0031-3998/87/2104-0313$02.00/0
PEDIATRIC RESEARCH

Vol. 21, No. 4, 1987
Printed in U.S.A.

Pulmonary Function in the Sick Newborn Infant

ELLEN M. McCANN, STEVEN L. GOLDMAN, AND JUNE P. BRADY

Departments of Pediatrics, Children's Hospital of San Francisco and the University of California, San Francisco and the Cardiovascular Research Institute, University of California, San Francisco, California

Measurement of pulmonary function in the sick infant provides important clinical information and is an important tool for scientific investigation. Herein we review the techniques and limitations of pulmonary function measurements in small, sick newborn infants. Reference values for some of these measurements are provided in Table 1. Many techniques entail some risk and it is vital that the baby's care not be compromised. We perform studies at the bedside with at least two investigators and observe and monitor the baby continuously. We occasionally use chloral hydrate sedation in irritable babies who could not otherwise be studied. However, the value of natural sedation should not be overlooked. As Nicholas Nelson wrote in 1966 (1):"These 'untrained' subjects have proved to be immensely cooperative in the careful hands of patient investigators cognizant of the anesthetic powers of a full stomach."

SKIN SURFACE GAS TENSION AND OXYGEN SATURATION

Definition. The tensions of O_2 and CO_2 measured at the skin surface (transcutaneous) and oxygen saturation measured with an ear oximeter or pulse oximeter estimate the arterial values.

Background. Skin surface PO_2 (PsO_2) was first measured in babies by Huch *et al.* in 1972 (2). Chemically induced hyperemia did not raise PsO_2 to arterial levels but in 1974, they found that thermal hyperemia did (3). Measurement of PsO_2 has been routine in many nurseries since 1980. Skin surface PCO_2 ($PsCO_2$) was first measured in babies by Hansen and Tooley in 1979 (4) after studies in adults assessed the effects of skin metabolism and electrode temperature (5). This technique is not yet routine in all intensive care nurseries. Oxygen saturation (SO_2) has been measured noninvasively for many years in adults (6). Both ear oximetry (6, 7) and, more recently, pulse oximetry (8) have been applied to babies.

Technique. PsO_2 is measured with a miniature Clark electrode heated to 43–45°C which increases capillary blood flow by 100-fold (9). The *in vitro* time constant (the time between the onset and 63% of the pen deflection in response to a square wave change in gas concentration) is 10–20 s but the *in vivo* time constant, lengthened by diffusion through tissue, is 1–2 min (10, 11).

$PsCO_2$ is measured with a miniature Stow-Severinghaus pH electrode or metal oxide electrode. The *in vitro* time constant is 20–40 s, but the *in vivo* time constant is about 3 min (4, 5). $PsCO_2$ is greater than $PaCO_2$ due to the difference in temperature between the body and the electrode and the contribution of the skin. The temperature correction is 1.31 at an electrode temperature of 43°C and 1.37 at 44°C (12). The contribution of the skin is a constant, independent of PCO_2 or temperature, due to skin metabolism and other possible mechanisms (13). This difference is 3 torr in adults (5) and 2 torr in sick infants (4), but significantly greater in older babies, particularly those with chronic lung disease (14, 15). For both electrodes, the transit time (or delay time, the time between the appearance of gas at the membrane and the onset of pen deflection) is approximately 30 s (5, 10).

Oximetry is a spectrophotometric technique in which red and infrared light is transmitted through the "arterialized" ear lobe, fingertip, forehead, hand, or foot (6). In early models, the photocells were next to each other resulting in errors from tissue and venous blood absorbance (6). Although smaller oximeters which alternately transmitted and received light minimized these errors, they occasionally caused burns in babies and were cumbersome (7). Pulse oximetry detects arterial pulsations and compares the absorbances of the two wavelengths during systole and diastole; there is no interference from venous blood, skin, connective tissue, or bone and no need to heat the site (8).

Applications. PsO_2, $PsCO_2$, and SO_2 are particularly valuable during studies of variables that are affected by PO_2 and PCO_2. After very small decreases in inspired oxygen in babies with chronic lung disease, Halliday *et al.* (16) found an increase in pulmonary vascular resistance and Teague *et al.* (17) found an increase in airway resistance. PsO_2 electrodes on the right upper chest and abdomen have been used to document right-to-left ductal shunting and PsO_2 and $PsCO_2$ are often measured during sleep studies. Recently, combined PO_2 and PCO_2 electrodes have been developed; these have an obvious advantage in tiny babies (13, 18). In very immature babies with fragile skin, a heated electrode may cause skin necrosis and saturation measurements are preferable. The sensor may be left on for 3–4 days, versus 2–4 hours for a PsO_2 electrode.

Limitations. Halothane anesthesia interferes with the PO_2 measurement when a polypropylene, but not a fluorinated ethylene propylene membrane is used. The skin surface-arterial PO_2 gradient is minimal at birth but increases with age and is affected by blood flow (9). Most $PsCO_2$ instruments allow correction for temperature but not skin metabolism. Some manufacturers recommend a correction factor of 1.5–1.7% for electrode temperatures of 44–45°C; 1.5% is probably too high for an immature baby and too low for a baby with chronic lung disease. Corrections for both temperature and skin metabolism are preferable for babies with chronic lung disease. To make this correction, an arterial blood gas is essential. Because the puncture may cause hypo- or hyperventilation, the transit time and time constant must be known.

An averaging time is used for SO_2 measurement so that beat-to-beat values are not displayed. The Nellcor pulse oximeter has three averaging times: 2–3, 5–7, and 10–12 s; the first may be underdamped and the third, overdamped. A potential danger of pulse oximetry is the failure to recognize hyperoxia which may lead to retinopathy of prematurity. Fetal hemoglobin reduces the apparent functional hemoglobin determined by oximetry; the pulse oximeter may thus show a falsely low value (50–100% fetal hemoglobin causes a 3–4% error) (19, 20).

Received November 19, 1986; accepted November 25, 1986.
Address correspondence to Ellen M. McCann, M.S., Neonatal Services Department, Children's Hospital of San Francisco, 3700 California Street, San Francisco, CA 94118.
Supported by The National Heart, Lung, and Blood Institute (Grant HL24075), the Northern California Chapter of the National SIDS Foundation, the California Lung Association, and the Bay Area Heart Research Association.

Table 1. *Pulmonary function in well and sick infants**

Measurement	Units	Well infants	RDS	CLD	Source
Tidal volume	ml/kg	5–7	4–6	4–7	98, 52, 115
Respiratory rate	breaths/min	30–40	50–80	45–80	98, 52, 115
Minute ventilation	ml/kg/min	200–300	250–400	200–400	98, 52, 115
Functional residual capacity	ml/kg	25–30	20–33	20–30	47, 52, 115
Thoracic gas volume	ml/kg	30–40	20–35	35–50	47, 46, 60
Dynamic compliance	ml/cm H_2O/kg	1–2	0.3–0.5	0.2–0.8†	52
Lung resistance	cm H_2O/liter/s	25–50	60–150	30–150†	150, 86
Work of breathing	g cm/min/kg	500–1000	800–3000†	1800–6500†	70, 71
P_ACO_2	torr	30–40	32–50	40–55	140, 52, 115
P_AO_2 in air	torr	105–115	92–108	94–112	98, 102, 125
Alveolar ventilation	ml/kg/min	110–160	55–90	90–170†	105, 52
Physiologic dead space	ml/kg	2–3	3.0–4.5	3.0–4.5†	105, 52
Dead space/tidal volume	%	22–38	60–80	35–60†	105, 52
Anatomic dead space	ml/kg	1.5–2.5	2.5–4.2	2.0–3.5†	98, 52
Alveolar dead space	ml/kg	0–0.5	0.2–0.7	0.2–1.0†	105, 52
Pulmonary clearance delay	%	0–30	7–40	90–350	44, 102, 115
Effective pulmonary capillary perfusion (nitrous oxide)	ml/kg/min	160–230	75–140	120–200†	118, 119
Venous admixture in air	%	8–22	25–60	30–75	102, 125
$P(a\text{-}A)CO_2$	torr	−2 to +4	8–25	5–15†	140, 52
$P(A\text{-}a)O_2$ in air	torr	20–40	25–60	37–69	102, 125
in O_2	torr	230–380	270–550	165–465	102, 125
CO_2 response	ml/kg/min/torr CO_2	25–70	NA	NA	145

* RDS, respiratory distress syndrome; CLD, chronic lung disease; NA, not available. Ranges are 1 SD below and above the mean for spontaneously breathing babies.

† Data from our laboratory.

TIDAL VOLUME AND MINUTE VENTILATION

Definition. Tidal volume (V_T) is the volume of gas inspired or expired in an average breath. Minute ventilation is the volume of gas expired in 1 min.

Background. The first attempt to measure tidal volume and minute ventilation in babies was made in 1890 with a spirometer (21). However, it was not until 1931 that reliable measurements were made in term and preterm infants using a plethysmograph with no dead space (22, 23). In 1949, Cross (24) replaced the neck seal with an inflatable ring surrounding the face making the plethysmograph safer and simpler. Miller and Smull (25) used a wet test gas meter and one-way valves to measure ventilation during normoxia and hypoxia.

Because these devices are difficult to use and may affect ventilation (26, 27), noninvasive methods to estimate tidal volume were developed (28, 29). Impedance was evaluated in infants by Polgar in 1965 (30). In 1970 Milner (31) described a respiratory jacket to measure tidal volume. Induction plethysmography was first used in infants in 1981 (32).

Technique. Qualitative measurements of V_T include impedance pneumographs and thermistors. In impedance pneumography, an alternating current is passed continuously across the thorax between skin electrodes. Changes in thoracic circumference and blood volume during respiration cause a change in impedance roughly proportional to tidal volume (28–30). A thermistor at the proximal airway senses temperature changes caused by the flow of respiratory gas (33).

Semiquantitative methods detect changes in ventilation but may not be accurate enough to quantitate these changes. As the circumference of the thorax increases, the resistance of a mercury-in-rubber strain gauge placed around the chest changes in proportion to changes in volume (30). Respiratory inductive plethysmography uses Teflon-coated wires incorporated into bands which surround the abdomen and rib cage (32). Inductance is related to the cross-sectional area. $V_T = (AB \times I_{AB}) + (RC \times I_{RC})$ where AB and RC are the abdominal and rib cage constants and I_{AB} and I_{RC} are the changes in inductance of the abdomen and rib cage signals. The device is calibrated with a standard quantitative method and the constants are determined. At least two markedly different sets of values for V_T, I_{AB}, and I_{RC} are required (34). Semiquantitative measurements are also obtained using a jacket plethysmograph (31) or magnetometers (35).

Quantitative measurements are made with a plethysmograph, spirometer, or pneumotachograph. The plethysmograph is an airtight box into which the infant is placed with only the head, face, or airway in communication with the outside (24). During tidal breathing, the change in volume of the thorax causes a proportional change in the box pressure measured by a differential pressure transducer and tidal volume is calculated using Boyle's law. To calibrate the plethysmograph, known volumes are added and withdrawn. The related barometric technique has not been widely used (36).

Spirometry measures volume directly (37). V_T subtracted or added to a water-sealed chamber causes a proportional displacement of a light-weight lid. This mechanical signal is changed to an electrical signal and recorded. If volume is recorded with respect to time, flow can be calculated.

The pneumotachograph is the most common and most practical method of measuring ventilation, particularly in sick infants. With laminar flow, the pressure drop across a resistance is linear (38). This pressure, proportional to flow, is measured by a differential pressure transducer. The flow signal is integrated with respect to time to obtain volume. A pneumotachograph suitable for the small, sick infant has a low mass, low dead space, and low resistance (39). The pneumotachograph and integrator should be validated with a spirometer to be certain that the signal

is linear (±5%) within the expected range of flow, volume, and combined frequency of the ventilator and baby (39).

Gas concentration, humidity, and temperature affect the flow signal and must be considered during calibration (39). The pneumotachograph is attached to an endotracheal tube, nasal prongs, nasal mask, face mask, or face chamber. To minimize dead space and resistance, we have designed several pneumotachographs to replace the infant's nasal prong or endotracheal tube adaptor (Fig. 1) (39, 40).

Applications. Qualitative methods are used clinically to monitor ventilatory rate and recognize apnea. The thermistor may be useful in detecting obstructive apnea, especially in infants with tracheostomy tubes.

Semiquantitative methods are used both clinically and for research purposes. For example, respiratory inductive plethysmography can measure changes in ventilation accurately enough to evaluate CO_2 response and other respiratory reflexes (41).

Quantitative methods are used primarily for research. Plethysmography is most useful for larger neonates; once set up, this technique allows repeated, reproducible measurements in a short period of time. The pneumotachograph is the best device for measuring ventilation in the small, sick newborn infant. The spirometer, while the most accurate, is the least used.

Limitations. Because impedance signals vary over time and with slight changes in position, the technique is only used to detect respiratory movement. Chest wall movement, and therefore a normal impedance signal, will be present with airway obstruction and no gas flow (42).

If calibrated properly, inductive plethysmography is useful and accurate in larger babies. Calibration factors may change, however, with movement of the bands or changes in the baby's position (32). We have been unable to calibrate the device in infants <1.5 kg who have significant chest wall distortion.

Errors associated with plethysmography include leaks in the box or around the baby's face and temperature and humidity changes in the box. Once sealed inside, the infant is not easily accessible and may be prone to temperature instability. Apnea and aspiration are major dangers. Small, sick babies may not tolerate being moved into a plethysmograph.

Even well-designed pneumotachographs have problems; condensation, especially on the screen, causes turbulent flow and a change in calibration. This is avoided in the ventilated infant by bypassing the ventilator humidifier during the study and keeping the ambient temperature close to body temperature or by heating the pneumotachograph. Some amount of drift in the integrator baseline is unavoidable and will limit the length of time that a continuous recording of volume can be made. Drift results from improper electronic calibration or a leak in the system. The differential pressure transducer must be linear over the range of pressures being measured. The volume of gas in the transducer and connecting tubing must be equal on either side of the diaphragm. An equal pressure applied to both sides of the transducer should result in no signal. If the transducer is unbalanced, the pressure measured may be inaccurate, especially if continuous positive airway pressure or mechanical ventilation is used.

The spirometer has little use in the small, sick infant. Unless a series of one-way valves is used, there will be unacceptable rebreathing after a few breaths. Spirometry is not feasible in ventilated babies.

LUNG VOLUME

Definition. Functional residual capacity (FRC) and thoracic gas volume (TGV) are defined as the volume of gas in the lungs at the end of a tidal breath; in normal subjects they are equal. FRC is the volume of gas that communicates with the airways; TGV also includes the volume of trapped gas.

Background. In 1956, Berglund and Karlberg (43) reported results of FRC measurements by helium dilution in healthy newborns. In 1962, problems associated with rebreathing techniques were avoided by Strang and McGrath (44) who measured the FRC of healthy term infants in a plethysmograph by nitrogen wash-in after oxygen breathing. The same year, Klaus *et al.* (45) measured TGV by plethysmography in well infants from 7 min to 17 days of age. This technique was used in sick infants by Auld *et al.* (46). Nelson *et al.* (47) found that, unlike the normal adult, well babies frequently have evidence of gas trapping (TGV > FRC). Because of technical problems in studying ill babies, noninvasive estimates of the changes in FRC have recently been described (32, 48, 49).

Technique. FRC is measured with a closed circuit (rebreathing) or open circuit (nonrebreathing) apparatus. With the rebreathing method, the baby breathes from a bag containing known concentrations of oxygen and a tracer gas (helium or nitrogen) until equilibrium is reached (30–60 s). The final concentration of the tracer gas is measured after absorption of and correction for CO_2 (50). FRC is then calculated: $FRC = [(ViCi)-(VfCf)-(V_DCf)]/Cf$ where Vi and Vf are the initial and final bag volumes, Ci and Cf are the initial and final tracer gas concentrations, respectively, and V_D is the apparatus dead space. Some investigators have added oxygen during the equilibration period (43, 51).

To calculate FRC by nitrogen washout, breath-by-breath N_2 is measured with a rapidly responding mass spectrometer (44) or nitrogen analyzer (52) while breathing 100% O_2. FRC is obtained from the dilution factor (w) and the average tidal volume minus anatomic dead space (V_T-V_D): $FRC = w(V_T - V_D)/1\text{-}w$ where w is the slope of a semilog plot of F_AN_2 *versus* breath number. This may be a single or two compartment model.

Gerhardt *et al.* (53) calculated FRC by collection and integra-

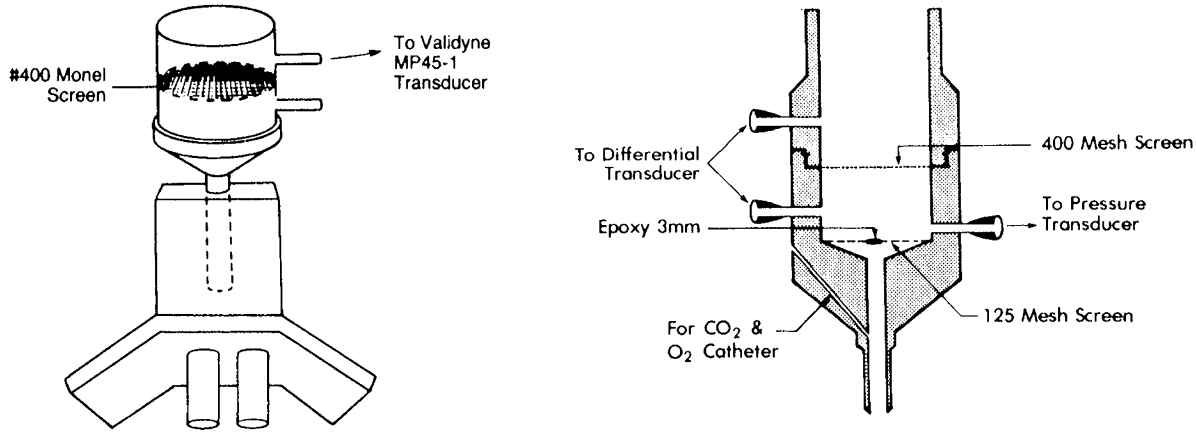

Fig. 1. Diagram of pneumotachographs that replace nasal prong and endotracheal tube adaptors. The 125-mesh screen and drop of epoxy in the endotracheal flowmeter make expiratory flow laminar. [Adapted from Goldman *et al.* (40) and Brady *et al.* (39).]

tion of the N_2 washed out with a constant flow of oxygen or a helium-oxygen mixture. Richardson *et al.* (54) developed a four-breath estimate of FRC that assumes a single compartment. Richardson and Jung (55) described a new method for calculating FRC from the breath-by-breath integration and summation of expired nitrogen with respect to expiratory flow. Richardson and Anderson (56) then reported an attractive modification which minimizes hyperoxia by using only a 10–20% change in inspired oxygen. These techniques are better suited to the premature infant. We use a 20% change in inspired oxygen and calculate FRC by the dilution factor method when V_T is constant or by summation of the product of expired nitrogen concentration and expired alveolar volume when tidal volume varies.

Ozanne *et al.* (57) used a mass spectrometer and on-line computer in sick adults and alternated nitrogen and argon in the washout gas mixture. Leaks were detected immediately by comparison of the results of duplicate measurements. To date, this very elegant and useful approach has not been applied to well or sick babies.

Thoracic gas volume is measured with a plethysmograph during an airway occlusion at end-expiration (45). Inspiratory effort changes box pressure (volume, ΔV) and mask pressure (ΔP). TGV is calculated with Boyle's law: $TGV = (P_B - P_{H_2O})\ \Delta V/\Delta P$ where P_B and P_{H_2O} are barometric and water vapor pressures, respectively. The glottis must be open for alveolar pressure to equal mask pressure.

Respiratory inductive plethysmography measures the changes in FRC noninvasively. The absolute changes in FRC are measured if tidal volume is recorded simultaneously (32). The changes in FRC are also measured during a passive exhalation following airway occlusion (48, 49). A plateau in mask pressure is obtained indicating a Hering-Breuer relaxation, the occlusion is quickly released, and the ensuing exhalation is analyzed. The linear portion of the flow-volume curve is extrapolated to zero, the "passive FRC" (Fig. 2*A*) (49). An alternative technique involves multiple occlusions. The regression of pressure and volume is plotted and extrapolated to zero, the "passive FRC" (Fig. 2*B*) (48).

Applications. Although a normal lung volume is critical in sick babies, it is rarely measured. Nonetheless, it has been used to assess changes in ventilator settings (55, 58), surfactant replacement (52), and diuretic therapy (59, 60).

Limitations. Unlike the adult where FRC (TGV) is stable, it may vary with each breath in the preterm infant with deformable airways and chest wall. Therefore, it is difficult to obtain reproducible results and different normal values have been reported. Rebreathing techniques are particularly difficult to use in ill babies requiring high ventilatory pressures. In babies with poor distribution of ventilation, equilibration time is prolonged and rebreathing causes hypoxia and hypercarbia. Leaks are a great source of error; Fox *et al.* (61) described a method that mathematically corrects for leaks and some investigators use cuffed endotracheal tubes. Finally, helium analyzers must be corrected for the effects of high oxygen.

The use of 100% oxygen for nitrogen washout may cause significant hyperoxia and may result in absorption atelectasis in areas with a low ventilation/perfusion ratio (62). Some FRC calculations require a relatively constant tidal volume and an accurate calculation of anatomic dead space (44). The integrated N_2 washout described by Gerhardt *et al.* (53) can be performed on intubated babies but not mechanically ventilated babies. It has the advantage of using oxygen-helium mixtures, but some nitrogen analyzers and mass spectrometers are inaccurate when >10% helium is present.

Helium-oxygen breathing decreases airway resistance in babies with chronic lung disease (63); it is not known whether this changes FRC. In babies with chronic lung disease and subglottic stenosis, Butt *et al.* (64) reported a decrease in oxygenation during breathing 70–80% helium in oxygen which was not seen when continuous positive airway pressure was given, suggesting that FRC might have changed.

Thoracic gas volume measured by plethysmography is impractical for sick babies and is prone to errors due to leaks and changes in water vapor pressure. Klaus *et al.* (45) used a reference volume as an internal check. Godfrey *et al.* (65) found that TGV was underestimated in babies with bronchiolitis and questioned whether it can be measured accurately when the airways are obstructed.

Inductive plethysmography is useful for following TGV changes over the short term. Long-term studies require an automatic baseline return (AC coupling) which obliterates the changes in end-expired volume. The occlusion method for "passive FRC" is ideal for spontaneously breathing babies but more difficult to apply in mechanically ventilated babies. Valves which add dead space and resistance are required. Leaks around the endotracheal tube make a pressure plateau impossible to achieve.

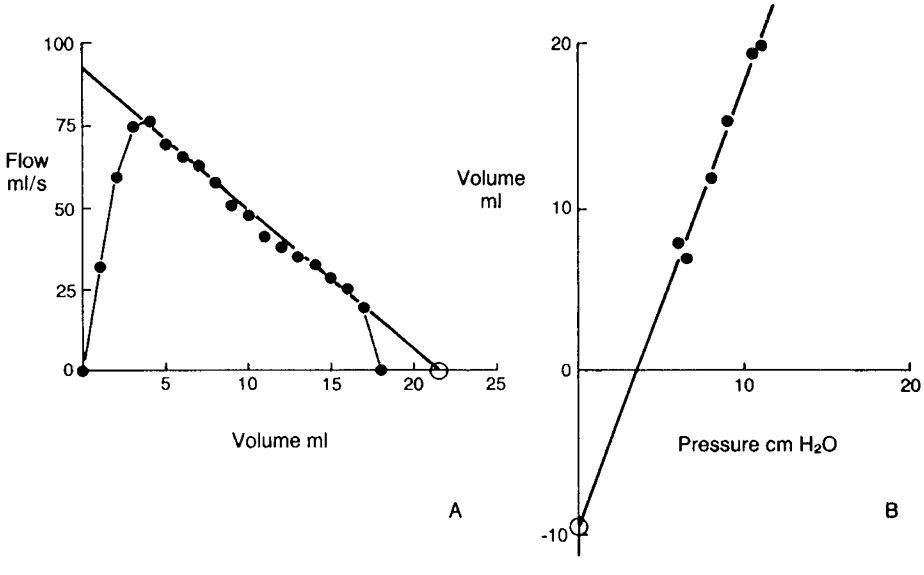

Fig. 2. Calculation of "passive FRC" and the passive mechanics of the respiratory system in a 2-kg well premature baby. *A*, passive exhalation following airway occlusion. The slope of the flat portion is the time constant of the respiratory system, 0.23 s, and the X-intercept is the "passive FRC." *B*, the regression of volume and pressure obtained with multiple airway occlusions. The slope of the line is the compliance of the respiratory system, 2.7 ml/cm H_2O, and the Y-intercept is the "passive FRC."

MECHANICS OF RESPIRATION

Definition. Compliance reflects the elastic properties of the respiratory system and is defined as the change in volume per unit change in pressure (ml/cm H_2O). The compliance of the total respiratory system (Crs) can be divided into lung compliance (C_L) and chest wall compliance (Ccw) where $1/Crs = 1/C_L + 1/Ccw$ (66).

Resistance of the respiratory system (Rrs) is a reflection of the friction encountered by gas flowing through the airways and by tissue moving against tissue. It is defined as the change in pressure required for a unit change in flow (cm H_2O/L/s). Rrs is the sum of airway resistance (Raw), lung tissue resistance (Rlt), and chest wall tissue resistance (Rcw). Lung resistance (R_L) is the sum of Raw and Rlt (67). Conductance is the inverse of resistance.

Work of breathing integrates the elastic and resistive properties and is equal to the cumulative product of pressure and the volume of air moved at each instant: Work = $\int PdV$ (67).

Background. Observations on the mechanical properties of the newborn infant's lungs were made by Karlberg *et al.* in 1954 (68). Using a 1-mm diameter polyethylene tube, they found that infants with respiratory distress syndrome had greater esophageal pressure changes than did normal infants. In 1955, using a body plethysmograph, pneumotachograph, and esophageal catheter, McIlroy and Tomlinson (69) calculated work of breathing and "elastic resistance" in 12 infants, three of whom were premature.

Cook *et al.* (70) described classical methods for measuring compliance and resistance and reported normal values in well and sick infants. Swyer *et al.* (71) were among the first to use a face-mask pneumotachograph and esophageal balloon to calculate mechanics of breathing.

Technique. Calculations of lung mechanics require the measurement of the pressure affecting the lung component of interest. For example, to calculate the respiratory system compliance of an infant receiving positive pressure ventilation, the changes in airway pressure (Paw) are measured and to calculate lung compliance, the changes in transpulmonary pressure (the pressure difference between the airway and the pleural space) are measured (Fig. 3).

Because direct measurement of pleural pressure is not feasible, it is estimated with esophageal pressure (Pes) (72–74). Esophageal pressure is measured with a pressure transducer attached to either a balloon catheter or a fluid-filled catheter in the lower third of the esophagus. Balloons can be handmade (73, 75) or manufactured (6.5 mm wide, 30 mm long, 0.06 mm wall thickness, Alto Development Company). We double tie the balloon to an 8-Fr feeding tube with six side holes and connect it to a pressure transducer (Gould Statham PM131TC) with 50 cm of PE205 tubing.

The accuracy of the measurement is affected by the balloon and catheter dimensions, the frequency response of the pressure transducer and catheter system, and the volume of air in the balloon. All these must be assessed *in vitro* with the equipment configuration used for the study. We have found that 8-Fr catheters are adequate (Fig. 4) but that 5-Fr catheters are not (Fig. 5). The 5-Fr balloon catheter signal in Figure 5 is signifi-

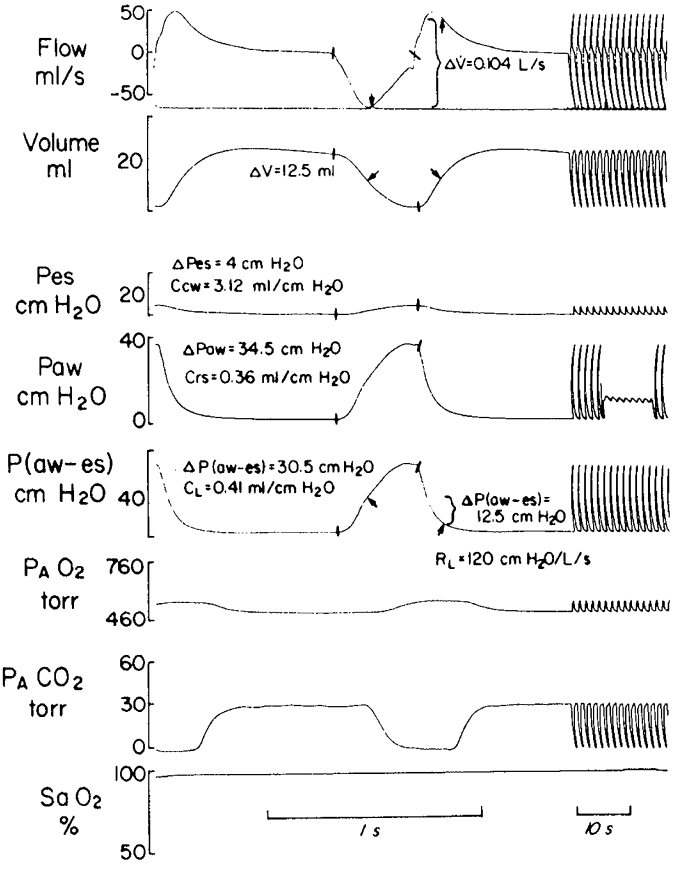

Fig. 3. Calculation of mechanics of ventilation in a 1.2-kg infant with severe chronic lung disease. Measurements at points of zero flow (|) are used to calculate chest wall compliance (*Ccw*), respiratory system compliance (*Crs*), and lung compliance (C_L). Measurements corresponding to mid-tidal volume (↑) are used to calculate lung resistance (R_L, the sum of airway resistance and lung tissue resistance). Mean airway pressure, obtained by electrical damping of the airway pressure signal, is 11 cm H_2O.

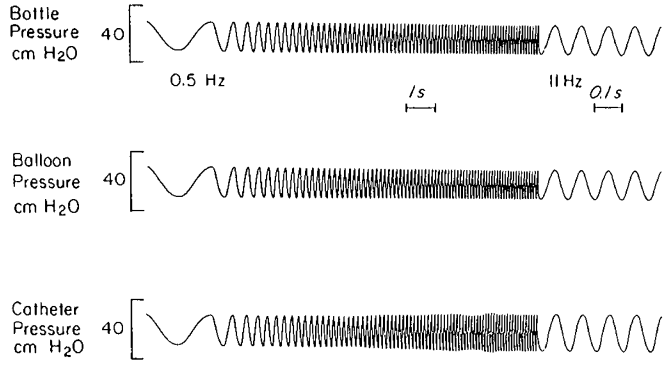

Fig. 4. Response of pressure transducers and 8-French catheter systems to changes in frequency from 0.5–11 Hz. The balloon pressure signal is from a 6.5 × 30 mm balloon attached to an 8-French feeding tube and the catheter signal is from a water-filled 8-French feeding tube, both with six side holes. The frequency response for all signals is linear (±5%) to 11 Hz.

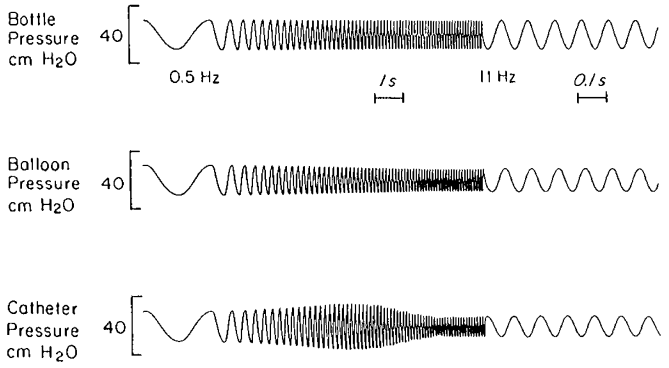

Fig. 5. Response of pressure transducers and 5-French catheter systems to changes in frequency from 0.5–11 Hz. With the same balloon as in Figure 4, but now attached to a 5-French feeding tube, the signal is overdamped at frequencies >6 Hz. The water-filled 5-French catheter signal is underdamped at frequencies >4 Hz and overdamped at frequencies >9 Hz.

cantly overdamped at frequencies >6 Hz; the 5-Fr fluid-filled catheter signal is underdamped at frequencies >4 Hz and overdamped at frequencies >9 Hz. A flat frequency response (±5%) to 10 times the fundamental frequency is required. The correct amount of air inside the balloon is determined by constructing a pressure-volume curve as described by Beardsmore *et al.* (75). The volumes which produce a negligible change in balloon pressure are appropriate. To evaluate its accuracy *in vivo*, the balloon or catheter is positioned in the lower third of the esophagus and an occlusion test is performed (75). During an occluded inspiratory effort, the pressure measured at the proximal airway should equal (±5%) the esophageal (alveolar or pleural) pressure.

Measurement of static compliance is not practical in sick infants and therefore the pressure used to overcome the respiratory system's elastance must be distinguished from that used to overcome its resistance. At end-inspiration and end-expiration there is no flow and therefore no resistance. The changes in volume and pressure at these points are used to calculate dynamic compliance (Fig. 3). Static compliance may be approximated if the infant is receiving positive pressure ventilation and has minimal spontaneous respiratory effort by sustaining the inspiratory pressure plateau for approximately 1 s (76).

In the newborn, Crs approximates C_L (Ccw is high and 1/Ccw is very low) and its measurement avoids the estimation of pleural pressure. Tepper *et al.* (77) used the weighted spirometer technique in infants. A weight placed on the bell of the spirometer produces a continuous positive pressure (ΔP) which causes an increase in end-expiratory volume (ΔV). The technique assumes that the increased pressure completely equilibrates within the lung.

Teague *et al.* (78) modified a constant flow method for measuring Crs in mechanically ventilated infants. The technique is based on the principle that gas flowing into a container at a constant rate causes a constant increase in pressure that is inversely proportional to the compliance of the container. The ventilator flow rate during inspiration (ml/s) divided by the slope of the airway pressure tracing (cm H_2O/s) equals the "pulse" compliance of the respiratory system.

In spontaneously breathing infants, not all of the pressure generated by the inspiratory muscles is used efficiently; some is wasted in distortion of the chest wall. Thus, in the immature infant with the most deformable chest wall, compliance may be underestimated (48). The magnitude of this wasted pressure can be determined by comparing the passive compliance of the respiratory system with dynamic compliance. Passive compliance is calculated during respiratory muscle relaxation (48, 49, 79, 80). The airway is occluded during expiration at different lung volumes and the proximal airway pressure (or mouth pressure) is plotted against volume; the slope of the linear regression represents compliance (Fig. 2*B*) (48). In spontaneously breathing infants, relaxation of the respiratory muscles is induced with the Hering-Breuer reflex (49).

To calculate resistance, the change in flow and the corresponding change in pressure must be measured. As with the calculation of compliance, the pressure used to overcome resistance must be differentiated from that used to overcome elastance. To do this, a pressure-volume loop is constructed (Fig. 6) (81). The slope of the line AC is the lung compliance and the distances EB and ED are the additional pressures needed to overcome airway and tissue resistance during inspiration and expiration. Because compliance is not always linear (82), it is better to calculate total resistance, the sum of inspiratory and expiratory resistance. A second method uses the flow, volume, and pressure tracings (Fig. 3). R_L is calculated using the differences in transpulmonary pressure, P(aw-es), and flow at equal volume points during inspiration and expiration. At equal volumes, elastic components should be equal and opposite; mid-tidal volume is usually used (83).

Airway resistance is measured using the plethysmograph (84). The driving pressure is the alveolar pressure inferred from the pressure change within the box. The flow is measured directly with a pneumotachograph or calculated from the volume tracing. The adult subject must pant during this measurement because large breaths may cause an artifact due to temperature and humidity. As infants cannot pant voluntarily, a heated rebreathing system was developed by Stocks *et al.* (85).

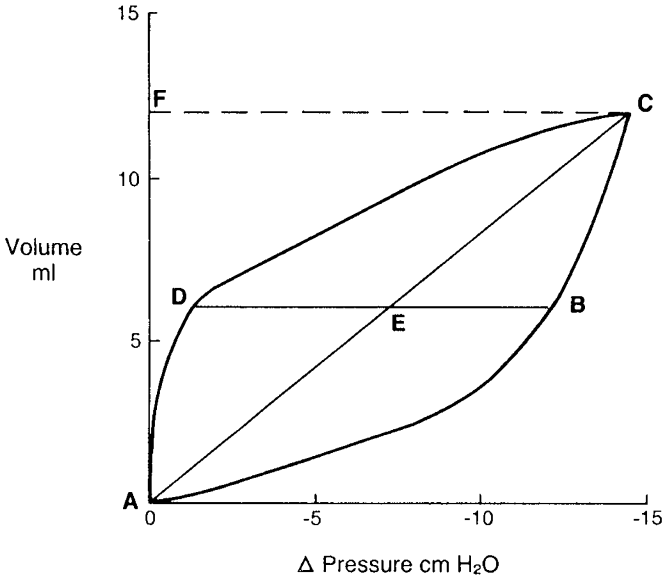

Fig. 6. Pressure-volume loop for calculation of mechanics of ventilation in a 1.6-kg infant with chronic lung disease. The slope of line AC is lung compliance, 0.86 ml/cm H_2O. The distances EB and ED represent the additional inspiratory and expiratory pressures needed to overcome airway and tissue resistance. The distance DB divided by the difference in flow at those points is equal to the total lung resistance, 150 cm H_2O/liter/s. The work of breathing, the area ABCF, is 145 g cm/breath.

Respiratory system resistance is calculated using the techniques for passive Crs (48, 49, 79, 80). The slope of the linear portion of the expiratory flow-volume curve is the respiratory system time constant, the product of Crs and Rrs (Fig. 2*A*). If Crs is known, Rrs can be calculated.

Work of breathing is calculated by constructing a pressure-volume loop and measuring the area (Fig. 6). The area can be measured by hand; we use a microcomputer and digitizer. There are several equations that estimate the work of breathing (70). McIlroy used the formula: Work = 0.6 PV_T where P is the peak pressure generated. The formula assumes that the pressure is a sine wave and that 70% of total work is elastic.

Applications. All of these techniques have been used to study small, sick infants. We have evaluated the effects of disease state, medication, and mechanical ventilation on respiratory mechanics (40, 86–88). Recently available computerized systems have the potential for routine clinical use. Modifications of resistance measurements such as flow-volume curves with gases of different densities and viscosities have been used to diagnose small airway disease in infants (89).

Limitations. It is extremely important that all of the instruments be properly calibrated, balanced, and in phase. Because the calculations use the temporal relationships of two to three variables, any equipment problems will be magnified (90). The rigorous quality control needed is described by Beardsmore *et al.* (75). A major limitation of many techniques is the estimation of intrapleural pressure by esophageal pressure. Air bubbles or mucus in the fluid-filled catheter lead to inaccurate measurements. LeSouëf *et al.* (91) demonstrated that pleural pressure is unevenly distributed around the esophagus, especially in premature infants with significant chest wall distortion. In these infants, results of the occlusion test are variable. Beardsmore *et al.* (92) demonstrated that when FRC is significantly increased

or when positive pressure is used, Pes may not reliably estimate pleural pressure. The occlusion technique for verifying Pes assumes that there is instantaneous equilibration of pressure throughout the airways. This is not true with heterogeneous time constants or with partial airway obstruction (93–95).

Even if accurate measurements of compliance and resistance are made, their significance may be limited if the lung volume is not known. Compliance is greatly affected by lung volume; an over- or underdistended lung has a lower compliance. As the lung grows, the compliance of the whole lung increases, whereas the compliance of each lung unit is relatively constant. Thus the low compliance measured in infants with respiratory distress syndrome is due, in part, to smaller lung volumes. Specific compliance (compliance/FRC) or compliance/kg is more meaningful (1, 76).

The effect of lung volume on resistance is equally critical. As lung volume decreases, resistance increases exponentially. This relationship is more conveniently illustrated using conductance as there is a direct linear relationship between conductance and lung volume. Resistance or conductance should also be standardized using FRC (specific conductance), weight, or length (1, 76). When conductance is compared in premature infants of different gestational ages, its relationship to age should be considered. Stocks and Godfrey (96) demonstrated that there was a rapid decrease in specific conductance until 40 wk postconceptual age. An additional limitation is the effect of resistance on dynamic compliance. If airway resistance is elevated or the breathing rate is rapid, dynamic compliance will be falsely lowered; this is termed frequency dependence of compliance (97).

ALVEOLAR GAS TENSIONS AND ALVEOLAR VENTILATION

Definition. Alveolar gas tensions are the partial pressures of O_2, CO_2, and N_2 in alveolar gas; they are estimated with end-tidal gas tensions. Alveolar ventilation is the volume of inspired gas that takes part in gas exchange with pulmonary capillary blood. Wasted ventilation is the volume of inspired gas that does not take part in gas exchange and only comes in contact with dead space. Dead space consists of conducting passages (anatomic dead space), nonperfused or underperfused alveoli (alveolar dead space), and equipment dead space.

Background. Early estimations of end-tidal gas tensions were made on gas withdrawn from a miniature Rahn sampler (98). Although the sampler dead space was small, the total equipment dead space was large, resistance was high, and contamination with dead space gas was possible. These problems were avoided with continuous measurement of inspired and expired gas by Strang (99) in well babies using a mass spectrometer and Chu *et al.* (52) in sick babies with N_2 and CO_2 analyzers in series. When a rapidly responding O_2 analyzer became available, all three gases were measured simultaneously (100). The concept of ideal alveolar gas tensions (101) was applied to well and sick babies by Nelson *et al.* (102). Ideal alveolar PCO_2 was assumed to equal arterial PCO_2 and ideal alveolar PO_2 was calculated with the alveolar gas equation. Corbet *et al.* (103) used this method to calculate alveolar PN_2 and measured arterial PN_2 by gas chromatography in well and sick babies.

The first calculations of alveolar ventilation were reported by Karlberg *et al.* (68) in 1954 using the plethysmograph and arterial PCO_2. Mixed-expired CO_2, diluted in 5–6 liters of gas, was measured with the Scholander method. In 1961, Strang (99) used a plethysmograph, mass spectrometer, and the graphical method of Fowler (104) to measure anatomic dead space in well newborns. Nelson *et al.* (98, 105) measured both anatomic and physiologic dead space in well and sick infants using their end-tidal sampler, a spirometer, and arterial PCO_2. Chu *et al.* (52) calculated physiologic and anatomic dead space with the Bohr equation in very ill babies using arterial PCO_2, end-tidal PCO_2, and mixed-expired PCO_2 obtained either by hand integration of the expired CO_2 tracing with respect to volume or by collection of expired gas.

Technique. Alveolar gas tensions are very difficult to measure in the sick baby with a rapid breathing rate and irregular tidal volume. In ill babies, the alveoli may not empty uniformly making end-tidal tensions poor estimations of alveolar tensions (Fig. 7). Gas analyzers and mass spectrometers require a gas sampling rate of approximately 70 and 15 ml/min, respectively. We only accept end-tidal values when the mean expiratory flow rate is more than six times the sampling rate and the end-tidal plateau is more than three times the time constant of the gas analyzers and sampling system. This latter condition may not be achieved when the breathing rate is >90/min.

The transit time and time constant are affected by the sampling rate, the catheter and connecting tubing dimensions, and the vacuum system. We use 75 cm of unheated polyethylene tubing (0.38 mm ID) and Duo-Seal pump with CO_2 (Beckman LB2) and O_2 (Applied Electrochemistry S3A) analyzers connected in series (39). A powerful vacuum pump is required to create a pressure of −660 torr in the CO_2 sample cell (106). A second Duo-Seal pump draws gas through a needle valve interposed between the O_2 and CO_2 analyzers to the N_2 analyzer (Med Science 505). The transit time and time constant must be measured *in vitro* with a square wave change of flow and gas concentrations (Fig. 8). For these measurements, the polygraph pens should be in phase and the equipment in the configuration used for the study.

Ideal alveolar gas tensions (those present when there is no wasted ventilation or wasted perfusion) are calculated with the alveolar gas equation: $P_AO_2 = P_IO_2 + [P_ACO_2F_IO_2(1 - RQ)/RQ] - (P_ACO_2/RQ)$ where P_AO_2 and P_IO_2 are alveolar and inspired PO_2, respectively, P_ACO_2 is the alveolar PCO_2 assumed to equal arterial PCO_2, F_IO_2 is the fraction of inspired O_2 and RQ is the respiratory quotient. The respiratory quotient, CO_2 output divided by O_2 intake, has been measured (98, 107) or estimated (103).

As alveolar ventilation ($\dot{V}_A$) represents the portion of minute ventilation that reaches perfused alveoli, it is inversely proportional to PCO_2: $\dot{V}_A = \dot{V}CO_2(863)/P_ACO_2$ where $\dot{V}_A$ is in ml/min BTPS, $\dot{V}CO_2$ is the CO_2 output in ml/min STPD, P_ACO_2 is the alveolar PCO_2, assumed to equal arterial PCO_2, and 863 is a constant which converts $\dot{V}CO_2$ to BTPS and the fraction of CO_2 to the partial pressure. The first measurements of alveolar ventilation in babies were made in this way (68, 107). As arterial PCO_2 was used, physiologic dead space was calculated.

When rapidly responding mass spectrometers and gas analyzers are available, the Bohr equation is used to calculate dead space: $V_D/V_T = (P_ACO_2 - P_{\bar{E}}CO_2)/P_ACO_2$ where P_ACO_2 and $P_{\bar{E}}CO_2$ are alveolar and mixed-expired PCO_2, respectively. When ideal P_ACO_2, estimated by arterial PCO_2 is used, physiologic dead space is calculated; when end-tidal PCO_2 is used, anatomic dead space is calculated. We determine the mixed-expired PCO_2 with the integration method of Chu *et al.* (52) assisted by a computer and digitizer. Chu *et al.* (52) found that the time constant correction resulted in a difference of <5%. We find a 5% error

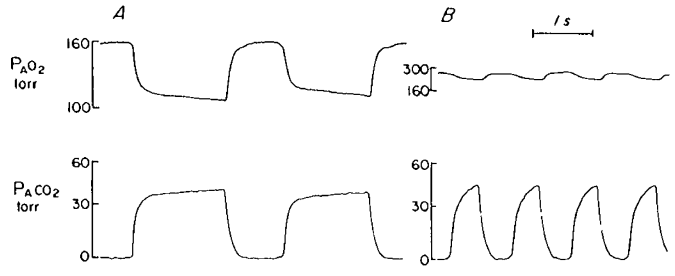

Fig. 7. End-tidal PO_2 and PCO_2 in an 11-wk-old term baby with normal lungs (*A*) and an 11-wk-old premature baby (28 wk gestation) with severe chronic lung disease (*B*). Note the normal PCO_2 and good alveolar plateaus in A contrasted with the high PCO_2, rapid breathing rate, and absence of alveolar plateaus in B.

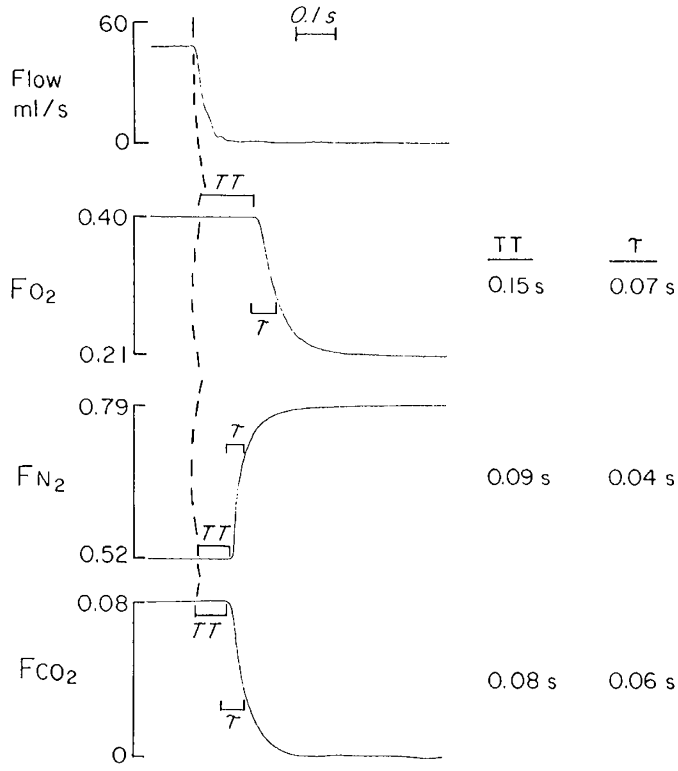

Fig. 8. Calculation of transit time and time constant for alveolar gas tensions. The *dotted line* marks the event, a square wave change in flow. The transit time (*TT*) is the time between the change in flow and the onset of pen deflection. The time constant (τ) is the time between the onset and 63% of the total pen deflection.

when the breathing rate is 30–60/min but a 25% error when it is >80/min and therefore apply it in every case.

Applications. Although alveolar ventilation is critical for gas exchange, it is rarely measured; the $PaCO_2$ is commonly used to estimate it. End-tidal gas tensions and alveolar ventilation measurements have been used to study the effects of surfactant replacement and diuretic therapy in sick babies (52, 87).

Limitations. In babies with severe maldistribution of ventilation, it may be impossible to obtain alveolar plateaus (Fig. 7) and calculation of ideal alveolar PO_2 is preferable. However, calculated ideal tensions are not always alveolar tensions. Corbet *et al.* assumed that the arterial-alveolar PCO_2 difference was zero in normal infants and 15 torr in sick infants (103). The respiratory quotient is usually assumed to be 0.7 or 0.8 and small deviations from this result in only small differences for P_AO_2.

DISTRIBUTION OF VENTILATION

Definition. Tests of the distribution of ventilation measure how evenly or unevenly inspired gas is distributed to all areas of the lung.

Background. Strang and McGrath (44) were the first to measure distribution of ventilation in well newborns. They used nitrogen wash-in after oxygen breathing and calculated pulmonary clearance delay as described by Fowler *et al.* (108). The following year, Nelson *et al.* (102) made these measurements in sick newborns. More recently, radioactive tracers have been used to assess the distribution of ventilation (109, 110).

Technique. Most tests of the distribution of ventilation are based on measuring how efficiently a tracer gas is removed from the lung (washed out) or equilibrated within the lung (washed in). Mathematical expressions of this efficiency include pulmonary clearance delay, inspired gas distribution index, and moment analysis (108, 111, 112).

Nelson *et al.* (102) used the method of Briscoe and Cournand (113) in which gas is sampled from the Rahn end-tidal sampler and F_AN_2 plotted on semilog paper as a function of time. When mass spectrometers and gas analyzers with suitable sampling rates are available, the method of Fowler *et al.* (108) is used. A semilog plot of F_AN_2 *versus* breath number is analyzed and the pulmonary clearance delay (PCD) is calculated: PCD = [(actual breath number-ideal breath number)/ideal breath number] × 100%. The breath numbers are calculated from the semilog plot and represent the average number of breaths required to remove a molecule of gas. Hanson and Shinozaki (111) measured cumulative alveolar ventilation and calculated the inspired gas distribution index, the ratio between the ideal and actual cumulative alveolar ventilation values required to reduce F_AN_2 to 0.02. Weygandt (114) described a five-breath index of the distribution of ventilation. This attractive technique reduces the duration of hyperoxia, but has not been used in babies.

Applications. Distribution of ventilation is commonly measured in adults but only rarely in babies. It is markedly abnormal in babies with chronic lung disease and may become a very important measurement as this population grows (115). Pulmonary clearance delay is most useful for studying these babies and their response to therapy. Heaf *et al.* (110) used ^{81}Kr ventilation scans in babies with unilateral lung disease and found, in contrast to the adult, that gas exchange was improved with the good lung uppermost.

Limitations. The calculation of pulmonary clearance delay by the method of Fowler *et al.* (108) depends on the accurate determination of mixed-expired N_2 or end-tidal N_2. When severe maldistribution of ventilation is present, end-tidal plateaus may not be obtained. As oxygen breathing may result in resorption atelectasis, areas of low ventilation/perfusion ratio may not be detected (62).

The use of radioisotopes is limited. The half-life of ^{13}N is 10 min; ^{81}Kr has a low radiation dose and is eluted from ^{81}Rb (half-life, 4.6 h). ^{133}Xe has a high radiation dose and is soluble in tissues permitting only single views. These techniques are rarely used for research because of ethical and technical considerations.

PERFUSION AND THE VENTILATION/PERFUSION RELATIONSHIP

Definition. Pulmonary capillary perfusion ($\dot{Q}pc$) is the volume of blood flowing through the lungs, composed of blood that participates in gas exchange (effective) and that which perfuses nonventilated or underventilated alveoli (shunted).

The PO_2 and PCO_2 of blood leaving the lungs depend not on ventilation alone or perfusion alone, but on the relationship between alveolar ventilation and pulmonary capillary perfusion (67). When there is perfect matching of ventilation and perfusion, there is virtually no wasted ventilation or wasted perfusion. The pioneering work of Riley and Cournand (101), Rahn and Fenn (116), and West (117) in understanding the importance of this relationship has been applied to well and sick babies by examining alveolar-arterial gas differences and the measured or calculated ventilation/perfusion ratio.

Background. Effective pulmonary capillary perfusion has been measured in well and sick babies using the soluble gases freon (52) and nitrous oxide (118, 119). The total shunt fraction (venous admixture) has been calculated in well and sick babies with the Berggren equation (120). Cardiac catheterization and injection of radioactive tracers have been used to measure total pulmonary blood flow (76).

The ventilation/perfusion relationship was first assessed in babies with the alveolar-arterial differences for CO_2, O_2, and N_2. Using the arterial-alveolar PCO_2 difference, Nelson *et al.* (105) suggested that the lung of the newborn with respiratory distress is overventilated relative to perfusion and, using the alveolar-arterial PO_2 differences in air and oxygen, they suggested that there was a significant right-to-left shunt in well and sick babies

(102). This latter finding was not confirmed by Ledbetter *et al.* (121) who found significant mismatching of ventilation and perfusion (rather than right-to-left shunt) in well babies as evidenced by a high urinary-alveolar PN_2 difference; urinary PN_2 was used to estimate arterial PN_2.

Technique. For the noninvasive measurement of effective pulmonary capillary perfusion ($\dot{Q}$pc eff), the baby rebreathes from a bag containing a known amount of nitrous oxide in oxygen. V_T is measured with a flowmeter or spirometer (118, 119). The decrease in gas concentration is proportional to the effective pulmonary capillary perfusion, the solubility of the gas in blood, and the lung volume. $\dot{Q}$pc eff = $(\dot{V}N_2O)\ 60/F_AN_2O\ \lambda\ t$ where $\dot{V}N_2O$ is the N_2O uptake in ml during t s, F_AN_2O is the mean alveolar N_2O concentration, and λ is the solubility of N_2O in cord blood in ml N_2O/ml blood. The percent of shunted blood is calculated with the Berggren equation: $\dot{Q}s/\dot{Q}t = (C\acute{c}O_2 - CaO_2)/(C\acute{c}O_2 - C\bar{v}O_2)$ (120) where $C\acute{c}O_2$ is the end pulmonary capillary O_2 content in ml O_2/ml blood calculated from the ideal alveolar PO_2 (101), $C\bar{v}O_2$ is the mixed-venous O_2 content assumed to be 0.02 or 0.03 ml O_2/ml blood less than arterial content (122). Invasive measurements of pulmonary blood flow include cardiac catheterization and injection of radioisotopes. During cardiac catheterization, pulmonary blood flow is calculated using the Fick principle by the measurement of O_2 consumption and the arterial-venous O_2 difference. Radioisotope studies involve the injection of ^{133}Xe, ^{13}N, or ^{99}Te-labeled albumin (76).

The alveolar-arterial PO_2 difference represents the right-to-left shunt caused by diffusion impairment, low ventilation/perfusion ratio, and anatomic shunt (117). Theoretically, true anatomic shunt is measured during breathing of 100% O_2 which overcomes both the diffusion barrier and mismatching of ventilation and perfusion. However, resorption atelectasis may occur creating a greater right-to-left shunt. The arterial-alveolar PN_2 difference reflects only areas of low ventilation/perfusion ratio and the arterial-alveolar CO_2 difference reflects areas of high ventilation/perfusion ratio (alveolar dead space).

The ratio of alveolar ventilation to pulmonary blood flow is calculated by measurement of both or with the equation: $\dot{V}_A/\dot{Q}pc = K(C\acute{c}O_2 - C\bar{v}O_2)/(P_IO_2 - P_AO_2)$ where P_IO_2 and P_AO_2 are inspired and alveolar PO_2, respectively, and K is a constant which converts the units to BTPS, the fractions of gases to the partial pressures and corrects for the effect of RQ on P_AO_2; if RQ = 1, K = 863 (67, 117). The ratio thus calculated represents an average for the whole lung, and in normal adults, is approximately 0.8. However, even in normal lungs, there is a spectrum of ventilation/perfusion ratios; the apex is relatively overventilated and the base, relatively overperfused. This is illustrated with the O_2-CO_2 diagram (Fig. 9) (116). In sick babies, the spectrum of ventilation/perfusion ratios is certainly greater. Increased right-to-left shunt causes the arterial PO_2 and PCO_2 to move away from the ideal alveolar PO_2 and PCO_2 toward the mixed venous point and increased alveolar dead space causes the alveolar PO_2 and PCO_2 to move toward the inspired gas point, resulting in large alveolar-arterial differences for both O_2 and CO_2 (117).

Applications. These techniques have been used in babies to understand how the lung functions in health and disease. The ideal alveolar-arterial PO_2 difference is the most widely used assessment of the ventilation/perfusion relationship (102, 123, 124). As this difference is affected by the inspired O_2, the ratio of alveolar to arterial PO_2 and the ratio of F_IO_2 to arterial PO_2 have been used to compare babies when F_IO_2 varies. Adamson *et al.* (125) calculated anatomic shunt (in O_2) and venous admixture (in air) in babies with respiratory distress syndrome and chronic lung disease and found decreased anatomic shunt but increased venous admixture in the latter group.

Limitations. The noninvasive technique for pulmonary capillary perfusion measures only flow through ventilated alveoli, whereas the invasive techniques measure total flow. The latter techniques are only rarely used for research. Both the Berggren equation and the $\dot{V}/\dot{Q}$ equation make assumptions regarding the arterial-venous O_2 difference, the affinity of fetal hemoglobin for O_2, and the pulmonary capillary PO_2.

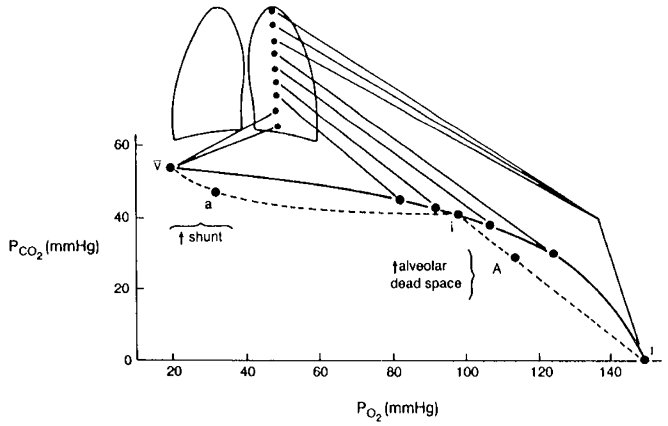

Fig. 9. The O_2-CO_2 diagram illustrating gas exchange in a lung with a poorly perfused upper zone and a poorly ventilated lower zone. Only the middle zone is contributing significantly to gas exchange. Increased shunt causes the arterial point (*a*) to move away from the ideal point (*i*) along the blood RQ line toward the mixed venous point ($\bar{v}$). Increased alveolar dead space causes the alveolar point (*A*) to move away from i along the gas RQ line towards the inspired point (*I*). These result in large alveolar-arterial differences for O_2 and CO_2, 80 and 20 mm Hg, respectively. [Adapted from West (117).]

CONTROL OF VENTILATION

Definition. Richards (126) described the control of breathing as a strange phenomenon "caught midway between the conscious and the unconscious, and peculiarly sensitive to both." The conscious responses are controlled by the cortex and the unconscious and vagal responses are controlled by the brain stem (Fig. 10) (127). In the newborn, control of breathing is unique because it varies with maturity, activity, noise level, oxygenation, and temperature (128).

Background. Much time and effort was devoted to discovering the cause of the onset of breathing at birth (129–131). Although in 1905, Ahlfeld (132) described breathing movements *in utero*, most physiologists discounted his work and unquestioningly accepted Barcroft's (129) findings of apnea in the unasphyxiated exteriorized lamb fetus. In 1960, there were three theories about peripheral chemoreceptor function in the newborn: Girard *et al.* (133) believed that it was absent at birth, Miller (134) believed that it was weak, and Cross and Warner (135) believed that it was hyperactive. Both Miller (134) and Cross *et al.* (136) believed that central chemoreceptor function was mature in term and preterm infants. For many years, 5% CO_2 in oxygen was used for resuscitation of the newborn in the belief that CO_2 would initiate breathing.

Difficulties in understanding peripheral chemoreceptor function in newborns were related to the biphasic response to low oxygen (an immediate hyperventilation followed by a depression in breathing) (136–138). Ceruti (139) found that the initial hyperventilation was abolished in a cool environment (Fig. 11). Both Cross *et al.* (136) and Rigatto and Brady (140) attributed the depression in breathing to a central hypoventilation since low O_2 decreased the CO_2 response and high O_2 increased it (141). These findings, unique to term infants for the first 2 wk of life and preterm infants for the first 4 wk, were consistent with the rediscovery of fetal breathing movements in 1977 which cease with hypoxemia and increase with hypercapnea (142). Central chemoreceptor responses were found even in very immature infants, but the slope of the CO_2 response curve was

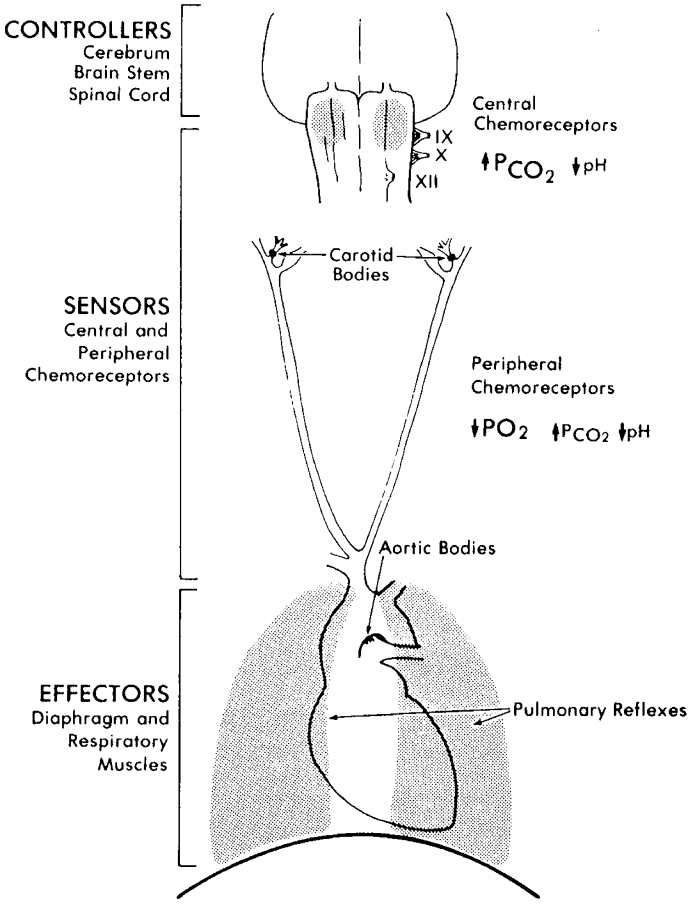

Fig. 10. Diagram of the brain centers, peripheral chemoreceptors, and effectors in man. The peripheral chemoreceptors respond to decreased PO_2 and pH and increased PCO_2 and the central chemoreceptors respond to decreased PCO_2 and pH. [Adapted from Berger *et al.* (127).]

shifted to the right, probably due to their unstable chest wall and FRC (143).

Technique. Chemoreceptor control is tested by measuring the changes in minute ventilation in response to a change in inspired oxygen or carbon dioxide and vagal control, by the changes in the duration of inspiratory effort during airway occlusion. Ideally, studies are performed during quiet sleep determined by an EEG (128) but often sleep state is inferred from behavior (144). The infant should be in a neutral thermal environment (139) and the concentrations of inspired and expired O_2 and CO_2 must be measured precisely to be sure of the stimulus. To evaluate the peripheral chemoreceptors in older infants, a 30-s challenge of high or low O_2 is adequate; in younger infants, 2–3 min are required to elicit the biphasic response. To evaluate the central chemoreceptors, air and one or two levels of CO_2 (2% and 4–5% CO_2) are administered for 4–6 min each. The change in minute ventilation in response to a change in arterial, end-tidal, or skin surface PCO_2 is calculated (the CO_2 response curve) (145). Because of difficulties in keeping a mask or nose piece over the sleeping infant's face, we have devised a method using only a nasal catheter to measure inspired and expired CO_2 and O_2 (146). Other investigators have looked at arousal response, the lowest end-tidal CO_2 which produces arousal from sleep during hypercapnea (147). Vagal reflexes are measured by occlusion of the airway at end-expiration (Fig. 12) (148). The duration of the subsequent inspiratory effort is compared with the unoccluded inspiratory time and percentage prolongation calculated. High values suggest active vagal reflexes and low values, absent ones. Many trials and a rapid paper speed (100 mm/s) are essential for valid results.

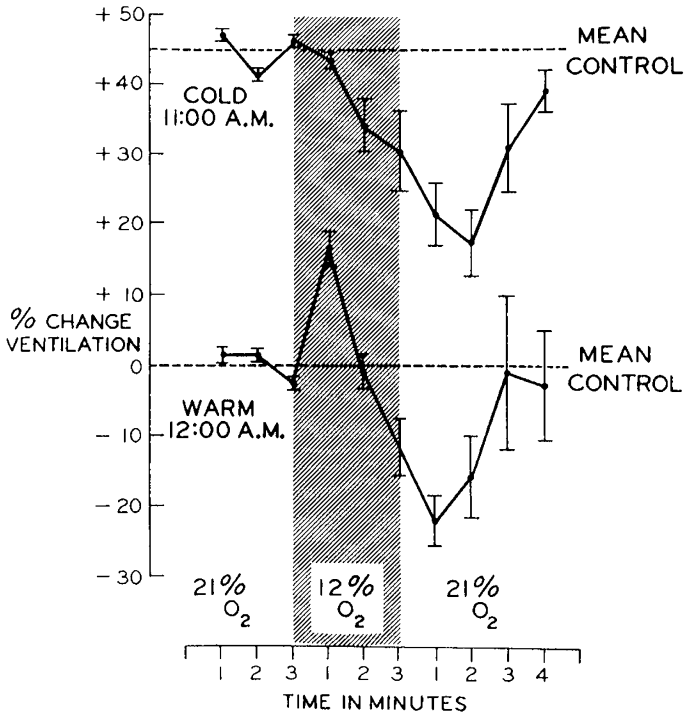

Fig. 11. Ventilatory response of the newborn to hypoxia. In a warm (neutral thermal) environment, there is a brief hyperventilation which is followed by a depression in breathing; in a cool environment, the hyperventilation is abolished. [From Ceruti (139). Reproduced by permission of *Pediatrics*.]

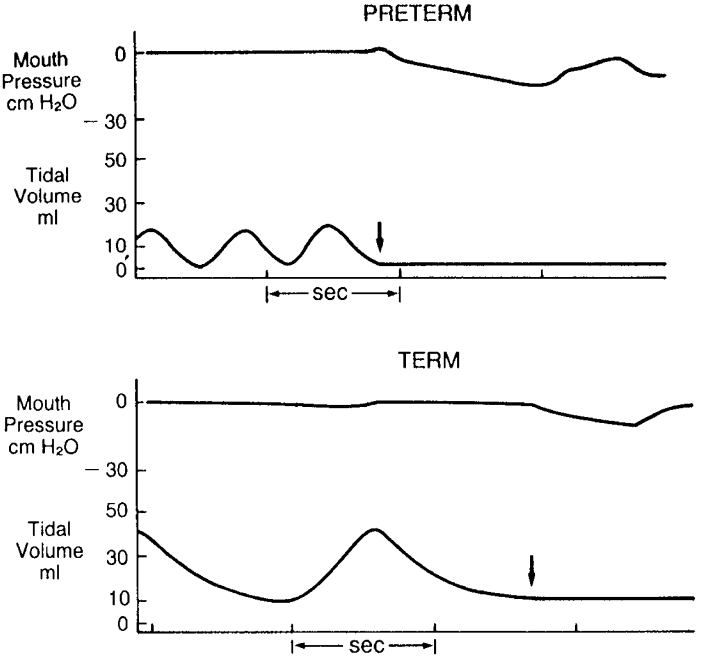

Fig. 12. Airway occlusion at end-expiration in preterm and term infants. In the preterm, occluded inspiratory effort is prolonged (1.1 *versus* 0.3 s) suggesting an active Hering-Breuer reflex; in the term infant, it is not (0.65 *versus* 0.7 s). [Redrawn from Olinsky *et al.* (148).]

Applications. There are many opinions and a plethora of studies, but no clear evidence that studies of control of ventilation are of value in detecting the infant who is at risk for prolonged apnea or sudden infant death syndrome. CO_2 responses are neither very reproducible nor easy to obtain. However, preterm

infants with recurrent apnea may have a reduced CO_2 response (149) and an absent response (less than 10 ml/kg/min/torr PCO_2) is diagnostic of central hypoventilation syndrome. In all these infants, the response to therapy can be monitored by this technique.

Limitations. Adequate evaluation of the central chemoreceptors requires at least 10 min of quiet sleep (5 min of air and 5 min of CO_2). Values obtained before the 4th min of hypercapnea underestimate the response. There is no consensus about the effect of chloral hydrate on the results but it is unlikely that arousal responses are valid if sedation is used.

COMMENT

Many pulmonary function techniques used in adults, even when modified for well newborns, are unsuitable for sick or small newborns. The frailty of these babies magnifies the difficulties of performing research. Clearly, however, efforts have been worthwhile; much has and is being learned about pulmonary disorders in the newborn.

Pulmonary function testing has become commonplace in adult medicine and is used routinely by the clinician. Many of the same tests are used only for research by those who care for sick newborns. Self-contained, on-line, computerized systems may make pulmonary function testing in newborns more common. It would be unfortunate, however, if these systems do not receive the same rigorous quality control that research pulmonary function laboratories follow.

Measurement of pulmonary function in babies has been developing for almost a century. We anticipate with excitement the developments of the next decade.

Acknowledgments. The authors thank Myrna Pantangco for expert manuscript preparation and Mary Helen Briscoe for illustration.

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