moderate baseline hypoxemia. Usually, this involved oxygen desaturation to just below 90%, but in two infants there were more profound desaturations, including in one the need for bag and mask ventilation.

**Infants with upper airway obstruction.** Chloral hydrate has been shown to reduce the activity of upper airway muscles (52), a factor that may predispose the airway to collapse during sedation, particularly in infants at risk of airway obstruction. This includes infants with craniofacial abnormalities, enlarged tonsils and/or adenoids, and those with obstructive sleep apnea. Hershenson and coworkers (52) reported a near-fatal airway obstruction and respiratory arrest shortly after a repeated dose of 50 mg·kg<sup>-1</sup> of chloral hydrate in a 3-yr-old child with obstructive sleep apnea syndrome. Similarly, Biban and coworkers (53) have reported two cases of respiratory failure in 2-yr-old children with suspected obstructive sleep apnea, following single doses of chloral hydrate (80 mg·kg<sup>-1</sup>) given before PFT. Thus, clinical assessment of the infant before sedation should include evaluation of any history of airway obstruction during sleep and visual assessment of the upper airway. Although complications after sedation are rare, upper airway problems undiagnosed before PFT emphasize the need for continual monitoring and availability of resuscitation equipment during all PFTs.

**Cardiac risks.** Cardiac arrhythmia has been reported in children receiving hypnotic doses of chloral hydrate. In the case report of Nordenberg and colleagues (43), cardiac arrhythmia occurred in a healthy 2.5-yr-old child after a large (118 mg·kg<sup>-1</sup>) oral dose of chloral hydrate. Silver and Stier (44) reported sinus arrhythmia following oral chloral hydrate sedation in two infants aged 13 and 18 mo being investigated for seizure disorders (doses of 70 and 40 mg·kg<sup>-1</sup>, respectively).

Recent experiments in isolated perfused rabbit heart showed that chloral hydrate and TCE in clinically achievable concentrations are predominantly cardiac depressants and may produce conduction defects (54).

Finally, investigators should be aware of a recent publication (55) suggesting that chloral hydrate could be a potential carcino-

gen in humans. This issue is presently unresolved but is being addressed in committee by the American Academy of Pediatrics (34). Reviewing the evidence, Steinberg (56) suggests avoiding both prolonged sedation in neonates and chronic use of large doses.

#### Repeated Sedation

Infants who are tired fall asleep more quickly following sedation (57). The timing of measurements should therefore be planned to coincide with the infant's normal sleep/walking routine as far as possible to minimize any need for repeat sedation.

The subject of repeat sedation (top-up) remains controversial. Issues to resolve include what dose, if any, should be used, and whether there should be a maximum dose limitation within any given measurement session/24-h period.

Until further information is available on this subject, it is recommended that: (1) additional doses of chloral hydrate should not be given in excess of a total dose of 120 mg·kg<sup>-1</sup> (or equivalent dose for derivatives such as triclofos); (2) a delay of at least 1 h should be allowed before administering a top-up dose within this dose limit.

The only circumstances under which these recommendations might be breached is when an infant has vomited all the syrup immediately after administration, in which case a repeat half-dose might be given. It should be noted that absorption of chloral hydrate can occur across the oral mucous membranes and that some absorption may have taken place even in an infant who has apparently vomited the entire dose.

In premature infants no repeat doses should be given within 48 hrs of sedation for PFT or other tests (such as echocardiography) (26, 30, 56).

#### MIDAZOLAM

The common effects of benzodiazepines include sedation (58–60). Midazolam is a water-soluble, short-acting benzodiazepine. It is metabolized in the liver, less than 1% being excreted in the urine unchanged. Midazolam has been used for preoperative sedation by the intravenous, intramuscular, rectal, oral, and nasal routes (17, 30, 60, 61). Nasal administration has the advantage of rapid absorption of the drug directly into the systemic circulation. The half-life is similar after administration by the intravenous and intranasal routes (2.4 vs 2.2 h) in children (61). Midazolam has been administered nasally at doses from 0.1 mg·kg<sup>-1</sup> (63). The lowest dose has been shown to be effective at rapidly sedating children before the induction of anesthesia (62). No additional benefit was seen from a dose of 0.3 mg·kg<sup>-1</sup> as compared with 0.2 mg·kg<sup>-1</sup> (62) to 0.3 mg·kg<sup>-1</sup> (63). Mean onset time was 7 min. Maximal effect and peak plasma concentration were obtained in about 10 min (62, 64). No significant difference was observed between nasal drops and nasal spray administration concerning onset and duration of effect. Repeated doses (0.2 mg·kg<sup>-1</sup>) have been administered for effective echocardiograph sedation (64). Recovery of normal activity occurred 20–45 min after sedation (64).

Available reports do not mention significant respiratory and/or cardiovascular side effects after intranasal midazolam administration. However, consideration needs to be given to the following: (1) no study has reported the use of intranasal midazolam in infants younger than 5 mo; (2) available reports do not give precise details of the clinical status of the sedated children: (3) SaO<sub>2</sub> may fall after midazolam administration; in one report an 8% fall in SaO<sub>2</sub> was observed in one infant (64); and (4) systolic and diastolic arterial blood pressures have been reported to fall by 10 mm Hg

(65). In addition, the effect of midazolam on the nasal mucosa must be clarified since this may influence measurements of resistance.

Further studies are required to assess the safety and suitability of midazolam administered intranasally for rapidly sedating infants for PFT before its widespread use can be recommended.

#### ASSESSMENT AND MONITORING OF THE SEDATED INFANT

As outlined in the guidelines recently published by the American Academy of Pediatrics (33), patient safety with careful monitoring by qualified personnel is of utmost importance, especially when infants are volunteered for research. Presedation assessment should include a physical examination, and observation of vital signs and any other unusual physical findings should be noted.

Infants under sedation must be monitored continually with pulse oximetry until they are fully awake. Electrocardiography and other methods of automated monitoring of heart rate, respiratory rate, and oxygen saturation may be used as a supplement. If vital signs are not being continuously recorded, these should be measured at baseline and at frequent intervals thereafter, and recorded on the patient's medical record or a flow sheet designed for this purpose.

To avoid unnecessary and potentially dangerous transfer of deeply sedated infants and children, sedation should be administered at the location at which the test is to be performed. Infants should not be released home after sedation until fully rousable and capable of swallowing (drinking). In addition, parents should be advised that the infant may be drowsy and unsteady for several hours following sedation, and, therefore, should not be left unattended unless asleep, until the infant has fully recovered normal control of body movement.

#### SLEEP STATE

The importance of considering sleep state in relation to pulmonary function testing will depend to some extent on the purpose of the investigation. Sleep state may be less important in an assessment of lung mechanics in a ventilated infant for clinical purposes than in research studies of respiratory control in normal infants. However, little is known about the influence of sleep and sleep state on respiration. In some areas, data are conflicting, making this an important area of study in its own right. The age and maturation of the infant has a major influence on patterns of sleep and respiration and must always be considered.

When attempting to record sleep state, several practical issues need to be taken into account, including time available for the study, acceptability to parents and infant, possible disruption of nursing procedures, and accessibility, e.g., repositioning and recalibration of respiratory inductance plethysmograph may not be straightforward if the infant is lying within a whole-body plethysmograph. It is important to be aware that differences in sleep state definition may arise when different criteria or combinations of signals are used (66, 67), such that the estimated proportion of active sleep can vary from 40–66% in normal infants (68).

#### Development of Sleep States Organization

Using neurophysiologic and behavioral criteria, sleep can be differentiated into three states in the neonatal period (active [REM sleep], quiet [NREM sleep], and indeterminate sleep) (66, 69). Some workers prefer the term paradoxical sleep to active sleep (70, 71), and also recognize a further subdivision that they claim resembles the awake state except for the absence of awareness. The proportions of active, quiet, and indeterminate sleep vary with

age and maturity of the infant and with time of day (72–74). Active and quiet sleep can be recognized in preterm infants of 27 wk gestation and older (75, 76), although preterm infants spend a high proportion of their time in indeterminate sleep (66, 77). A newborn infant falls asleep in active sleep. After 1 mo of age, the infant increasingly starts to fall asleep in quiet sleep (69). With advancing postnatal age, the proportion of active sleep falls from approximately 50% in the newborn to 20–25% at 6 mo, while the proportion of quiet sleep increases (72). The duration of sleep cycles is approximately 45 min at 31–34 wk GA and 65–70 min at 35–41 wk GA (66). Daytime sleep episodes may consist of quiet sleep only in infants (69, 74). Changes in respiration during sleep include an increase in the amount of regular respiration (77) and a fall in the amount of rapid eye movement (REM)-associated apnea over the first 12 wk (78).

#### Monitoring of Sleep States

Although it is impractical for each laboratory to monitor sleep state fully during all infant function tests, it is important to be aware of the potential influence of sleep on measurements of lung mechanics. Where neurophysiologic monitoring is possible, it is always recommended, since it is easier to quantify and check than behavioral observations and records can always be re-examined at a later date. In the absence of neurophysiologic monitoring, behavioral criteria (79) should be noted, including body and eye movements and the relationship between rib cage and abdominal movement. Although these observations should not be taken as conclusive evidence of any given sleep state, they may facilitate comparisons between different studies and help explain apparently conflicting data. Active sleep is defined clinically by frequent eye, limb, and facial movements and by irregular respiration with paradoxical rib cage movements. In the preterm newborn, clinical characterization of sleep state may be difficult, since the preterm infant has periods of paradoxical rib cage movements during quiet sleep and synchronous movements during active sleep (80).

It is important to note that sleep staging should not be based on respiratory criteria alone, especially when examining the influence of sleep state on respiratory parameters. Inappropriate classification can occur due to the respiratory instability of newborn infants and those with respiratory disease, in whom abdominal/rib cage asynchrony and an unstable respiratory pattern may be present even during quiet sleep (67).

#### Influence of Sleep State on Functional Residual Capacity

The potential influence of active versus quiet sleep on the end-expiratory lung volume, FRC, remains controversial. Two studies have assessed changes in FRC in active compared with quiet sleep, using inductance plethysmography to detect changes in anteroposterior diameters of both rib cage and abdomen in preterm infants (81) and alterations in the baseline signal from a respiratory jacket in term infants (82). In both studies, FRC was found to fall slightly during the transition from quiet to active sleep, although in the healthy term infants FRC recovered to previous levels within 20–40 s (82). Two studies using a body plethysmograph have reported a significant fall in FRC in active compared with quiet sleep in healthy full-term newborns (83, 84). The mean fall in FRC was 31% in six infants and 12% in eight. There may be methodologic rather than purely physiologic explanations for these differences, including lack of support of the upper airways (84). Three studies have measured FRC using the helium dilution technique during active and quiet sleep assessed by neurophysiologic criteria (85–87). In healthy full-term newborns, no significant

changes in FRC were observed, related either to sleep state or regularity of respiration, but no attempt was made to measure rib cage and abdominal motion (85). Two studies concerning both preterm and full-term newborns showed no change in FRC in relation to change in sleep state, but a fall in FRC only when rib cage and abdominal motion were 180° out of phase, regardless of sleep state (86, 87). Discrepancies between these different studies may be related to the method of measurement. Using body plethysmography, repeat measurements of FRC can be achieved over much shorter time periods than when using helium dilution, when time must be allowed for helium to wash out of the lungs between repeat measurements. If there is a rapid recovery in FRC following any reductions during active sleep (82), any sleep-related changes in FRC may be detected by plethysmography but missed using helium dilution techniques. However, as stated above, the magnitude of changes during plethysmographic measurements may have been overestimated due to poor equilibration of airway pressures during airway occlusion in active sleep (84).

It is difficult to resolve these conflicting observations. However, some reduction in the end-expiratory level (EEL) is to be expected during active sleep, due to the loss of intercostal muscle activity associated with periods of REM during active sleep. Further research investigations looking at the fall in FRC in active sleep should consider the density of REM during the period of measurement. It is well documented that expiratory airflow braking mechanisms are disabled in active REM sleep in premature infants. Both Lopes and coworkers (81) and Stark and coworkers (88) have shown that postinspiratory diaphragmatic activity is reduced in REM. Animal studies have demonstrated a substantial reduction of laryngeal adduction during expiration in REM sleep (89, 90). Furthermore, recordings of airflow during quiet sleep in human preterm neonates show clear evidence of expiratory braking, whereas during REM sleep flow-volume curves appear to be passive, with no evidence of braking (88). Thus, although the expiratory time constant appears to be shorter in REM sleep in premature infants, expiratory time ( $t_E$ ) may be longer during quiet sleep. In term infants, followed from birth to 4 mo of age, Haddad and coworkers (91) have shown the opposite to be true,  $t_E$  being greater and respiratory rate slower during quiet sleep compared with active sleep at all ages. Either expiratory braking during quiet sleep or more rapid respiratory rate during active sleep may serve to maintain an elevated lung volume. Changes in lung volume with changing sleep state may be more marked in neonates than older infants, the former showing considerable instability of their EEL (88).

For routine practice, whether testing during natural or induced sleep, it is recommended that FRC be measured during quiet sleep, when breathing is regular and when rib cage and abdominal motion are in phase. In preterm infants and neonates who manifest frequent periods of paradoxical rib cage motion during quiet sleep and a large proportion of active sleep, measurement of FRC when rib cage and abdominal movements are in phase is difficult. Other indications of quiet or indeterminate sleep, including the absence of limb and eye movements, should be used to time measurements.

#### SUMMARY RECOMMENDATIONS

##### Laboratory Conditions

1. Environmental temperature 20–25° C.
2. Resuscitation equipment always available.
3. Full monitoring, including at least pulse oximetry, of vital signs during sedation.

- Second person to be responsible for monitoring in intensive care environment and during sedated studies on any "high risk" infants (see below).
- All apparatus (mask, valves, pneumotachographs, connectors, etc.) must be cleaned/sterilized as appropriate between each infant.

#### Preparation of the Infant, Feeding, and Position

- Defer measurements for 3 wk after onset of upper respiratory tract infection.
- Length and naked weight measured on each occasion (if > 1 wk apart).
- Fasting is not usually indicated.
- Record posture; avoid flexion or rotation of the neck.
- Reference values are available mainly for the supine position.

#### Sedation

- Contraindication for sedation—known upper airway obstruction.
- High risk infant groups: a) preterm and full-term neonates ( $\leq$  44 wk postconceptional age) even when healthy; b) infants presenting a history of acute life-threatening events; c) infants at increased risk of upper airway obstruction; d) infants with known respiratory embarrassment; and e) infants with hepatic, renal, or cardiac disorders. High risk infants must be monitored (oxygen saturation, heart rate) after sedation. Overnight hospitalization may need to be arranged for infants who are clinically unstable.
- Sedate with caution—wheezy infants (51).
- Resedation should be avoided; the total dose of chloral hydrate should not exceed 120 mg·kg<sup>-1</sup> (and dose equivalents for related drugs, triclofos sodium).
- Always advise parents of possible unsteadiness in infants after sedation.

#### Sleep State

- Measurements should be made during quiet sleep, assessed by behavioral criteria in the absence of more sophisticated monitoring.
- Avoid inappropriate dependence on respiratory definitions of quiet sleep.

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