FACTORS AFFECTING THE COMPLIANCE OF THE LUNGS AND RESPIRATORY SYSTEM IN NEWBORN MAMMALS.

BY

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FOR MY PARENTS.

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ABSTRACT

The effect of lung deformation upon its mechanical properties was studied by measuring the quasi-static (Cstat) and dynamic (Cdyn) compliances of excised newborn piglet lungs deformed by a vertical pleural surface pressure gradient. Cstat was not affected by deformation. Cdyn was less than Cstat in the deformed and undeformed lungs but the difference was greater in the deformed lungs. This behavior suggests that distortion of the chest wall may increase the external (PV) work of breathing in newborns.

The contribution of lung viscoelasticity to the difference between Cstat and Cdyn of the undeformed lung was examined by measuring stress relaxation, Cstat, and Cdyn of excised lungs from newborn kittens and adult cats. The relative difference between Cdyn and Cstat and the magnitude of stress relaxation decreased with age, indicating that the viscous nature of the newborn's lungs causes larger, rate dependent changes in its compliance compared to the adult's.

Age related changes in the viscoelastic properties of the rat respiratory system were examined in rats between 1 and 40 days old. The rate of stress relaxation increased in the first week and thereafter decreased. Mean rates of stress relaxation were used to predict rate dependent changes in the passive recoil pressure of the respiratory system using an empirical model of viscoelasticity. Predictions were close to actual values suggesting that frequency dependent changes in the dynamic compliance of the newborn's respiratory system can occur independently of mechanisms involving the distribution of ventilation.

RÉSUMÉ

La déformation du poumon entraine des modifications de ses proprietés mécaniques. Ces changements ont été étudiés en mesurant les compliances quasi-statiques (Cstat) et dynamiques (Cdyn) de poumons de porcelets nouveaux-nés excisés et déformés par un gradient vertical de pression pleural. Cstat ne varie pas quand la déformation est appliquée. Cdyn est inférieur á Cstat aussi bien dans les poumons déformés que dans les poumons non déformés, l'écart étant plus grand pour les poumons déformés. Un tel comportement suggère qu'une distorsion de la paroi thoracique peut accroitre le travail (P.V.) nécessaire á la ventilation chez les nouveaux-nés.

La part de la différence entre Cstat et Cdyn imputable aux propriétés viscoélastiques du poumon a été examinée en mesurant les relations de contrainte-relaxation et les parametres Cstat et Cdyn sur des poumons éxcisés de chatons nouveaux-nés et de chats adultes. La différence relative entre Cstat et Cdyn et l'amplitude de la relation de contrainte-relaxation diminuent avec l'âge. Ceci indique que le caractère visqueux du poumon de nouveau-né provoque des variations de sa compliance qui dépendent de facon plus marquée de la vitesse de remplissage et qui sont plus importants que ce qui est observé chez l'adulte.

Les variations des proprietés viscoélastiques du système respiratoire du rat en fonction de l'âge ont été étudiées sur des animaux agés de la 40 jours. La vitesse de la contrainte-relaxation augmente durant la première semaine et rediminue par la suite. Les vitesses moyennes de contrainte-relaxation ont été utilisées pour prédire les changements de la tension passive de repliement qui dependent du temps. Cette étude repose sur un

modèle empirique de viscoélasticité. Les prédictions du modèle sont en bon accord avec les données expérimentales. Ceci indique que les variations de la compliance dynamique du système respiratoire du nouveau-né qui dépendent la fréquence peuvent exister indépendament des mécanismes qui font appel á la distribution de la ventilation.

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Preface

This thesis conforms to the guidelines concerning thesis preparation outlined by the Faculty of Graduate Studies and Research of McGill University. The Faculty offers the Candidate "the option, subject to the approval of the Department, of including as part of the thesis the text of an original paper, or papers, suitable for submission to learned journals for publication."[1]

Chapters 2 and 3 of this thesis are published in the Journal of Applied Physiology, and Chapter 4 is published in Respiration Physiology. Chapter 5 was recently submitted for review to the Journal of Applied Physiology. Each published study is listed in the Bibliography at the end of this thesis.

The unit of pressure measurement (cm H_2O) employed in this thesis is commonly used in studies of the respiratory system and accepted by the above mentioned journals. The SI unit of pressure is the Newton/m^2 which has units kg m^{-1} s^{-2}. One Newton/m^2 is usually referred to as one Pascal which is abbreviated 1 Pa. The conversion factor for cm H_2O to Pascals is given by

$$1 \text{ cm } H_2O = 99.75 \text{ Pa}$$

1. From "Guidelines Concerning Thesis Preparation", Faculty of Graduate Studies and Research, McGill University. Revised, April 1984.

CHAPTER 1

INTRODUCTION

LUNG DEFORMATION

During inspiration, the diaphragm is displaced in to abdomen, causing pleural pressure to fall and drawing air into the lung. Simultaneously, the pressure within the abdomen increases as the abdominal contents are pushed against the elastic abdominal wall. Part of the wall distends outward and the dimensions of the abdomen vary according to the change in abdominal pressure (Goldman and Mead, 1973). The motion of the abdomen and rib cage together describe changes in the configuration of the respiratory system (Konno and Mead, 1967). During quiet breathing in an adult upright man for example, the motion of the abdomen and rib cage is similar to the pattern observed during a relaxed expiration. This pattern is determined solely by the passive recoil of the chest wall and lung and thus reflects the least elastic work of breathing. Distortion of the respiratory system may be defined as any process which causes the configuration of the respiratory system to deviate from its relaxed configuration.

In adult man, the increase in abdominal pressure during inspiration acts to expand the lower rib cage, thus counteracting the effect of the decreasing pleural pressure (Goldman and Mead, 1973). The action of abdominal pressure does not affect the upper rib cage, where the change in pleural pressure encourages the rib cage to move inward and thus reduce the volume of the thorax. However, the effect of decreasing pleural pressure on the upper rib cage is counteracted by the contraction of the parasternal, scalene and sternomastoid muscles which pull the rib cage upwards and out-

wards thus expanding the rib cage circumference and increasing thoracic volume (Druz and Sharp, 1981) Inhibiting these muscles eliminates their influence on rib cage dimensions and causes an inward movement or collapse of the upper rib cage during inspiration (Iscoe et al , 1977) The situation is somewhat different in the newborn The diaphragm of the newborn inserts nearly horizontally into the rib cage in contrast to the adult diaphragm which inserts at an oblique angle (Muller and Bryan, 1977) This arrangement tends to draw the rib cage inwards during inspiration not only because the force of the contracting diaphragm is transferred more directly to the rib cage but also because the diaphragm is less displaced into the abdomen thus causing relatively smaller changes in abdominal pressure As a result, the respiratory system of the neonate commonly displays inward or 'paradoxical' respiratory movements characterized by partial collapse of the lower rib cage (Knill et al , 1976)

Although the action of the newborn diaphragm would appear to encourage distortion of the respiratory system, there are other factors which predispose the chest wall to deviate from its relaxed configuration One factor appears to be the compliance of the chest wall Newborn mammals have a relatively compliant chest wall compared to the lung, such that the chest wall/lung compliance ratio is greater than that found in adults (Avery and Cook, 1961, Fisher and Mortola, 1980, Mortola, 1983) This causes the chest to be more easily deformed by the action of the contracting diaphragm and the variations in pleural pressure Furthermore, the compliance of the chest wall is likely increased by inhibition of the intercostal muscles which tend to

stiffen and stabilize the chest wall (Tusiewicz et al, 1977). Inhibition of the intercostal and other postural muscles typically occurs during the active phase of sleep that is commonly called REM (Rapid Eye Movement) sleep. The newborn infant spends much more time asleep and in the REM state than adults (Parmalee et al, 1967) during which time there is a marked increase in chest wall distortion (Knill et al, 1976).

Since distortion of the chest wall represents a departure from its relaxed configuration, it will increase the work of breathing. Diaphragmatic EMG in the newborn infant increases more than 150% during chest wall distortion associated with REM sleep, suggesting that the work-load of the diaphragm is increased to compensate for the work of distorting the chest wall in addition to the work of ventilating the lung (Muller et al, 1979). Furthermore, prolonged distorted breathing causes shifts in the high/low ratio of the EMG frequency spectrum that are indicative of muscle fatigue, and are associated with an increase in the incidence of apneic spells. The total work of breathing represents the work performed by the respiratory muscles in order to ventilate the lung and consists of two forms, internal and external. The internal work is the work done in deforming the chest wall whereas the external (pressure-volume) work of breathing is the work done on the lung and is the conventional measure of respiratory work (Otis et al, 1950). Though part of the increase in the total work of breathing during chest wall distortion is undoubtedly due to an increase in the internal work, it is not clear how distortion affects the mechanical properties of the newborn lung. Conceivably, lung distortion may alter its

pressure-volume characteristics and therefore, the work of ventilating the lung. The external work of breathing is generally calculated from the relationship of transpulmonary pressure and volume, which is determined during spontaneous breathing by using an esophageal balloon to estimate changes in pleural pressure. Measurements of esophageal pressure in newborn infants during non-distorted, quiet breathing appears to be a reliable method of estimating variations in pleural pressure provided that a thin-walled balloon (Beardsmore et al, 1980) or a fluid-filled catheter (Asher et al, 1982) is used. During periods of marked distortion however, variations in the dimensions of the rib cage causes uneven distribution of pleural pressure in preterm and term infants, indicating that esphageal pressure may be an unreliable measure of mean pleural pressure (LeSouef et al, 1983). Consequently, this approach may not provide accurate information concerning the affect of lung distortion upon its mechanical properties. An alternative approach is to examine lung distortion using excised lung preparations in which the transpulmonary pressure can be measured with greater precision. Excised lung preparations have been used to examine the effect of lung distortion in adults using a variety of methods to produce distortion (Glaister et al, 1973; D'Angelo, 1975; Lai Fook et al, 1976; Murphy et al, 1983). However, no comparable studies have been done using the lungs of newborns. The object of the first study of this thesis then, is to assess the affect of lung distortion on excised lungs of newborn piglets.

LUNG VISCOELASTICITY

Viscoelasticity refers to the mechanical behavior of materials which are viscous but possess certain elastic properties such as the ability to store the energy of deformation. Most biological tissues are viscoelastic and can be distinguished from elastic materials by the viscoelastic phenomena of stress relaxation, creep and hysteresis. Stress relaxation refers to the time dependent decay in tissue stress that occurs when the tissue is stretched and held at its new length. Creep is the converse of stress relaxation and describes the gradual extension of a tissue under constant stress. If the tissue is subjected to cyclic loading, the loading process differs from the unloading process and a loop or hysteresis appears in the stress-strain curve over a complete cycle. Each of these phenomena are present to varying degrees in different tissue types, and because they are interrelated, a tissue which exhibits pronounced stress relaxation will also display pronounced creep and hysteresis (Fung, 1981).

The viscoelastic properties of a tissue are often examined using mechanical models composed of ideal springs and dashpots. One advantage of this approach is that the mechanical behavior of a tissue can be separated into hypothetical elastic and viscous components corresponding to the individual elements of the model. The method has been used for a variety of tissues such as arteries (Bergel, 1961), strips of aorta (Patel et al., 1970), and heart valves (Lim and Boughner, 1976) to characterize the mechanical behavior of the tissue during forced deformations. In general, the elastic and

viscous components of biological tissues increase rather slowly over a wide range of frequency and the energy dissipated per cycle, or tissue hysteresis, is nearly independent of frequency (Fung, 1972). In terms of viscoelastic models, this behavior can be simulated by a model composed of a large number of spring-dashpot combinations (ie. Maxwell elements) in parallel.

Since the lung and respiratory system are composed of viscoelastic tissues, their mechanical behavior, in terms of inflating pressure and volume, exhibit characteristics that are qualitatively similar to those observed in tissue strips. Stress relaxation within the lung and respiratory system for example, appears as a time dependent decay in transpulmonary or transrespiratory system pressure (Figure 1-1). The viscoelastic properties of the whole lung or respiratory system therefore, can be characterized in terms of time or frequency dependent variations in the relationship between inflating pressure and lung volume.

One of the first systematic studies of the viscoelastic properties of whole lungs was performed by Bayliss and Robertson in 1939. In that study, the pressure-volume characteristics of the lungs of adult cats were measured during forced mechanical ventilation and subsequently partitioned into viscous and elastic components. Lung elastance was defined as the change in pressure per unit change in volume due to the elastic forces within the lung and 'lung viscance' was the term used to describe the total non-elastic pressure expended during each cycle of ventilation. 'Lung viscance' was considered to be a combination of 'structure viscance', which is a

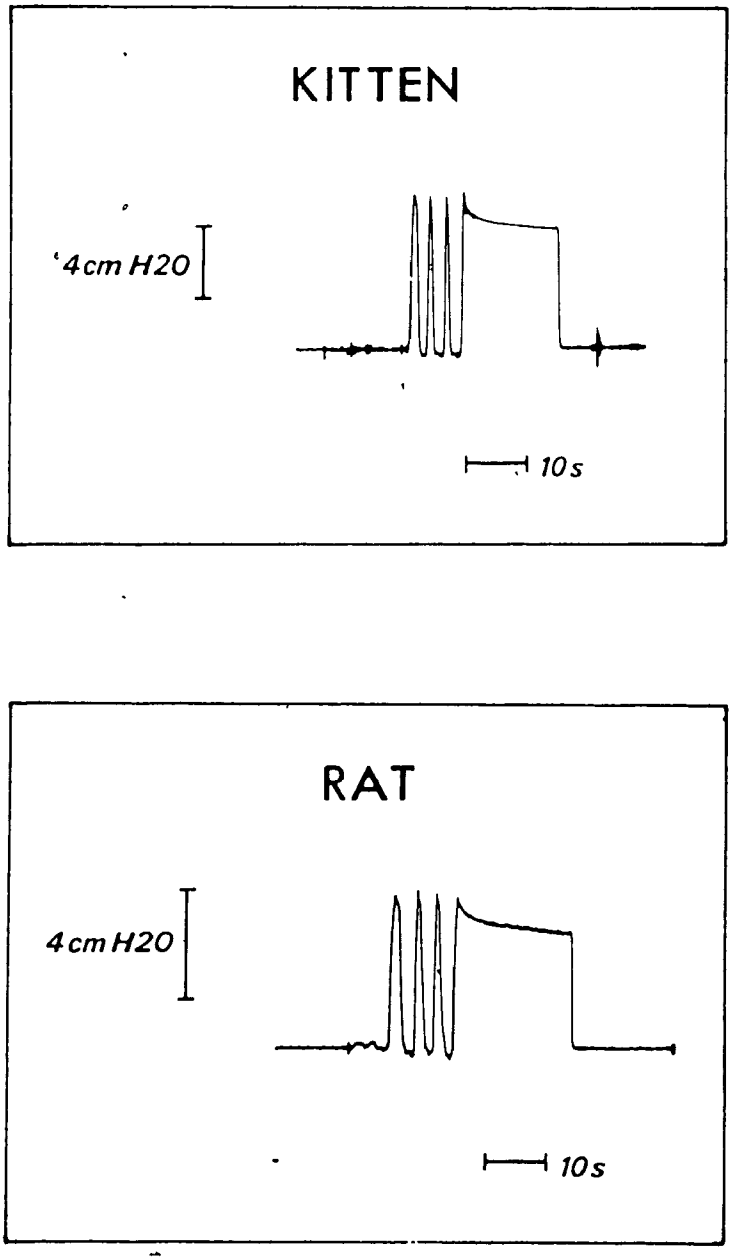

FIGURE 1.1 Examples of the time dependent decay in inflating pressure caused by stress relaxation within the excised lungs of a kitten, and the respiratory system of a newborn rat. Note that the decay process continues up to the moment the lungs are allowed to deflate.

property of the tissue, and 'air viscance', which is the pressure loss associated with the flow resistance of the airways. The relative contributions of structure and air viscance were estimated by varying the viscosity of the gases used to ventilate the lung. Several features of the lungs' viscoelastic properties were noted. Among these were: 1) lung elastance increased slowly with increasing frequency, 2) structure viscance was unaffected by ventilation frequency unlike air viscance which increased with frequency, and 3) structure viscance was about three times greater than air viscance and therefore was the principal source of total lung resistance. Bayliss and Robertson remarked that the lungs' structure viscance was unlike a simple viscous force since it did not vary with the rate of flow or the frequency of ventilation. However, structure viscance appeared to be related to lung elastance because changes in lung viscance often occurred simultaneously with changes in lung elastance. These observations were subsequently confirmed in studies of dog lungs by Dean and Visscher (1941), and rat and cat lungs by Mount (1955, 1956) who coined the term "tissue deformation resistance" in place of 'structure viscance'.

At about the same time, McIlroy et al. (1955) re-examined the method of using gases of different viscosity or density to estimate tissue resistance. They observed that the total pressure drop along the airways reflects the combination of laminar (viscous) flow resistance and non laminar, or turbulent, flow resistance. At a constant flow rate, the flow characteristics of a hypothetical segment of the airways is governed by its Reynolds number, which is given by:

$$Re = V D \left(\frac{\eta}{\rho}\right)^{-1} \qquad (1\text{-}1)$$

where D is the diameter of the airway, V is the mean velocity of the flow, and η and ρ are gas viscosity and density, respectively. For a hypothetical smooth-walled airway, laminar flow is characterized by a Reynolds number of less than 1500. Transitional flow that is neither fully laminar nor fully turbulent occurs at a Reynolds number of between 1500 and 2000 and turbulent flows generally develop a Reynolds number equal to or greater than 2000.

Since the Reynolds number associated with each airway depends upon the physical characteristics of the gas, McIlroy et al. reasoned that changing gas density or viscosity will alter the distribution of laminar and turbulent flows within the lung. As a result, the total pressure drop along the airways will not vary strictly in proportion to the change in gas viscosity or density, but will also vary according to the re-distribution of laminar and turbulent flows. To avoid changing the flow distribution within the lung, they proposed that gases of equal kinematic viscosity be used, where the kinematic viscosity of a gas is given by

$$\nu = \frac{\eta}{\rho} \qquad (1\text{-}2)$$

Under these conditions, the resistive pressure drop of the airway should vary in proportion to changes in viscosity and density, and tissue resistance may be estimated by extrapolating to conditions of zero viscosity and density. With this approach, McIlroy et al. showed that the lungs' tissue resistance in man accounted for about 30-40% of the total pulmonary resistance, or roughly half of the values reported by Bayliss and Robertson.

Although later studies have demonstrated that the pressure-flow characteristics are not strictly dependent upon gas viscosity and density (Macklem, 1980; Lisboa et al., 1980; Isabey and Chang, 1981), the results that McIlroy provided were the first indications that airflow resistance rather than tissue resistance was the largest source of the nonelastic properties of the lung.

Shortly after McIlroy et al. published their observations concerning lung tissue resistance, Marshall and Dubois (1956) measured lung tissue resistance in man using the plethysmographic method of estimating changes in intra-alveolar pressure developed by Dubois et al. (1956). Unlike previous methods where airflow and tissue resistance were calculated from two or more measurements made at different times, this method offered the advantage that total pulmonary, tissue, and airflow resistances could be measured simultaneously. To avoid variations in resistance due to changes in the humidity and temperature of the inspired and expired gases, Marshall and Dubois had their subjects pant through a heated flowmeter. The average value of tissue resistance obtained in this manner was about 17% of the total pulmonary resistance, or half again the value calculated by McIlroy et al. (ie. 0.10-0.35 cm H_2O/l/s versus 0.6 cm H_2O/l/s).

Though the plethysmographic method appeared to provide a more reliable method of estimating air and tissue resistances, Marshall and Dubois found the disparity between their measurements and previous measurements difficult to explain. Indeed, subsequent studies (Bachofen, 1966; Ferris et al., 1964; Jaeger et al., 1964) reported values of tissue resistance of between

2 and 40% of the total pulmonary resistance, using the same method. The cause of the variability in tissue resistance measurements remained obscure until Bachofen (1968) re-examined the factors governing the distribution of total pulmonary resistance in adult subjects. Bachofen measured airway and tissue resistance at various ventilation frequencies, mean lung values, and tidal volumes, and observed that lung tissue resistance differed from a simple viscous resistance because the energy dissipated by it did not vary with the frequency of ventilation. In other words, tissue resistance was similar to the 'structure viscance' measured by Bayliss and Robertson. However, since the energy dissipated by airflow resistance increases with the frequency of ventilation, the proportion of total pulmonary resistance that is tissue resistance will decrease and will be particularly low during panting maneuvers. Thus, the large variability in tissue resistance could be explained by differences in the breathing pattern used in the measurement of total pulmonary and airflow resistance.

Shortly after Bachofen described the features of lung tissue resistance, Hildebrandt (1969a) published the results of a study of lung viscoelasticity performed on the excised lungs of adult cats. In that study, the trachea was sealed to prevent airflow into and out of the lung, and lung volume was varied by expanding and compressing the gas within it, using a fluid-filled plethysmograph. Under these conditions, the energy dissipated by airflow resistance is minimized and the mechanical behavior of the lung was due primarily to its viscoelastic properties. Hildebrandt noted that the hysteresis area of pressure-volume loops obtained during sinusoidal variations in lung

volume, did not vary between 0.01 and 2 Hz but that dynamic lung elastance increased about 10% for every tenfold increase in frequency. Since the change in dynamic lung elastance was small over a wide range of frequency, Hildebrandt concluded that the frequency dependent changes in lung elastance caused by its viscoelastic nature are normally completely masked by other mechanisms that affect dynamic lung elastance, notably those affecting the distribution of ventilation within the lung (Otis et al., 1956; Mead, 1969).

From the various studies of lung viscance, lung tissue resistance and lung viscoelasticity, two salient features of the lungs' viscoelastic properties emerge. The first is that the energy dissipated by the lungs' viscoelasticity is nearly independent of the rate of flow or the frequency of ventilation and is probably less than the energy dissipated by the flow resistance of the airways. The second feature is that frequency dependent changes in lung compliance due to its viscoelastic nature are small over a wide range of ventilation frequency and therefore are practically negligible over the normal range of breathing frequency. Each of these features of lung viscoelasticity however, pertain only to the mature adult lung and it is unclear to what extent the viscoelastic properties of the newborns' lungs are similar. There is some evidence from studies of lung tissue resistance in children (Bachofer and Duc, 1968) and infants (Polgar, 1966) to indicate that these lungs are more viscous than the lungs of adults. This suggests that they may exhibit relatively greater frequency dependent changes in compliance than adult lungs. However, there are no studies which have correlated the lungs viscoelastic properties with the relationship between static and dynamic

measurements of compliance. This then, is the subject of the second study of this thesis. Since developmental changes in the viscoelastic properties of the lung will determine, in part, the changes in the passive mechanical properties of the respiratory system, the third and fourth studies of this thesis will examine the viscoelastic characteristics of the respiratory system at different ages.

CHAPTER 2

THE EFFECT OF LUNG DEFORMATION UPON THE MECHANICAL PROPERTIES OF EXCISED LUNGS FROM NEWBORN PIGLETS

SUMMARY

During breathing, the relatively high chest wall/lung compliance ratio of the newborn favors distortion of the respiratory system In this study we have examined the effect of lung deformation, generated by a hydrostatic pleural surface pressure gradient, upon the static (Cstat) and dynamic (Cdyn) compliance of the isolated newborn piglet lung Seven lungs from piglets 2-7 days old have been studied in a saline filled plethysmograph Static pressure-volume (P-V) curves were obtained by changing the volume a known amount and measuring the corresponding changes in transpulmonary pressure Dynamic P-V curves were obtained by ventilating the lung at a fixed pressure and at 20 cycles per minute These experiments were repeated in an air plethysmograph on the undeformed lung Lung volume history was standardized prior to each maneuver by three inflations to 20-25 cm H_2O Lung collapse was avoided by applying an end-expiratory load equal to the transpulmonary pressure at functional residual capacity Cstat was not significantly different between the deformed and undeformed lung ($P > 0.05$) Cdyn was less than Cstat in both cases ($P < 0.025$) and reduced further by deformation ($P < 0.05$) We conclude that 1) peripheral airway obstruction or the viscoelastic properties of the piglet lung, or both, decrease Cdyn, and 2) deformation increases the external (P-V) respiratory work by further decreasing Cdyn

INTRODUCTION

Newborn mammals have a relatively compliant chest wall which facilitates delivery through the birth canal. During spontaneous breathing the high chest wall/lung compliance ratio also encourages distortion of the thorax and its contents. The degree of deformation depends upon the activity of the accessory muscles of respiration, notably the intercostals, and is marked when the activity of these muscles is inhibited such as during active (REM) sleep (Hagan et al., 1976). A common observation in infants during active (REM) sleep, for example, is an inward or paradoxical movement of the rib cage on inspiration (Knill et al , 1976) Despite substantial changes in the dimensions of the rib cage, the newborn maintains approximately constant tidal volume and minute ventilation (Anderson et al., 1973) although some of the force generated by the diaphragm is used in deforming the rib cage (Bryan, 1979) This suggests that the work load upon the diaphragm is increased during deformation and ,in fact, the EMG of the diaphragm exhibits the characteristics generally associated with muscle fatigue during periods of rib cage distortion (Muller et al., 1979). If distortion of the lungs alters its mechanical properties, then the increased work load upon the diaphragm may be further augmented by an increase in the external (pressure-volume) work of breathing caused by chest wall deformation.

In this study we have examined the effect of deformation upon the static and dynamic compliance of the lung of newborn piglets in order to

determine how deformation affects the external (P-V) work of breathing The lung was immersed in a saline solution and was deformed by the combination of its buoyancy and a hydrostatic pleural surface pressure gradient Although other methods have been used to deform the lung (D'Angelo, 1975, Gillett et al 1981, Lai-Fook et al., 1976), this type of deformation is perhaps more appropriate in studies of the effect of deformation upon compliance since the hydrostatic pressure gradient resembles the pleural surface pressure gradient found in the intact thorax

MATERIALS AND METHODS

Seven newborn piglets between 2-7 days old were used for the experiment (Table 2.1) Each animal was anesthetized with Sodium Pentobarbital (35 mg/kg, i.p), tracheostomized and intubated with a small copper cannula (i.d = 4.5 mm) Following intubation, the animal was sacrificed by exsanguination. A pressure transducer (Statham, model 12174) connected to a high gain amplifier (Hewlett Packard carrier amplifier, model 8805A) was attached to the tracheal cannula and a bilateral pneumothorax was performed by puncturing the diaphragm where it inserts into the ribcage behind the sternum. The lungs collapse slightly against a closed airway and the tracheal pressure developed reflects the pressure due to the elastic recoil of the lung at its functional residual capacity (Pl_{FRC}) When a steady record of pressure was obtained, the lungs were allowed to collapse.

the ribcage was opened and the lungs were dissected away from the heart and removed. The tracheal cannula was repositioned so that it ended within 3 cm of the carina and was then fixed in position using surgical thread and adhesive. This step maintained an approximately constant tracheal length in all piglet lung preparations and minimized the contribution of the trachea to the total flow resistance of the lung. The lungs were then washed in a physiological saline solution (0.9gm% NaCl in distilled water) at room temperature (22-24° C) and placed inside the plethysmograph. Static and dynamic Pressure-Volume (P-V) curves were obtained from the lung suspended in air and immersed in saline. The shape of the lung under these conditions will be referred to as the undeformed and deformed condition, respectively.

The experiments were performed at room temperature. All variables were recorded on a multichannel pen recorder (Gould, model 260). At the end of the experiment, wet lung weight was determined using an analytical balance (Voland, model 220 D).

PRESSURE-VOLUME MEASUREMENTS OF EXCISED LUNGS

Figure 2.1A is a schematic of the apparatus used to obtain P-V curves of the isolated lung in air. The lungs were suspended vertically in the plethysmograph from the tracheal cannula which was open to the atmosphere (valve 1 open). Pressure within the plethysmogragh, P_B, was recorded using a pressure transducer (Statham, model 12174) connected to a carrier amplifier (Hewlett Packard, model 8805A). Transpulmonary pressure (-P) and

TABLE 2.1 PHYSICAL CHARACTERISTICS OF EACH PIGLET

Piglet No	Age (days)	Body Wt. (g)	Lung Wt (g)	Pl (cm H_2O)	H (mm)
1	6 5	2370	8 91	1 8	70
2	7 0	2040	6 45	1 9	96
3	6 0	1115	3 73	1 8	[illegible]
4	5 0	2320	7 89	2 9	80
5	2 0	1130	4 75	2 5	85
6	7 0	1250	4 47	2 5	84
7	6 0	2400	7 50	1 7	63

Physical characteristics of the piglets used to study lung deformation Pl, the quasi-static recoil pressure of the lung at its functional residual capacity (FRC). H, the length of the saline immersed lung

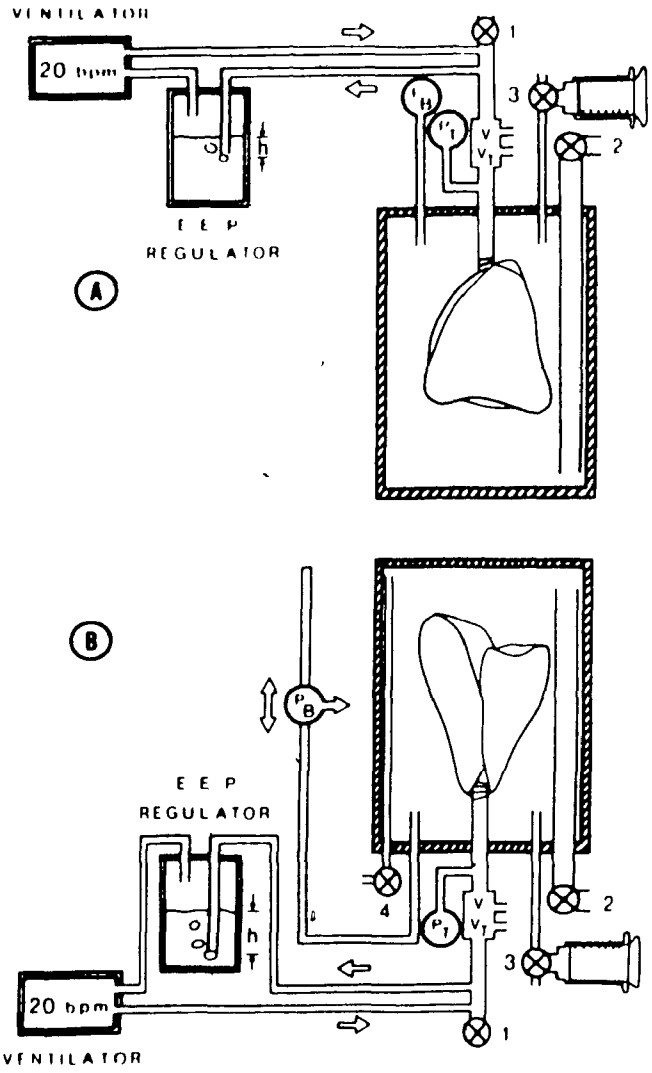

FIGURE 2.1 A schematic of the apparatus that was used to determine the effect of deformation upon the mechanical properties of the isolated piglet lung. Air (A) and a saline (B) filled plethysmographs were used to obtain the pressure-volume characteristics of the undeformed and deformed lung, respectively. P_B, plethysmograph pressure; P_T, tracheal pressure; EEP, end-expiratory pressure; V, flow; V_T, tidal volume.

lung volume were increased by withdrawing air from the plethysmograph into a 100 ml syringe, with valve 2 closed To obtain a static P-V curve of the piglet lung in air, lung volume history was first standardized by inflating the lung three times to a transpulmonary pressure of approximately 25 cm H_2O Following the third inflation to 25 cm H_2O, the lung was slowly deflated until transpulmonary pressure was equal to $Pl_{T,CR}$ When a steady state record of pressure was observed, the lung was inflated in steps by withdrawing equal volume increments of air from the plethysmograph into the syringe at 10 s intervals Once transpulmonary pressure reached 20 - 25 cm H_2O, the lung was deflated in the same fashion, now adding equal volumes of air to the plethysmograph at 10 s intervals until P_B equalled $Pl_{T,RC}$ Three static P-V curves of the isolated lung in air were obtained in this manner Volume increments were read directly from the syringe and corrected for gas compression

The dynamic compliance of the lung in air was determined in the following way The plethysmograph was opened to the atmosphere (valve 2 is open) and the lung was ventilated (Harvard Apparatus, model 260) at a constant frequency of 20 cycles per minute. Transpulmonary pressure under these conditions is everywhere equal and was recorded as a change in tracheal pressure (P_T). Flow ($\dot{V}$) and the change in lung volume (V_T) were obtained from a Fleisch type 00 pneumotachograph connected to a differential pressure transducer (Hewlett Packard, model 270) and respiratory integrator Hewlett Packard, model 8815A) and the end-expiratory pressure was set at Pl_{FRC} by adjusting the height (h) of the bubble regulator connected to the

expiratory line of the ventilator. The stroke volume of the ventilator was adjusted to provide an end-inspiratory pressure of 20 cm H_2O Prior to each maneuver, lung volume history was standardized by three inflations to approximately 25 cm H_2O For each record, P_T , $\dot{V}$ and V_T were recorded for after about one minute at constant end-expiratory and end-inspiratory pressures

PRESSURE-VOLUME MEASUREMENTS OF THE IMMERSED LUNGS

Figure 2 1B is a schematic of the apparatus used to obtain P-V curves of the lung immersed in saline Because the air filled lung is buoyant the plethysmograph was carefully inverted then filled with saline A small diameter tube extended to the top of the plethysmograph and was used to eliminate any trapped air that occurred during filling (valve 4) With the lung completely immersed, the hydrostatic pleural surface pressure gradient exerts unequal pressure along the height of the lung. In order to construct P-V curves, the mean transpulmonary pressure in the presence of the gradient had to be estimated. This was accomplished by measuring pressure., P_B , within the plethysmograph with a fluid filled pressure transducer (Hewlett-Packard, model 1280C) adjusted to the middle height of the lung The hydrostatic pressure at middle lung height is the mean pressure exerted by the gradient upon the lung and consequently, changes in transpulmonary pressure at this level represent changes in the mean transpulmonary pressure in the presence of the gradient To obtain a single static P-V curve of the

lung, midlung height was determined at Pl_{FRC} and at a transpulmonary pressure of 20-25 cm H_2O using a transparent ruler fixed to one side of the plethysmograph. The change in lung height between corresponding lung volumes was less than 1 cm and the level of the saline transducer was set at the mean of the two height measurements. Because the change in height was small, the error in the computation of mean transpulmonary pressure due to changes in middle lung height was less than 0 5 cm H_2O. Lung volume history was standardized by three inflations to approximately 25 cm H_2O. Following the third inflation the lung was slowly deflated to Pl_{FRC}. When a constant record of pressure was obtained the lung was inflated in steps withdrawing equal volumes of saline from the plethysmograph with the syringe at 10 s intervals until a mean transpulmonary pressure of 20-25 cm H_2O was reached. Then the lung was deflated by adding equal volumes of saline to the plethysmograph at 10 s intervals. Unlike the static P-V curves of the lung in the air plethysmograph, the saline filled system requires no correction factor; the volume read directly from the syringe is exactly the volume change of the lung. Three separate P-V curves were obtained in this manner.

To measure the dynamic compliance of the saline-immersed lung, enough saline was introduced into the plethysmograph to immerse the lung, leaving an airspace above the lung open to atmospheric pressure through valve 2 This was necessary to allow room for the saline displaced by the change in lung volume during each cycle. As a consequence of this airspace, the hydrostatic pressure exerted on the lung was everywhere greater

than atmospheric pressure This was not the case of the completely filled system used to determine the static P-V curve of the lung where, at mid lung height, pressure was subatmospheric. To correct for the added pressure, the end- expiratory load (h) was adjusted using the bubble regulator until it was equal to the sum of Pl_{FRC} and the hydrostatic pressure at middle lung height. The stroke volume of the ventilator was similarly increased until end-inspiratory pressure was equal to 25 cm H_2O plus the hydrostatic pressure at middle lung height With these adjustments, the mean transpulmonary pressure during each cycle ranged from Pl_{FRC} to 25 cm H_2O The error in mean hydrostatic pressure introduced by the upward displacement of saline was approximately 0 5 cm H_2O at a transpulmonary pressure of 25 cm H_2O and was neglected For each dynamic P-V measurement of the saline immersed lung, volume history was standardized by three inflations to 25 cm H_2O and P_T , $\dot{V}$ and V_T were recorded for approximately one minute

In order to evaluate the effect of fluid inertia upon the dynamic lung compliance the experiment was repeated with a balloon substituted for the lung Figure 2 shows an example of the dynamic inflation P-V curves of the balloon under the two conditions. At the peak pressure a small but significant (approximately 10%) increase in the compliance of the balloon was observed. The significance of this difference with regard to the lung will be discussed in the section devoted to RESULTS

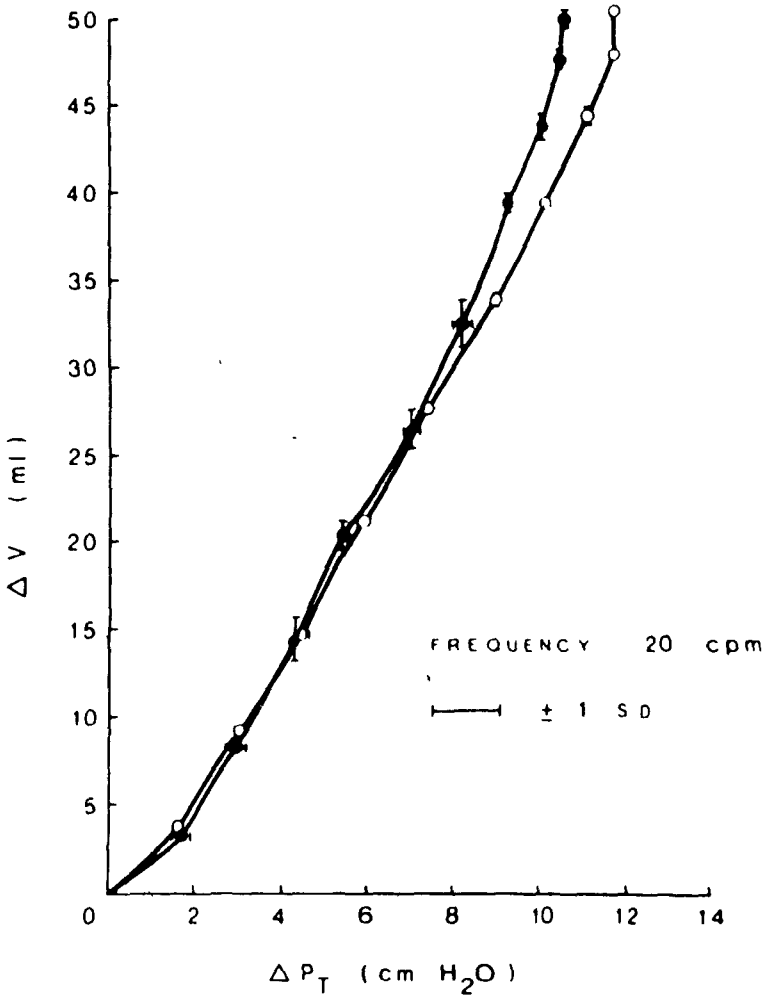

FIGURE 2 2 Dynamic pressure-volume (P -V) behavior of a balloon in air (open symbols) and immersed in saline (closed symbols) ventilated at 20 cycles per minute Symbols represent the mean of three trials and the bars represent one standard deviation When the standard deviations are very small, they have beep omitted for clarity

CALCULATION OF STATIC AND DYNAMIC COMPLIANCE

Static and dynamic P-V curves are constructed from the mean values of transpulmonary pressure and volume from three trials. Dynamic compliance (Cdyn) was measured as the ratio of the change in lung volume to the change in pressure between Pl_{FRC} and the transpulmonary pressure at the end of inflation (zero flow). The static compliance (Cstat) of the deflation limb was measured as the change in lung volume per unit change in transpulmonary pressure between Pl_{FRC} and 15 cm H_2O. Inflation limb static compliance is the ratio of the change in lung volume to the change in pressure between Pl_{FRC} and a transpulmonary pressure equivalent to the pressure at end-inspiration during dynamic ventilation. In this manner, static and dynamic compliance could be compared over the same range of transpulmonary pressure. The Student's t-test was used to determine if differences between groups of data were significant; a significant difference was defined at a P value <0.05.

RESULTS

The mean values of static and dynamic compliance for each piglet lung studied are presented in Table 2.2.

In Figure 2.3 are shown P-V curves obtained from a single isolated piglet lung. On the left are the static P-V curves and on the right are the inflation limbs of the dynamic P-V curves for the undeformed (continuous

TABLE 2.2 STATIC AND DYNAMIC MEASUREMENTS OF COMPLIANCE IN DISTORTED (IMMERSED) AND UNDISTORTED (AIR) LUNGS

Piglet No.	Cstat [Deflation] (ml / cm H_2O)		Cstat [Inflation] (ml / cm H_2O)		Cdyn (ml / cm H_2O)	
	Air	Immersed	Air	Immersed	Air	Immersed
1	1.65 (0.05)	1.89 (0.14)			2 06 (0 04)	0 80 (0 01)
2	2 46 (0.26)	2 30 (0.30)			2 09 (0 09)	1 49 (0 07)
3	4 25 (0.03)	2.68 (0.02)	2.70 (0 09	1 92 (0 05)	2 17 (0 04)	1 58 (0 05)
4	2 09 (0.08)	2.15 (0.02)	1 43 (0 16)	1 67 (0 07)	1 07 (0 02)	0 93 (0 00)
5	3.86 (0 05)	3 82 (0 15)	2 67 (0 02)	3 01 (0 03)	2 48 (0 03)	1 92 (0 02)
6	4.92 (0.26)	4.21 (0.40)	3 07 (0 11)	3 42 (0 05)	2.51 (0 03)	2.44 (0 04)
7	5.12 (0.40)	4.50 (0.03)	3 17 (0.00)	3 21 (0 04)	3 03 (0 00)	~~2~~ 35 (0 00)
Mean	3.48	3.08	2.61	2.65	2 20	1 64
S.D.	1.40	1.07	0.69	0.80	0.60	0.64

Mean (n=3) values of the quasi-static (Cstat) and dynamic (Cdyn) compliance of isolated piglet lungs ± 1 Standard deviation is given in parentheses

line) and deformed (dashed line) lung. Little or no change occurs in the static P-V curve when the lung is deformed In contrast, there is a marked reduction in the slope of the dynamic P-V curve of the deformed lung The results obtained for each piglet are presented in the identity plots of Figure 2 4, where the compliance of the deformed lung (x-axis) is plotted against the compliance of the undeformed lung (y-axis) Most of the Cstat values (top panel) lie on or near the identity line indicating that Cstat is similar under the two conditions regardless of whether inflation or deflation values are used Indeed, the ratio of Cstat in air to Cstat in saline is not significantly different from unity (Table 2 3) In contrast, an apparent difference in Cdyn occurs between the deformed and undeformed lung (Figure 2 4, bottom panel). In this plot, all of the experimental points lie to the left of the identity line, indicating that Cdyn was greater in the undeformed lung than in the deformed lung. In fact, the mean ratio of Cdyn in air to its value in saline was 1.44 and was significantly greater than 1.0 (Table 2.3) Dynamic compliance of the newborn piglet lung was therefore reduced by deformation, with the mean dynamic compliance of the saline immersed lung being 69% of the value obtained from the undeformed lung. Since the saline immersed balloon exhibited a small increase in its dynamic compliance caused by the inertia of the surrounding fluid (Figure 2 2), and assuming that the inertia of the surrounding fluid has an equivalent effect upon the saline immersed lung, then the dynamic compliance of the deformed lung is actually slightly less than observed.

In Figure 2.5, Cdyn is plotted against Cstat for both undeformed and

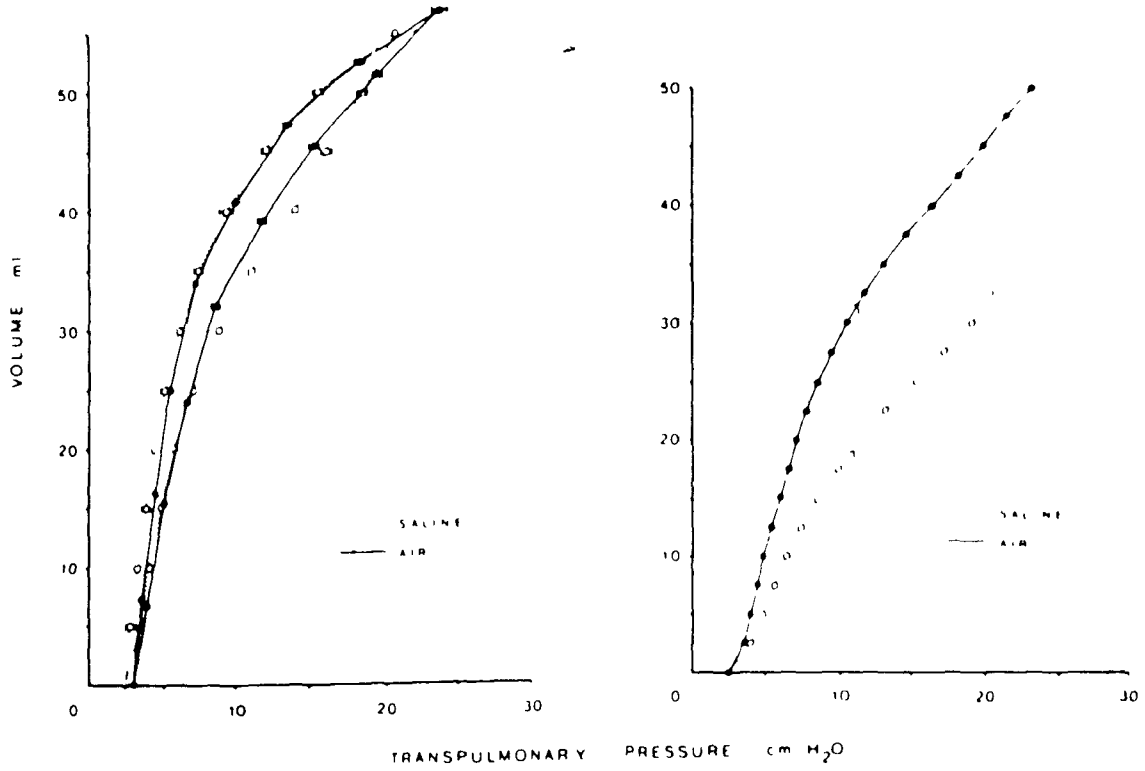

FIGURE 2 3 Quasi-static (left panel) and dynamic (right panel) pressure-volume curves of an excised newborn piglet lung. Each value represents the mean of three trials. Bars are standard deviations and when very small, have been omitted for clarity.

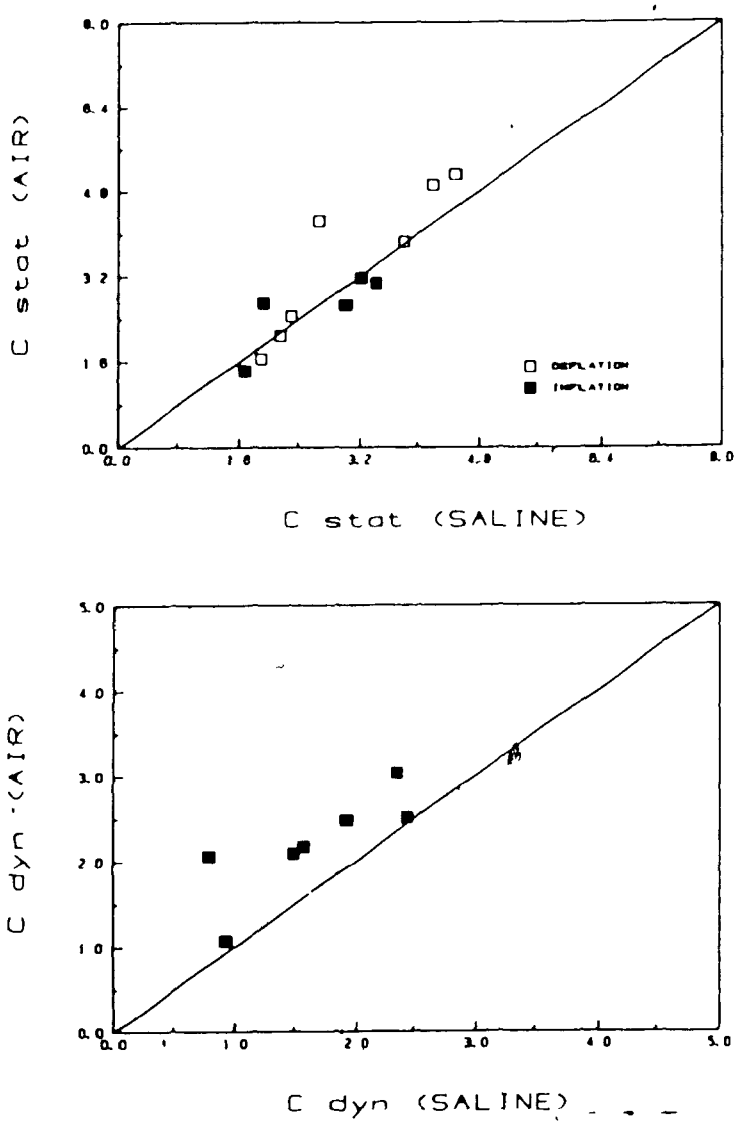

FIGURE 2 4 Identity plots of static (top) and dynamic (bottom) compliance for undeformed (air) and deformed (immersed) lung. The points represent mean values of compliance obtained in each piglet lung Units of compliance are ml/cm H_2O.

TABLE 2 3 COMPLIANCE RATIOS

Piglet No	Cstat (Air/Immersed) Deflation	Inflation	Cdyn/Cstat Air	Cdyn/Cstat Immersed	Cdyn Air/Immersed
1	0 89				2 58
2	1 06				1 40
3	1 60	1 41	0 80	0 82	1 37
4	0 97	0 86	0 75	0 56	1 15
5	1 00	0 89	0 93	0 64	1 29
6	1 17	0 90	0 82	0 71	1 03
7	1 14	0 99	0 96	0 73	1 29
Mean	1 12	1 01	0 85	0 69	1 44
S D	0 23	0 23	0 09	0 10	0 52
	N S	N S	p<0 025	p<0 005	p<0 05

Ratios of quasi-static (Cstat) and dynamic (Cdyn) compliance in undistorted (air) and distorted (immersed) lungs N S , not significantly different from 1 0 (P > 0 05)

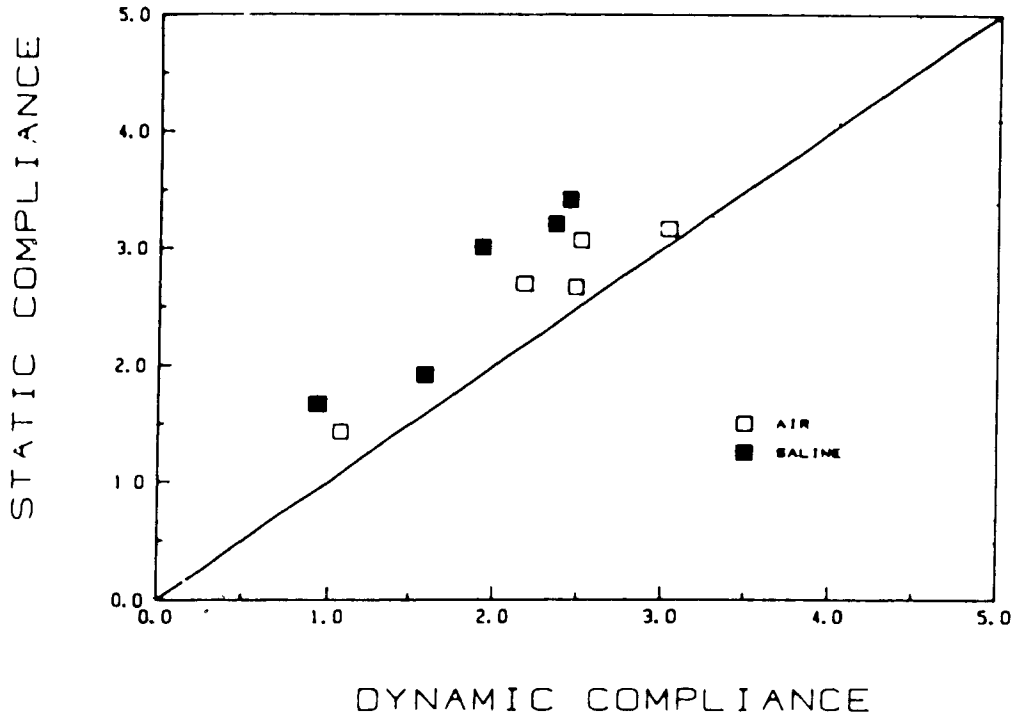

FIGURE 2 5 Identity plot of the static and dynamic compliance of each piglet lung in deformed (immersed) and undeformed (air) condition Units of compliance are ml/ cm H_2O

deformed lungs All of the points are to the left of the identity line, indicating that the Cdyn is less than Cstat Indeed, the ratio of Cdyn/Cstat is significantly less than unity in both conditions (Table 2.3). It is also apparent that the points representing values obtained from the deformed lung are shifted slightly more leftward than the points representing the undeformed lung, indicating that the difference between Cstat and Cdyn is increased when the lung is deformed Since Cstat did not change appreciably, this was due principally to the difference in Cdyn between the two states

DISCUSSION

When the lung is immersed in saline it is deformed by the combination of a hydrostatic surface pressure gradient and buoyancy caused by the displacement of saline Buoyancy exerts an upward directed force that is transmitted directly to the bronchus and trachea The magnitude of this force depends upon lung volume and varies throughout each static and dynamic maneuver The pressure exerted by the hydrostatic gradient acts perpendicular to the surface of the lung and can be resolved into a horizontal and vertical component The horizontal component of the gradient increases continuously towards the base of the plethysmograph and compresses the lung towards its central axis The degree to which the lung is compressed increases with depth and causes the shape of the lung to taper

towards the trachea The direction and magnitude of the vertical component depends upon the shape of the lung and distance below the surface of the saline. It is large and directed upwards in the lower regions but decreases towards the top of the lung where its direction is reversed The magnitude of the downward directed vertical component is small in the partially filled plethysmograph where the top of the lung is between 0-1 cm below the surface of the saline but it is substantially increased in the completely filled plethysmograph

Isolated lungs suspended from the trachea have been shown to expand uniformly and isotropically (D'Angelo, 1970) The pleural surface gradient along the saline immersed lung generates regional differences in transpulmonary pressure that prevent homogeneous inflation of the lung Consequently, volume expansion is greatest in the upper regions where transpulmonary pressure is more positive and decreases towards the lower regions. The transpulmonary pressure at any point along the lung can be estimated if the height of the lung and the mean transpulmonary pressure are known The average height of all of the saline immersed piglet lungs was 81 mm and the mean Pl_{FRC} was 2 1 cm H_2O (Table 2.1). Therefore, the average piglet lung was exposed to an estimated range of transpulmonary pressures between 6.2 (uppermost regions) and -2.0 cm H O (lowermost regions) Negative transpulmonary pressure in the lowermost regions of the lung encourages the collapse of airways and alveoli This is especially true in the newborn where collapse of airways occurs at a proportionally larger volume than in the young adult (Bryan et al., 1977) Furthermore, the

transpulmonary pressure associated with airway closure (closing pressure) is less positive than the pressure required to reopen closed airways (opening pressure) (Glaister et al , 1973) As a result of airway collapse, the inflation limb of the static P-V curve displays a decrease in slope between Pl_{FRC} and 10-15 cm H_2O accompanied by a prominent inflection or 'knee' in the curve near 10-15 cm H_2O signifying a substantial increase in airway recruitment (Bachofen et al , 1975 and Glaister et al., 1973) If substantial airway and alveolar collapse occurs in the piglet lung then the P-V behavior of the lung should exhibit the characteristics of airway closure and reduced lung volume A decrease in the slope of the P-V curve does not occur in the saline immersed piglet lung over any part of its inflation limb and no distinct inflection point is visible This suggests that the piglet lung is able to resist airway closure and volume loss due to alveolar collapse when exposed to negative transpulmonary pressure Similar behavior has been observed in the adult lung (Cavagna et al , 1967)

The pleural surface gradient that occurs in the intact thorax is inversely proportional to body size (D'Angelo, 1970) For adult mammals approximately the same size as the newborn piglet, that is, somewhere between a rabbit and a rat, the overall gradient of pleural pressure is between 0 73 and 0 88 cm H_2O / cm (Agostoni, 1970) Assuming the gradient in the newborn piglet follows the same inverse relationship with body size, then the magnitude of this gradient lies between these two values In this perspective, the hydrostatic gradient imposed upon the saline immersed lung is larger than the gradient expected in the intact thorax by about 14 to 37

percent but it is within the same order of magnitude. The pleural surface pressure along the saline immersed lung, however, increases towards the trachea which is different from the direction of the gradient observed in vivo. The question arises whether a legitimate comparison can be made of the isolated lung of the newborn piglet and the lung of the newborn infant where distortion most likely occurs in the caudal regions by changes in the shape of the rib cage. It is of interest to note that the degree of volume redistribution in isolated lung lobes of mongrel dogs appears to be independent of the orientation of the imposed gradient, (Murphy et al , 1983 and Gillet et al., 1981). This is due to the fact that the response of the lung to nonuniform deformation is determined by its elastic properties which are independent of the imposed forces that generate deformation (Lai-Fook et al., 1976; Olson et al., 1983)

The static compliance of the lung at a mean transpulmonary pressure of 20 cm H_2O is not affected by deformation regardless of which limb of the P-V curve is used in the calculation of compliance. Assuming that the regional mechanical properties of the piglet's lung are similar as demonstrated in kittens (Mortola et al, 1984), one would expect that the decrease in compliance of the most inflated regions of the deformed lung might decrease the mean compliance of the entire lung. The observation that the static P-V characteristics of the deformed lung do not substantially deviate from those of the undistorted lung was noted by Murphy et al. (1983) in experiments performed on isolated lobes from the lungs of adult dogs. Lobe deformation was accomplished by immersion in saline and regional differences in volume

were recorded using ^{133}Xe and radioisotope counting techniques. The experiment demonstrated that the differences in regional volume generated by immersion were less than predicted from a pleural surface pressure gradient of 1 cm H_2O / cm and the P-V curve of the uniformly inflated lung Alternatively, the redistribution of regional volume in the deformed lobe followed the pattern expected if the pleural surface pressure gradient was 0.65 cm H_2O/ cm. Murphy et al. (1983) concluded that the more homogeneous distribution of regional volume in the deformed lung was due to substantial mechanical interdependence between regions. Consequently, the over-expansion of the upper regions of the lung is reduced through its interdependence with the lower, less expanded regions For the lower regions, where transpulmonary pressure may be negative, airway collapse is limited by the influence of the more inflated part of the lung

Dynamic lung compliance is approximately equivalent to static compliance in the adult lung (Murray, 1976) but it is significantly less than the static value in newborn kittens (Mortola et al , 1984a), lambs (Schaffer et al., 1978) and in the piglets used in the present study (Figure 2. 5). A possible mechanism underlying the decrease in dynamic compliance is the viscoelastic behavior of the lung. Lung viscoelasticity is a property of the parenchyma as well as the surface-active material at the air-liquid interface and is responsible for stress relaxation, creep, and some part of the hysteresis in the pressure volume curve (Horie and Hildebrandt, 1971, Sugihara et al , 1972; Sharp et al., 1967; Lorino et al , 1982) Hildebrandt (1969a) determined that the viscoelasticity of adult cat lungs is

responsible for a significant decrease in the compliance of the lung with increasing frequency but concluded that its contribution to dynamic compliance is minor compared to that of flow resistance Although the viscoelastic properties of lung tissue were found to be relatively constant in human subjects between 18 and 88 years of age (Sugihara et al , 1972), it is possible that changes in the viscoelastic characteristics of lung tissue occur in the very young lung and may contribute substantially more than in the adult lung to the difference between dynamic and static compliance

We found that dynamic lung compliance was further reduced with deformation This can be due to factors that affect lung compliance or increase airway resistance The dynamic behavior of each region of the lung is governed by its respiratory time constant which is the product of total resistance and compliance of that region (Otis et al , 1956) Large differences between regional time constants will produce asynchronous ventilation and a dynamic compliance that decreases with increasing frequency. In the isolated adult lung regional differences in airway resistance and compliance are small and generally considered to be insignificant The homogeneous ventilation of all regions of the isolated adult lung indicates that the time constants of these regions are similar Synchronous behavior of adjacent regions is encouraged by interdependence, collateral ventilation and a peripheral airway resistance that contributes only a small fraction to the total airway resistance (Macklem, 1971)

Regional differences in ventilation do occur in the adult lung in situ

presumably due to deformation produced in conforming to the shape of the thorax. However, the differences in the dynamic behavior of individual regions is not great enough to produce a significant change in the compliance of the lung over the normal range of breathing frequency (Murray, 1976). Although no systematic changes have been found in the dynamic behavior of the separate lobes of the kitten lung (Mortola et al , 1984), no data are available concerning the mechanical properties of intralobular regions, particularly of the lung within the intact thorax. Pleural surface pressure gradients are postulated to shift the P-V characteristics of each region of the lung along the P-V curve for the entire lung, generating a distribution of compliances (Milic-Emili et al , 1966) Although the model of regional ventilation based upon this postulate does not account for interdependence, regional differences in compliance may augment the differences in time constants caused by an increase in flow resistance (West, 1979).

Uniform ventilation of adjacent regions within the lung has been shown to depend upon the presence of collateral channels of ventilation in the adult pig and dog (Menkes and Traystman, 1977) The lung of the adult pig, for example, is characterized by extensive intralobular septa and few collateral channels and its dynamic compliance appears to be more sensitive to obstruction of peripheral airways than in the adult dog or man which have well established collateral channels (Menkes and Traystman, 1977) Since the newborn piglet most probably also lacks functional collateral channels, this characteristic may have contributed to the reduction in the dynamic

compliance of the lung when it was distorted by immersion in saline. Intra-alveolar pores are absent in the lung of the infant at birth but increase in size and number with age (Menkes and Traystman, 1977). It is reasonable to expect, therefore, that the dynamic behavior of the lung of the newborn infant may be similarly affected by changes in the caliber of peripheral airways as the newborn piglet.

Hogg and his associates (1970) determined the conductance of the lower airways in infants and older subjects and concluded that the peripheral airway resistance of infants contributes more to the total flow resistance than found in adults. Consequently, the dynamic behavior of the newborn lung is more sensitive to changes in peripheral resistance. Flow through peripheral airways is approximately laminar and, therefore the resistance, described by Poiseuille's equation , is inversely proportional to the fourth power of the airway radius. Hence a relatively small decrease in airway diameter will produce a large increase in flow resistance. The lower regions of the saline immersed lung are considerably compressed towards the trachea and a reduction in their volume due to compression may decrease the caliber of the airways. The resulting increase in flow resistance will affect the ability of the region to expand synchronously with adjacent regions. In addition, the higher distending pressures across the airways of the upper regions may increase their diameter, shorten the time constant of the region, and further encourage asynchrony in the lung.

For the lung within the intact thorax, the tension across the tracheal bifurcation is almost zero in dogs and rabbits (Miserocchi and Agostoni,

1973). This contrasts with the tension generated when the lung is immersed by anchoring the trachea to the bottom of the plethysmograph. Since the trachea is an elastic structure, stretching the trachea along its length will result in a reduction of its internal diameter (Poisson ratio) This may alter the flow characteristics of the upper airways from predominantly laminar to predominantly turbulent and may cause a reduction in dynamic compliance. Since the probability of turbulent flow decreases towards the periphery, one may expect that the major site of turbulent flow to be the large airways. To minimize the contribution of turbulent flow caused by narrowing of the upper airways, the average flow generated during periodic ventilation was minimized by ventilating the lung at low frequency (20 cpm). The transition from laminar to turbulent flow in a straight pipe model of the trachea depends upon the velocity of flow and the diameter of the pipe At a ventilation frequency of 20 cpm and a tidal volume of 50 m^1, the mean flow during inflation is about 33 ml/s. At 760 mm Hg, the density of air is about 0.00113 gm/cm^3 and its viscosity is 0.000188 poise and so conditions for turbulent flow (Re = 2000) will exist only if the internal diameter of the pipe is less than 1.3 mm which is about one fifth of the diameter of the trachea in a newborn piglet (Mortola and Fisher, 1980). Although the prediction of turbulent flow may only approximate the flow behavior of the trachea, it suggests that nonlinear pressure-flow properties are likely not important factors in reducing dynamic compliance below the corresponding static value at low frequency.

The substantial distortion of the chest wall that occurs during

spontaneous breathing in the newborn causes uneven distribution of local pleural pressure and leads to regional variation in volume (i.e lung deformation) (LeSouef et al., 1976). The results of this study demonstrate that the compliance of the newborn lung is substantially reduced by deformation Chest wall deformation increases not only the internal but also the external (P-V) work of breathing. Moreover, to the extent that the reduction in dynamic compliance is due to inequalities in peripheral time constants, deformation likely worsens the distribution of ventilation, during maximal chest wall distortion, the degree of oxygenation of the blood is reduced, presumably due to regional inequalities in the $\dot{V}/Q$ ratio accompanying lung deformation (Martin et al , 1979)

In the spontaneously breathing infant the mechanical time constant of the respiratory system is substantially less than expected from passive measurements (Mortola et al., 1982). Several factors have been postulated to account for this difference including vagal control of respiratory output and the mechanical properties of the respiratory muscles. The difference between static and dynamic compliances of the newborns' lungs may be regarded as an additional factor contributing to the decrease in the dynamic time constant of the respiratory system, particularly during lung deformation.

CHAPTER 3

DYNAMIC LUNG COMPLIANCE IN NEWBORN AND ADULT CATS

SUMMARY

Static (Cstat) and dynamic (Cdyn) lung compliance and lung stress relaxation were examined in isolated lungs of newborn kittens and adult cats Cstat was determined by increasing volume in increments and recording the corresponding change in pressure and Cdyn was calculated as the ratio of the changes in volume to transpulmonary pressure between points of zero flow at ventilation frequencies between 10 and 110 cycles per minute (cpm) Lung volume history, end-inflation volume and end-deflation pressure were maintained constant. At the lowest frequency of ventilation, Cdyn was less than Cstat, the difference being greater in newborns. Between 20 and 100 cpm, the Cdyn of the newborn lung remained constant whereas the Cdyn of the adult lung decreased after 60 cpm. At all frequencies, the rate of stress relaxation, measured as the decay in transpulmonary pressure during maintained inflation, was greater in newborns than in adults. The frequency response of Cdyn in kittens, together with the relatively greater rate of stress relaxation, suggest that viscoelasticity contributes more to the dynamic stiffening of the lung in newborns than in adults. A theoretical treatment of the data based upon a linear model of viscoelasticity supports this conclusion.

INTRODUCTION

Studies in infants (Olinsky et al , 1976) and on isolated preparations from kittens (Mortola et al , 1984a) and piglets (Sullivan and Mortola, 1985) have shown that the dynamic compliance of the newborn lung is less than its static compliance This is contrary to the dynamic behavior of the adult lung in which static and dynamic compliances are approximately equal over the normal range of breathing frequencies (Macklem, 1971) A decrease in the dynamic compliance of the newborn lung may be caused by two mechanisms. The first mechanism involves an increase in peripheral airway resistance as described in patiencs suffering from pulmonary obstructive disorders (Woolcock et al , 1969) In these patients, the high flow resistance of the peripheral airways generates substantial non-uniformities in regional time constants and leads to frequency dependent abnormalities in the distribution of ventilation (Ingram and Schilder, 1967, Otis et al , 1956) A distinguishing feature of this mechanism is that once dynamic compliance falls below static compliance, its value depends primarily upon the rate of flow and will decrease continuously as the flow rate increases With regard to the lung of the newborn, differences in peripheral airway resistance may be due to the presence of pulmonary fluid, primarily within the first few postnatal hours, or to deformation of the lung within the relatively compliant chest wall (Sullivan and Mortola, 1985) Furthermore, since peripheral airway resistance constitutes a larger proportion of total airway resistance in the newborn than in the adult (Bryan et al , 1977, Polgar and

Weng, 1979), one may expect that the dynamic compliance of the newborn lung is more sensitive to changes in peripheral airway resistance than in the adult

The second mechanism that may account for the difference between dynamic and static compliance in the newborn involves the viscoelastic properties of the lung Lung viscoelasticity is a property of the parenchyma (Fukaya et al , 1975) and of the surface-active layer at the air-liquid interface (Horie and Hildebrandt, 1972) and is responsible for stress adaptation (Hughes et al , 1959, Sharp et al , 1967, Lorino et al , 1982), creep (Van de Woestijne, 1967) and some of the hysteresis of the pressure-volume curve (Sharp et al , 1967, Hildebrandt, 1969a; Lorino et al , 1982) In adult cats, lung viscoelasticity was reported to cause a decrease in dynamic compliance of approximately 10 % as frequency increased from 0 2 to 2 Hz (Hildebrandt, 1969a). Unlike the first mechanism where dynamic compliance falls progressively with increasing frequency, the viscoelastic properties of the lung of the adult cat caused a relatively large decrease in dynamic compliance at low frequencies followed by much smaller reductions in compliance as frequency increased

In this study, we have examined the effect of ventilation frequency upon the dynamic compliance of the lung of newborn kittens and adult cats in order to determine which of the two mechanisms is primarily responsible for the difference between static and dynamic compliance in the newborn animal The magnitude of lung viscoelasticity at each frequency was assessed by determining the rate of stress relaxation Stress relaxation is a

particular form of stress adaptation and refers to the time and volume dependent decay in transpulmonary pressure following an increase in volume. The contribution of viscoelasticity to the dynamic mechanical behavior of the lung was demonstrated using a simple model of viscoelasticity From this model we have developed an empirical equation to describe the effect of maintained lung inflation on the time course of passive deflation.

METHODS

Experiments were performed on 2 - 3 kg adult cats and 80 - 100 g newborn kittens within the first week of postnatal life Animals were anesthetized with sodium pentobarbital (30-35 mg/kg, i.p), tracheotomized and cannulated. The femoral vein was exposed and the animal was sacrificed with an overdose of sodium pentobarbital injected intravenously. Bilateral pneumothorax was performed by puncturing the diaphragm at its substernal insertion and the lungs were allowed to collapse The rib cage was then opened and the lungs were dissected away from the heart and removed.

Figure 3.1 is a schematic of the apparatus used to determine the pressure-volume characteristics of the excised lung, suspended by its tracheal cannula. The system between the tracheal cannula and valve was tested for air leaks before and after each experiment by connecting a syringe to the cannula, pressurizing the system to 20-30 cm H_2O and monitoring the pressure for 45 to 60 seconds. A decay of 0.2 cm H_2O or

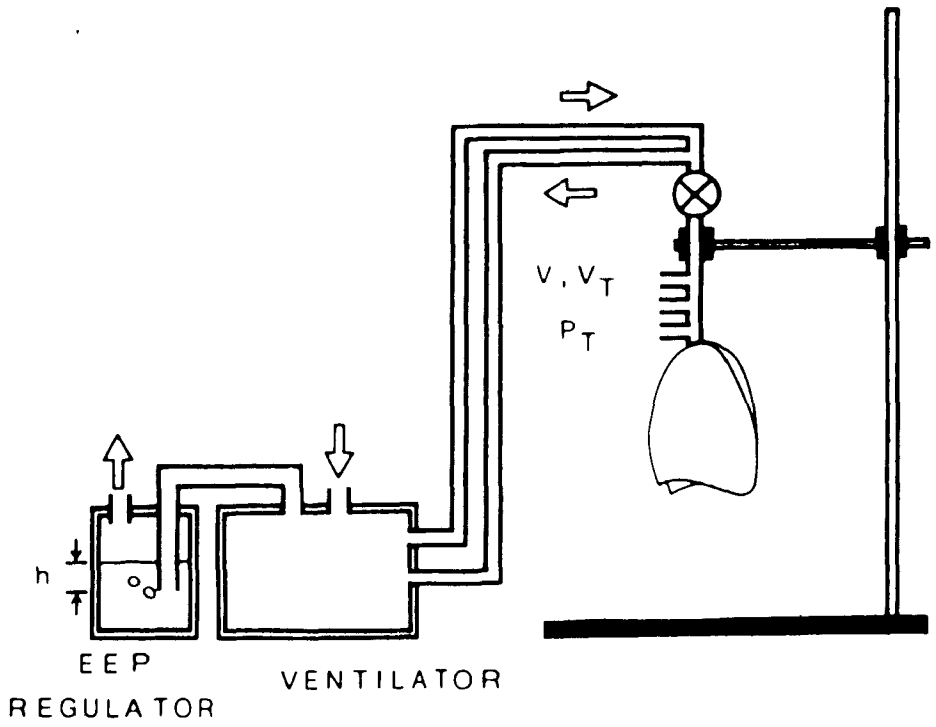

FIGURE 3 1 A schematic of the apparatus that was used to determine the dynamic compliance of excised lungs of newborn kittens and adult cats $\dot{V}$, respiratory flow; V_T tidal volume; P, transpulmonary pressure, EEP, end-expiratory pressure.

less over this time period in two separate tests was considered acceptable

Tests for leakage in the lung when connected to the apparatus were confounded by the decay in pressure due to stress relaxation. In order to assess whether a leak was present in the lung, it was inflated three times to a transpulmonary pressure of approximately 25 cm H_2O then the tracheal cannula was closed Changes in pressure were monitored for 90-120 seconds during which the rate of decay due to stress relaxation would decrease and approach an equilibrium value of between 15-20 cm H_2O In the presence of a leak, transpulmonary pressure would invariably decrease to below this value. If this occurred, either at the beginning or at the end of the experiment, the lung was rejected Of a total of 10 adult cats and 19 newborn kittens the lungs of 2 adults and 5 newborns were rejected on this basis.

All experiments were performed at room temperature (21-24°C) and variables were recorded on a multichannel pen recorder (Gould model 260) For the lung of the adult cat, tracheal pressure was measured from a single side arm of the tracheal cannula connected to a differential pressure transducer (Statham model 15184) and flow was obtained from a Fleisch type 00 pneumotachograph and differential pressure transducer (Hewlett Packard model 270). For the lung of the newborn kitten, a three side arm cannula replaced the pneumotachograph and was used to record tracheal pressure and flow. The dynamic characteristics of this pneumotachograph have been described elsewhere (Mortola and Noworaj, 1983) The frequency response of the system including tracheal cannula, transducers and pneumotachograph were

determined through an x-y plot of flow and pressure on an oscilloscope Both newborn and adult systems exhibited no phase shifts over the range of frequency used in the experiment. Tidal volume was obtained by electrical integration of the flow signal (Hewlett Packard respiratory integrator model 8815A) and tracheal pressure was displayed on two channels, one with a higher gain for greater resolution. Throughout the experiment, the surface of the lung was periodically moistened with a saline solution (0.9 g % NaCl in distilled water).

The study was divided into two parts. In the first part, the lungs of 4 newborn kittens and 4 adult cats were used to determine static compliance (Cstat) and dynamic compliance (Cdyn). Lung volume history was standardized by three inflations to a transpulmonary pressure of approximately 25 cm H20 With the lung ventilated at approximately 100 cpm (adults, Harvard respirator model # 665; newborns, New England Medical Instruments model # 380.), end expiratory tracheal pressure was set at 4.5 cm H_2O in the adult lung and 2.5 cm H_2O in the newborn lung by adjusting the level (h) of the end-expiratory pressure regulator (Fig. 3.1). These pressures are slightly higher than the corresponding pressures at functional residual capacity (Fisher and Mortola, 1980). The stroke volume of the ventilator was adjusted to provide a change in transpulmonary pressure at end-inflation of 5 cm H_2O. When steady records of pressure and volume were obtained, approximately 20 complete cycles were recorded. The same procedure was then repeated at various frequencies between approximately 10 and 100 cpm keeping the integrated volume and end-deflation transpulmonary pressure constant.

Static pressure volume curves were obtained by step inflations of the lung beginning at the same end-deflation pressure used to study the lungs' dynamic behavior. For each static pressure volume curve, lung volume history was first standardized by three inflations to 25 cm H_2O then the lung was inflated in steps, beginning each step from end deflation pressure At each volume increment, the lung was inflated four times with a graduated glass syringe and at the end of the fourth inflation, the trachea was occluded and transplumonary pressure was recorded for 15 seconds Lung volume at each increment was corrected for compression using Boyle's law In all lungs, the magnitude of the correction was less than 3 % of the change in volume recorded from the syringe[2]. Three or four static pressure-volume curves were obtained in this manner for each lung.

The second part of the study was designed to assess the magnitude of lung viscoelasticity in the lungs of 10 newborn and 4 adult cats. The procedure was similar to that used in the first part to determine Cdyn except during three cycles at each frequency, ventilation of the lung was suddenly interrupted at end-inflation by closing the tracheal valve for approximately three seconds (Figure 3.2). During this interval the decay in tracheal pressure due to stress relaxation was recorded.

The duration of a single experiment, from the time the overdose was administered to the end, lasted approximately two hours and thirty minutes

Records were digitized on a graphics tablet (Hewlett Packard 9111A) and the data stored and manipulated in a microcomputer (Hewlett Packard 85) for statistical analysis and graphic presentation. Dynamic compliance was

2. See Appendix 1

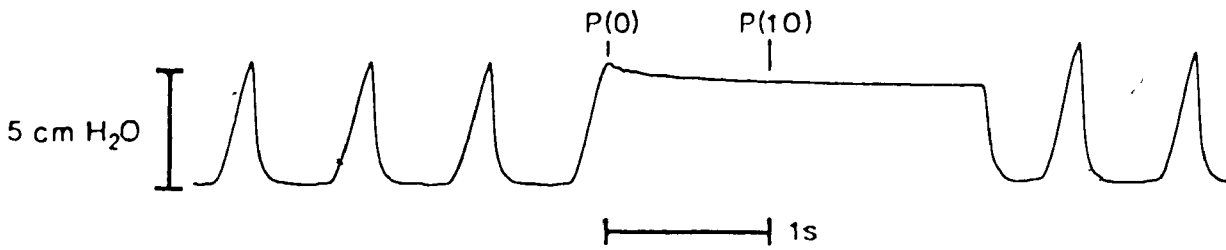

FIGURE 3.2 Record of the decay in transpulmonary pressure following occlusion of the trachea at the end of inflation. P(0) is the pressure at the end of inflation (zero flow) and P(1.0) is the pressure remaining one second later.

calculated as the ratio of the change in lung volume to the change in transpulmonary pressure between end-inflation and end-deflation points of zero flow. Values at each frequency represent the mean of 5 to 10 consecutive breaths. Static compliance was determined from the pressure-volume curve at the same volume set during dynamic ventilation The decay in transpulmonary pressure due to stress relaxation is presented as the ratio of pressure at one second P(1 0) to peak pressure P(0) Tabulated data are presented as means and standard deviations and the significant differences between groups were determined using the paired and unpaired Student's t test.

RESULTS

The values of Cdyn, Cstat, and Cdyn/Cstat for newborn and adult cats in the first part of this study are presented in Table 3 1 and the frequency response of Cdyn/Cstat for both groups is plotted in Figure 3 3 In both newborn kittens and adult cats, lung compliance appears to decrease rapidly at low frequency then more slowly as frequency approaches 100 cpm The greatest difference between the two groups occurs at low frequencies of ventilation where Cdyn/Cstat for the lung of the newborn at 13 cpm is 0 62(± 0.06 S.D) whereas for the lung of the adult, Cdyn/Cstat at 22 cpm is 0 78 (0.11). As frequency approaches 100 cpm, the ratios of Cdyn/Cstat become similar in both groups due to a gradual decrease in Cdyn of the lung of the

TABLE 3.1 DYNAMIC AND QUASI-STATIC COMPLIANCE OF EXCISED LUNGS FROM NEWBORN KITTENS AND ADULT CATS

				VENTILATION FREQUENCY				
				13 cpm	34	59	83	107
	AGE (days)	Wt (g)	Cstat (ml/cmH_2O)	Cdyn (ml/cm H_2O)				
NEWBORNS n = 4	4.3 (1.3)	146 (16)	0.41 (0.15)	0.25 (0.07)	0.22 (0.06)	0.22 (0.05)	0.21 (0.06)	0.21 (0.05)
			Cdyn/Cstat	0.63 (0.06)	0.58 (0.09)	0.57 (0.12)	0.55 (0.12)	0.53 (0.14)
				P<0.01	<0.01	<0.01	<0.01	<0.01

				VENTILATION FREQUENCY				
				22 cpm	44	65	83	104
ADULTS n = 4	2533 (375)	13.2 (1.1)		10.2 (1.7)	9.7 (1.4)	9.2 (1.2)	8.4 (1.1)	7.5 (1.2)
			Cdyn/Cstat	0.78 (0.11)	0.74 (0.08)	0.70 (0.04)	0.64 (0.07)	0.57 (0.06)
				P<0.05	<0.01	<0.01	<0.01	<0.01

Values are means with standard deviations in parentheses. Cstat, quasi-static compliance calculated from step inflations. Cdyn, dynamic compliance during periodic ventilation.

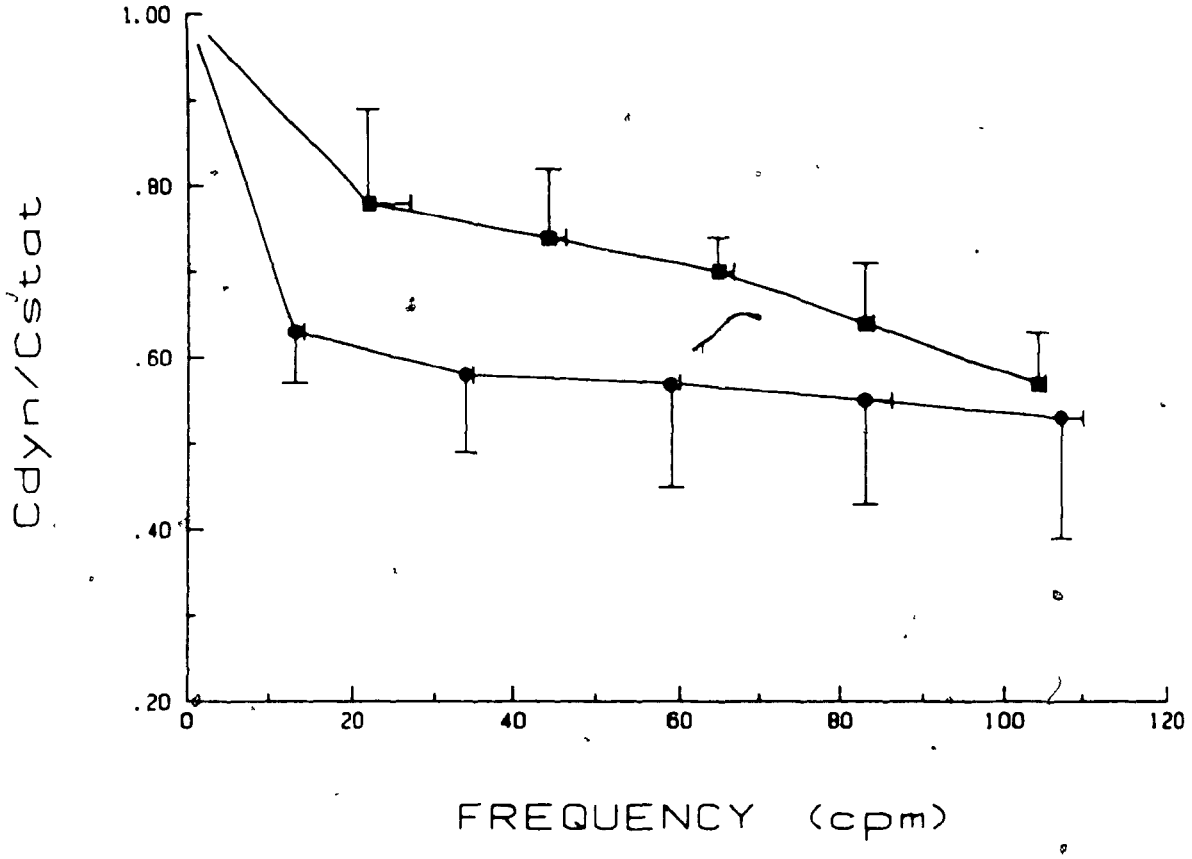

FIGURE 3.3 Cdyn/Cstat is the ratio of dynamic to static compliance Upper trace (squares), adult cats, Lower trace (circles) newborn kittens Frequency in cycles per minute (cpm). Data points are mean values for each group and bars are ±1 S.D.

adult cat. Hence, although the decrease in lung compliance at low frequency is greater in the newborn than in the adult, Cdyn of the adult lung appears more dependent upon frequency at higher frequencies. In contrast, Cdyn of the newborn lung remains relatively constant between approximately 20-100 cpm.

The dynamic behavior of the isolated lungs was further examined by comparing the effect of ventilation frequency upon Cdyn for the 14 newborn kittens and 8 adult cats used in both parts of this study The frequency response of Cdyn of each group is shown in Figure 3 4 where Cdyn is plotted as a fraction of the compliance measured at the lowest frequency of ventilation (C'dyn). Intra-animal variation in Cdyn at each frequency was less than 4 % of the mean value. Between 13 and 107 cpm Cdyn of the lung of the newborn kitten remained constant ($P>0.1$), whereas there was a significant decrease in the Cdyn of the adult cat lung after approximately 60 cpm ($P<0.05$).

In the second part of the study, the magnitude of stress relaxation in the lung of newborn kittens and adult cats was estimated from the rate of decay in transpulmonary pressure following occlusion at end-inflation during dynamic ventilation. The results are shown in Table 3.2 and Figure 3.5. Cdyn is the mean dynamic compliance at end-inflation, and P(1 0)/P(0) represents the normalized decay in transpulmonary pressure due to stress relaxation. For the lung of the newborn, P(1.0)/P(0) varied between 0.80-0.90 whereas for the adult, values of P(1.0)/P(0) ranged between 0 91 and 0.95. As a group, kittens (mean $P(1.0)/P(0)=0.85 \pm 0.03$), showed

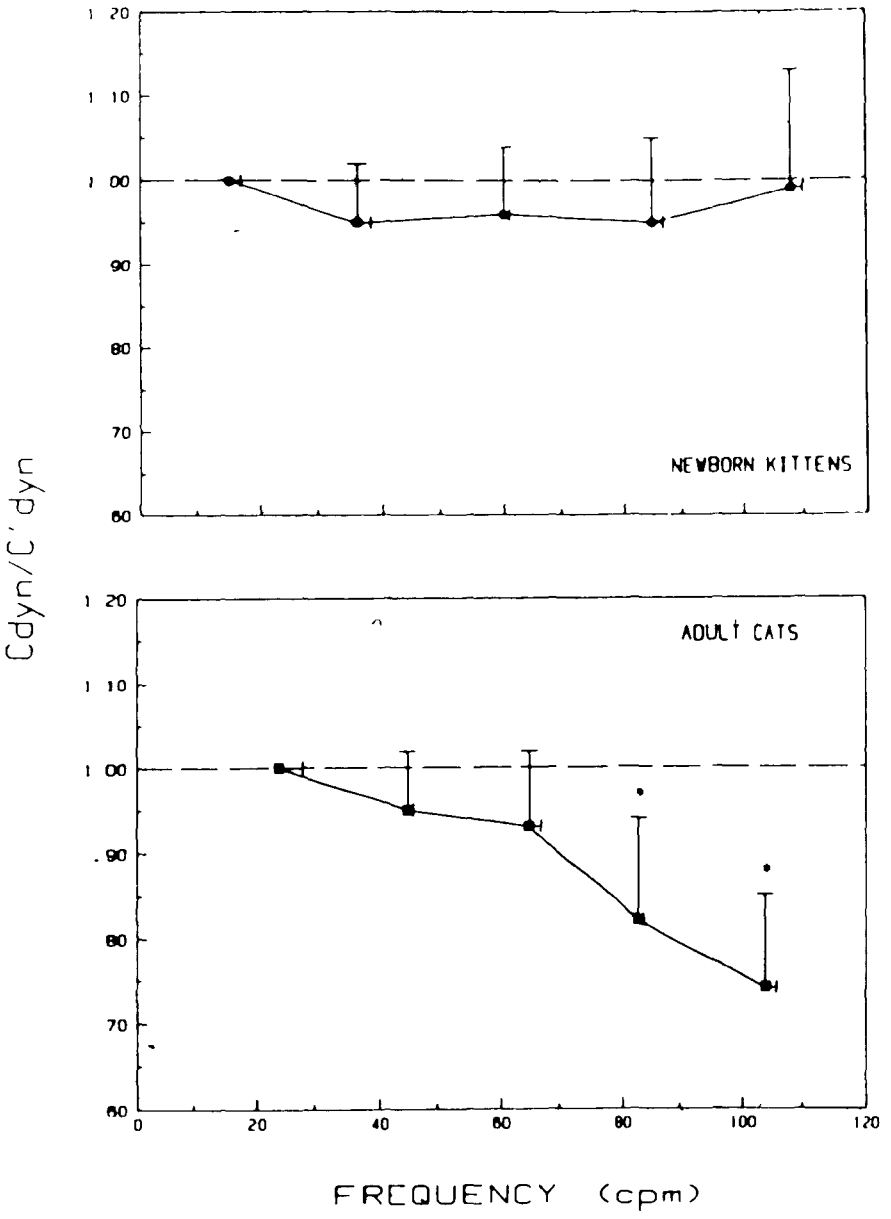

FIGURE 3 4 The dynamic compliance, Cdyn, of excised lungs at frequencies between 10 and 110 cpm Cdyn is presented as a fraction of Cdyn at the lowest frequency of ventilation (C'dyn) Top, newborn kittens, bottom, adult cats Data points are mean values and bars are ± 1 S D Asterisk *, Cdyn is significantly less than C'dyn ($P<0.05$)

TABLE 3.2 AVERAGE DYNAMIC COMPLIANCE AND STRESS RELAXATION WITHIN EXCISED LUNGS OF NEWBORN KITTENS AND ADULT CATS

	AGE (days)	Wt (g)	Cdyn (ml/cmH_2O)	Cdyn 1 0 (ml/cmH_2O)	P(1.0)/P(0)
NEWBORNS n = 10	4.3	139	0.26	0.30	0.85 *
	(2.5)	(35)	(0.04)	(0.04)	(0.02)
ADULTS n = 4	-	2765	8.7	9.3	0.93 *
	-	(422)	(3.2)	(3 5)	(0.03)

Values are means and standard deviations. Cdyn, is the dynamic compliance of the lung at end inflation. Cdyn(1.0) value of compliance after one second of maintained inflation. P(1.0)/P(0), represents the normalized decay in pressure due to stress relaxation at one second. Asterisks indicate values of P(1.0)/P(0) that are significantly less than unity.

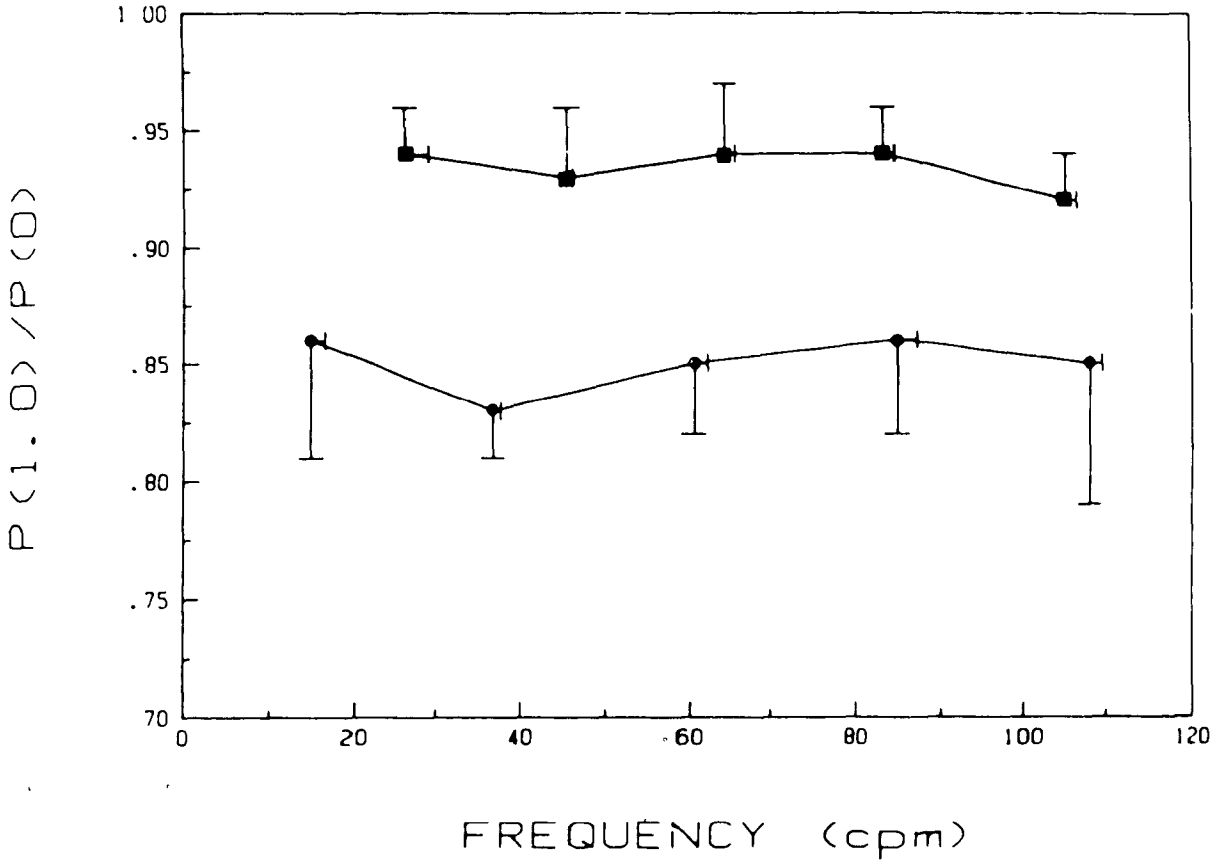

FIGURE 3.5 P(1.0)/P(0) is the ratio of transpulmonary pressure after one second occlusion to peak pressure at instant of zero flow. Upper trace (squares), adult cat. Lower trace (circles), newborn kitten. Data points are mean values, bars are ±1 S.D.

significantly greater stress relaxation than adult cats (mean $P(1.0)/P(0) = 0.93 \pm 0.02$) ($P<0.01$). The rate of decay was not significantly affected by frequency in either group ($P>0.1$). As a result of the decay in pressure, compliance measured after one second was always larger than Cdyn and more so in newborns than adults (Table 3.2).

DISCUSSION

Previous studies on premature infants (Olinsky et al., 1976) and on the excised lungs of kittens (Mortola, et al., 1984) and piglets (Sullivan and Mortola, 1985) found that the dynamic compliance of the newborn lung is less than its static compliance. In this study, we sought to determine whether the difference was primarily due to lung viscoelasticity or to mechanisms involving airflow resistance. The contribution of these factors was assessed by examining the relationship between static and dynamic compliance, the frequency response of dynamic compliance, and the rate of stress relaxation. In particular, we have based our analysis upon observations that frequency dependent behavior due to lung viscoelasticity has characteristics (Bayliss and Robertson, 1939; Mount, 1956; Hildebrandt, 1970) that differ from those of frequency dependent behavior caused by mechanisms involving flow resistance (Woolcock et al., 1969; Macklem, 1971)

The phenomenon of frequency dependent compliance due to increased peripheral flow resistance has been elucidated using a simple model of the lung (Otis et.al , 1956). In this model, the dynamic behavior of the lung is described by an electrical analog consisting of two resistor-capacitor (RC) circuits connected in parallel Each RC circuit represents a hypothetical pulmonary pathway comprised of a single compliant compartment ventilated through an airway of constant flow resistance The impedance of each pathway is governed by its time constant which is the product of flow resistance and compliance When the time constants of the pathways are equal, their impedances will change proportionally with increasing frequency Under these conditions, the distribution of flow and volume is not affected by the frequency of ventilation and the dynamic compliance of the lung remains constant. However, if the time constants differ, the impedances of the separate pathways no longer change proportionally and the distribution of flow and volume is determined by the frequency of ventilation As a result, dynamic compliance becomes frequency dependent

A notable feature of the lung model is that differences in time constants need not significantly affect dynamic compliance over the normal range of breathing frequency. This can occur if the differences in time constants between pathways are small compared with the period of ventilation (Macklem, and Mead, 1967). Nevertheless, as the frequency of ventilation is increased beyond the normal range, dynamic compliance will eventually begin to fall because the pathway impedances become

disproportionally dependent upon flow resistance. The loss of dynamic compliance above 64 cpm in the adult cat of the present study is comparable to the expected change in dynamic compliance with frequency due to regional differences in flow resistance and impedance.

Peripheral flow resistance in the lungs of children likely contributes more to total flow resistance than in adults (Bryan et al , 1977; Polgar and Weng, 1979) and therefore one may expect that they are more sensitive to changes in airflow resistance and have a greater tendency to exhibit frequency dependent behavior. However, the absence of frequency dependence in the lung of the newborn kitten indicates that differences in the peripheral time constants of ventilation are small relative to the period of ventilation and suggests that the difference between static and dynamic compliance is due to some mechanism other than airflow resistance. The most likely mechanism involves the viscoelastic properties of the lung.

For small changes in volume, the lung is generally considered to behave as an ideal elastic structure such that the recoil pressure of the lung depends entirely upon its volume. Unlike elastic materials however, the lung also exhibits characteristics that can be attributed to non-elastic viscous components. Stress relaxation is a typical viscoelastic phenomenon which describes the time dependent decay in transpulmonary pressure following inflation to a constant volume (Sharp et al., 1969; Lorino et al., 1982). Under these conditions, compliance depends not only upon lung volume but also upon the interval of time

over which the volume is maintained. The time dependence of compliance at constant volume also governs the dynamic behavior of the lung during periodic ventilation. By virtue of its viscoelastic nature, the dynamic compliance of the lung is not constant but depends upon the frequency of ventilation.

Lung viscoelasticity was examined by Hildebrandt (1969a) in adult cats. Using a fluid filled plethysmograph, the volume of the lung was altered without airflow such that the contribution of flow resistance to dynamic compliance was virtually eliminated. Viscoelasticity was found to increase lung elastance approximately 10% for a ten fold increase in frequency between 0.01 and 2 Hz (0.6 and 120 cpm) This corresponds to a decrease in dynamic compliance of about 19% between 1 and 100 cpm with more than half of the change in compliance occurring before 10 cpm. In other words, the viscoelasticity of the adult cat lung caused a rapid fall in compliance at low frequencies which then became relatively constant over the normal range of breathing frequency. In this study, the dynamic compliance of the adult lung at 22 cpm was 78 % of the static value whereas, the dynamic compliance of the lung of the newborn kitten was 62% of the static value at 13 cpm. These results suggest that a rapid decrease in compliance occurs at low frequencies of ventilation in both newborns and adults. It is unlikely that the loss of compliance at low frequencies was due to differences in peripheral flow resistance, since it would imply large variations in peripheral airway resistance and time constants. Moreover, as discussed above, the

loss of dynamic compliance does not increase with frequency as expected if it was due to variations in regional flow resistance (Figure 3.4). Conversely, the decrease in dynamic compliance at low frequencies of ventilation is comparable to the pattern of frequency dependent behavior predicted on the basis of the viscoelastic properties of the lung.

According to the classical linear theory of viscoelasticity, the difference between dynamic and static compliance is related to the degree of stress relaxation (Flugge, 1975). Hildebrandt (1969b; 1970) demonstrated that viscoelastic behavior of the lung can be approximated by a large number of linear viscoelastic (Maxwell) elements in parallel such that lungs which exhibit faster stress relaxation will show a greater decrease in dynamic compliance with increasing frequency. To further examine the possibility that lung viscoelasticity may be responsible for the difference between static and dynamic compliance, the magnitude of stress relaxation was assessed for both groups of animals from the decay in transpulmonary pressure following occlusion at end-inspiration. The fact that stress relaxation in the lung of the newborn kitten was significantly greater than that found in the adult cat provides additional evidence supporting the role of viscoelasticity as the principal mechanism causing the loss of lung compliance at low frequency.

The difference in Cdyn/Cstat and in the rate of stress relaxation between newborn and adult cats suggests that age is a factor affecting the viscoelastic properties of the lung. Changes in the viscoelastic

nature of other biological tissues has been found to occur with age and affect their dynamic mechanical behavior (Learoyd and Taylor, 1962) A recent study examining changes in the mechanical properties of newborn rat lungs with age has demonstrated that the hysteresis area decreases between 1 and 40 days following birth (Nardel and Brody, 1982) Since lung viscoelasticity is primarily responsible for hysteresis in the static pressure volume curve (Hildebrandt, 1970, Lorino et al , 1982) the change in hysteresis area with age in newborn rats is consistent with our finding of a reduction in the rate of stress relaxation between newborn kittens and adult cats Although there are no studies which directly compare the magnitude of stress relaxation in newborn infants and adult subjects, it is possible to assess the contribution of viscoelasticity from studies of lung tissue resistance Unlike airflow resistance, tissue resistance is insensitive to the frequency of ventilation but increases with tidal volume (Bachofen, 1968) In other biological tissues, frequency insensitive hysteresis which is strain dependent is a property of viscoelasticity (Fung, 1972) Since these characteristics are also predicted by the nonlinear time dependent properties of the lung (Fukaya et al , 1968, Hildebrandt, 1969b) one may expect that tissue resistance is more precisely a property of lung viscoelasticity. Using similar experimental protocol for children and adults, Bachofen and Duc (1968) found that tissue resistance is approximately three times greater in children than in adults indicating that the lung of the younger subject is more viscous than the adult. Simila-

observations have been made in infants (Polgar and String, 1966). The difference between children and adults suggests that the lung of the newborn infant likely exhibits considerable viscoelasticity and therefore its dynamic mechanical behavior may be similar to that found in the lung of kittens.

A THEORETICAL MODEL OF LUNG VISCOELASTICITY

To demonstrate how the combined viscoelasticity of the lung parenchyma and surface active material may contribute to the difference between static and dynamic compliance, a standard linear solid model of viscoelasticity (Fung, 1972; Flugge, 1975) was applied to the pressure-volume behavior of the lung. Since we wish to show how differences between static and dynamic compliance can occur independently of airflow resistance, we have considered only the pressure required to overcome the viscoelastic properties of the lung itself and have omitted the contribution of airflow resistance

The transpulmonary pressure at any instant following the volume step depends upon the elastance of the lung as well as time and may be described by the equation (Fung, 1972; Flugge, 1975);

$$P(V,t) = E^*(V) * G(t) \qquad [3\ 1]$$

where E is the elastic response of the lung to a sudden change in volume, V is the magnitude of the volume step and G(t) is a normalized relaxation function which depends only upon time. The normalized

relaxation function of a standard linear solid model of lung viscoelasticity for a step increase in volume is of the form

$$G(t) = Es + (1 - Es)*\exp(-t/T) \qquad [3\ 2]$$

where Es is the fraction of elastic response remaining after a long period of relaxation and T is the time constant of stress relaxation After a long interval of time pressure becomes virtually constant and the ratio of pressure to volume is the static elastance of the lung The parameter Es, therefore, reflects the difference between lung elastance during a rapid increase in volume and the static elastance following a long relaxation Since the mean flow rate generated at the lowest frequency is less than at any other frequency of ventilation studied, the difference between static and dynamic elastance is likely due principally to the viscoelastic properties of the lung. In this respect, Es was made equal to the mean Cdyn/Cstat ratio of each group at the lowest frequency of ventilation (Table 3 1).

A value for T was derived from the the magnitude of the decay in transpulmonary pressure during occlusion at end-inflation found in both groups of animals From the mean ratio of the transpulmonary pressure at 1 second following occlusion to peak pressure (i e, P(1 0)/P(0)), T was calculated according to the equation

$$1/T = -\ln[\ (Es - 1)\ /\ (\ Es - P(1\ 0)/P(0)\ )\ ] \qquad [3\ 3]$$

In Figure 3.6 are shown normalized stress relaxation curves of two

lung models using values of T derived from Equation 3.3. The upper trace (dashed line) represents the stress relaxation response of the lung of the adult cat whereas the lower trace (solid line) is the relaxation curve for the lung of the newborn kitten. For both models, transpulmonary pressure decays with time and becomes sensibly constant within 20 seconds with the greatest degree of stress relaxation occurring in the model which simulates lung viscoelasticity in newborn kittens.

When sinusoidal pressure oscillations are applied to the model of lung viscoelasticity, the resulting volume displacement varies sinusoidally over time but is out of phase with the imposed pressure. Under these conditions, the dynamic behavior of the model is described completely by its complex compliance which contains information about the phase angle and amplitude of volume displacement per unit change in pressure. At any frequency of ventilation, the normalized dynamic compliance of the lung model is equivalent to the amplitude of the complex compliance (adapted from Fung, 1972), and is given by

$$Cdyn/Cstat = [(1 + w^2*T^2)/(1+w^2*(T/Es)^2]^{\frac{1}{2}} \qquad [3.4]$$

where $w = 2\pi f$ is the angular velocity and f is frequency of ventilation in cycles per second. The effect of ventilation frequency upon the dynamic compliance of model lungs of newborn kittens and adult cats is shown in Figure 3.7, where lung compliance at frequencies between 0 5 and 500 cycles per minute is presented as a ratio of static compliance.

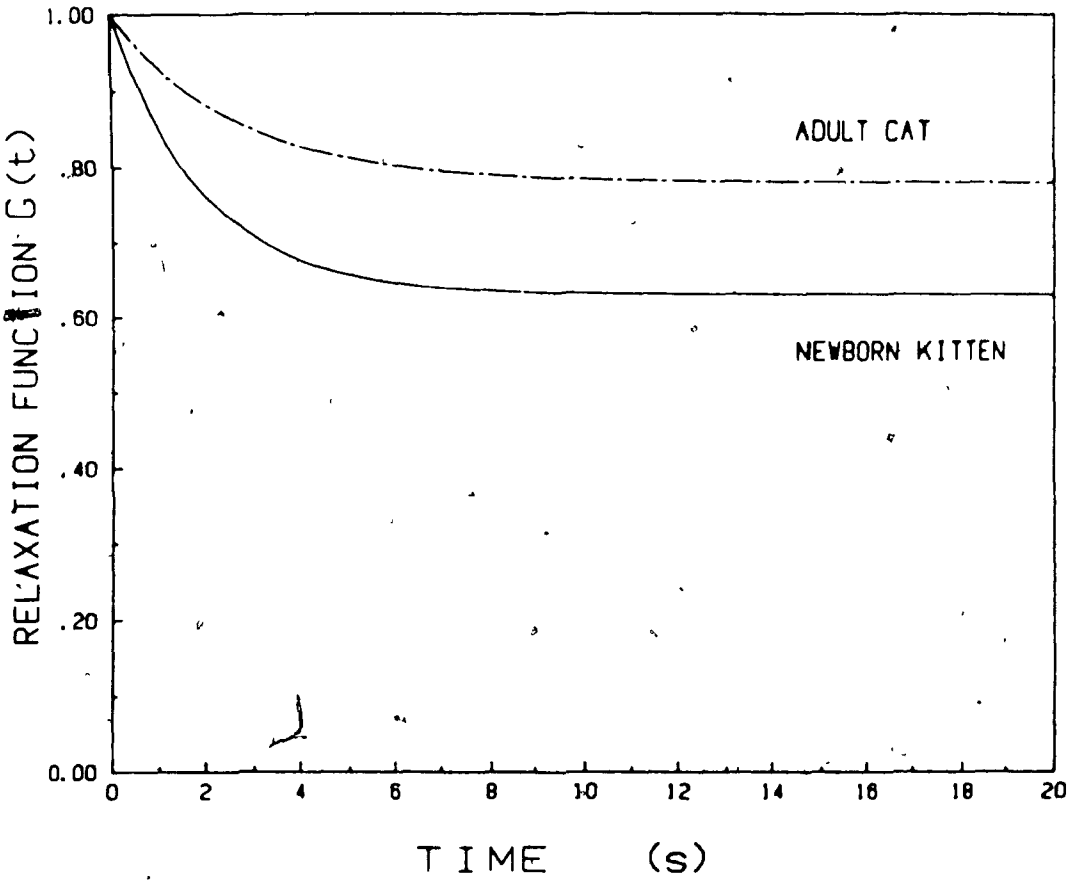

FIGURE 3.6 The stress relaxation response of a linear viscoelastic model. Each curve was computed from from mean relaxation data obtained from the lungs of newborn kittens or adult cats

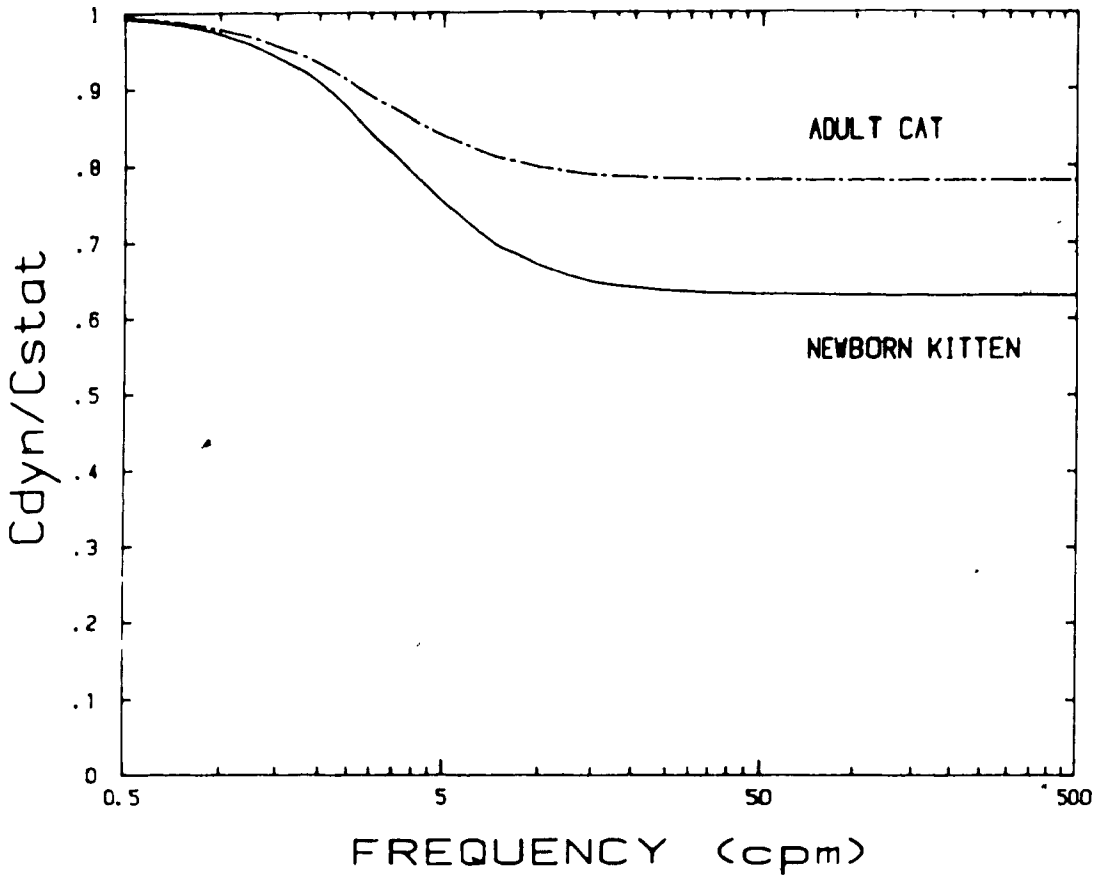

FIGURE 3 / Frequency response of dynamic compliance Cdyn as a ratio of quasi-static compliance Cstat for the two lung models. Upper trace (dashed line), adult; lower trace (solid line), newborn. Frequency in cycles per minute, cpm.

Each curve was calculated from Equation 3.4 using the same values of T and Es that were used to generate the normalized stress relaxation curves shown in Figure 3.6. In both newborn kitten and adult cat, the model predicts that lung compliance falls rapidly at low frequencies but becomes relatively constant over the range of normal breathing frequencies. The magnitude of the reduction in lung compliance is related to the viscous nature of the lung in that lungs which exhibit greater stress relaxation will also show a larger difference between static and dynamic compliance. Hence, the lung of the newborn kitten will be relatively more stiff during periodic ventilation than the lung of the adult cat.

An interesting feature of lung viscoelasticity is its effect upon the passive time constants of the respiratory system or lung. Brody (1954) demonstrated that in a passively deflating lung or respiratory system, the decay in volume with time may be described by a single exponential function where the time constant is equal to the product of compliance and resistance. As shown above, the compliance of the lung parenchyma and surface film depends upon its viscoelastic properties, hence the time required to passively deflate the lung from a fixed volume depends upon its past history. A lung ventilated at high frequency may have an effective time constant of passive expiration that is less than that found when the lung is ventilated at a low frequency. Furthermore, if the expiratory time constant is determined after a period of airway occlusion at end-expiration as recently proposed (Zin et al., 1982), one should expect that the experimentally obtained value

may not accurately reflect the dynamic time dependent properties of the lung.

To illustrate the effect stress relaxation may have upon the time constant of expiration, the phenomena may be described by an empirical equation of the form

$$E * V * G(t) \quad - \quad - R * dV/dt \qquad [3.5]$$

In this equation, the time dependent recoil of the lung is used entirely to overcome the flow resistance R, of the airways. However, the time course of expiration is determined not only by airflow resistance but also by the magnitude of stress recovery. Stress recovery is a feature of lung viscoelasticity analagous to stress relaxation and refers to the time dependent increase in transpulmonary pressure following a step decrease in volume. For the lungs of adult cats, the magnitude or rate of stress recovery is less than that of stress relaxation for the same volume step (Fukaya et al., 1968; Hildebrandt, 1969a). In this case one may expect that over the interval of time required to passively deflate the lung the contribution of stress recovery is much smaller than that of airflow resistance. Consequently, we assume that the principle factors affecting the time course of deflation are the time dependent decrease in lung recoil (i.e., stress relaxation) and the flow resistance of the airways. As shown in APPENDIX 3, the relationship of the time constant of passive expiration to the duration of the preceding maintained lung inflation

is described by

$$Te = To/\,[\,Es + (1-Es)e^{-t'/T}\,] \qquad [3\ 6]$$

where To is the time constant for a spontaneous breath, and Te is the time constant recorded after a period of maintained inflation of t' seconds. Using values of Es and T obtained from the data, the effect of lung viscoelasticity on the passive expiratory time constant is shown in Figure 3.8. In this figure, the values of the effective time constant are normalized as a fraction of the time constant after a 1.5 second occlusion. The equation predicts that lungs with greater viscous character will show a wider range of time constants. For the lung model of the newborn (continuous line), the time constant of a spontaneous breath is substantially less than that following an inflation maintained for 1.5 seconds. This predicted behavior is in agreement with experimental observations made on newborn mammals (Mortola, et al , 1984b). Since the lung of the adult cat appears to exhibit less stress relaxation than the lung of the newborn kitten, the effect of lung viscoelasticity upon the passive time constant of expiration is less pronounced.

The model of lung viscoelasticity that we have adopted is based upon a simple linear model of viscoelasticity whose stress relaxation response to a step increase in volume is governed by a single exponential time constant. It should be emphasized that lung viscoelasticity and stress relaxation are not well described by a single

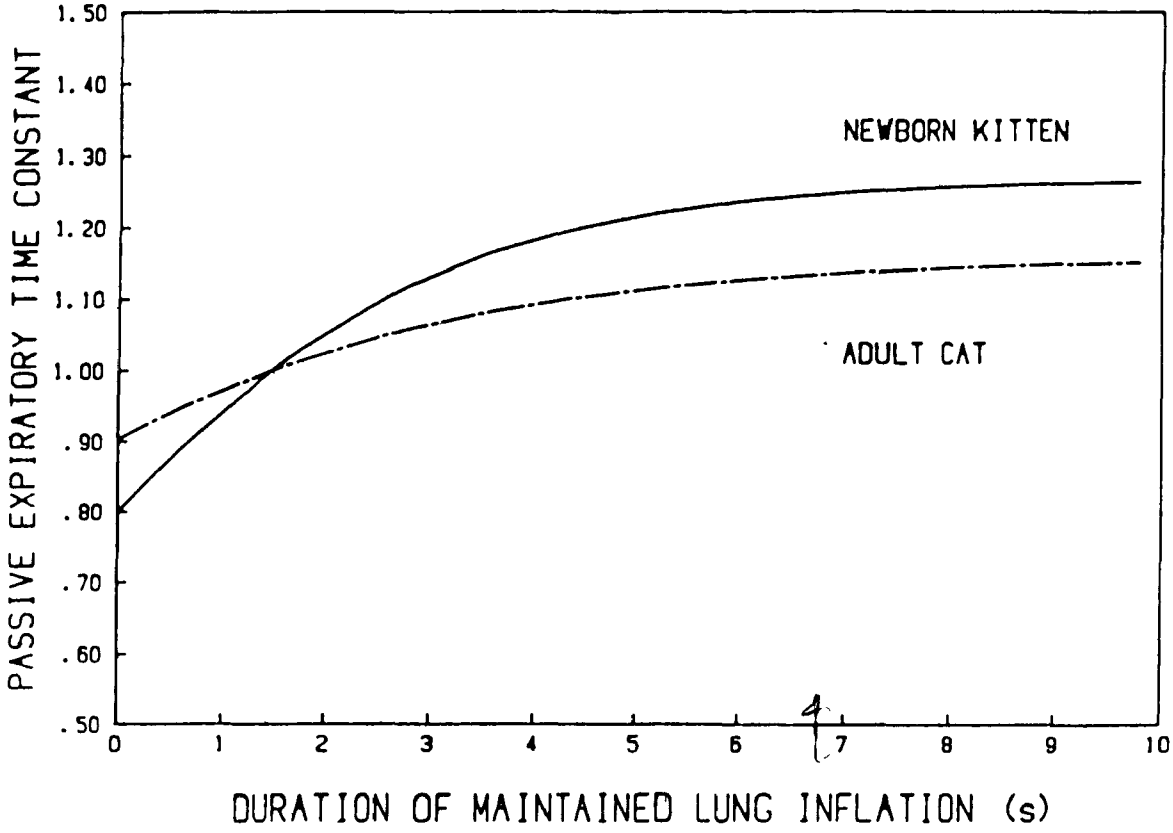

FIGURE 3.8 Expiratory time constant as a function of the occlusion interval. Values of time constant are presented as a ratio of the time constant for a 1.5 second occlusion. Dashed line, adult; solid line, newborn. s, seconds

time constant but rather require models having a wide distribution of time constants so as to render pressure-volume hysteresis insensitive to the frequency of ventilation (Hildebrandt, 1969b; Hildebrandt, 1970; Fung, 1972). However, regardless of whether the stress relaxation response is described by a single or wide distribution of time constants, an increase in the magnitude of stress relaxation will have the same effect, which is to increase the difference between static and dynamic compliance. In this respect, the standard linear model of lung viscoelasticity has provided information that can be used to interpret the mechanical behavior of the lung in vivo. The model predicts that the difference between static and dynamic compliance is larger for the lung of the newborn, which exhibits relatively greater stress relaxation than in the adult. The present experimental and theoretical analysis also suggest that the dynamic mechanical behavior of the newborn lung may depart substantially from that predicted on the basis of quasi-static measurements.

CHAPTER 4

AGE RELATED CHANGES IN THE RATE OF STRESS RELAXATION WITHIN THE RAT RESPIRATORY SYSTEM

SUMMARY

Stress relaxation within the respiratory system was examined in young rats at different ages Three age groups of rats were used. 0-1 day old (GPI), 4-5 days old (GPII) and 30-40 days old (GPIII) Each rat was anesthetized, tracheotomized and placed inside a saline filled plethysmograph with the tracheal cannula projecting through the wall of the plethysmograph. Volume history was standardized by three inflations to a mean transrespiratory system pressure (P) of 20-25 cm H_2O then P was set to zero and lung volume was abruptly increased by rapidly withdrawing fluid from the plethysmograph Following the volume step, lung volume was maintained constant and changes in P due to stress relaxation were recorded for 30 s. The rate of stress relaxation was obtained by calculating the slope (R) of the normalized change in P per unit of time on a semi-log plot. GPIII rats exhibited the slowest rate ($R = 0.068 \pm 0.004$ S.D) whereas GPII rats demonstrated the fastest rate ($R = 0.092 \pm 0.011$ S.D). Stress relaxation in GPI was intermediate ($R = 0.076 \pm 0\ 005$ S.D). Values of dynamic (Cdyn) and static (Cstat) compliance were determined for rats similar in age to the three age groups used to determine R. The difference between Cstat and Cdyn increased with R and was greatest in rats between 0 and 6 days old. We conclude: 1) that stress relaxation within the rat respiratory system increases with age between 0-1 and 4-5 days and thereafter falls with age such that, at 30-40 days, it is less than that found in rats less

than one week old and 2) age related variation in the difference between Cstat and Cdyn may be accounted for by changes in the viscoelastic properties of the respiratory system

INTRODUCTION

A common observation in studies of pulmonary mechanics is the time dependent decay of transpulmonary pressure that occurs when the lung is rapidly inflated and held at constant volume. This behavior is due to a decrease in the elastic recoil of the lung caused by stress relaxation within the parenchyma (Fukaya et al., 1968; Sugihara et al., 1968) and surface active layer (Horie and Hildebrandt, 1971). Similarly, the decay of transrespiratory system pressure at constant volume reflects stress relaxation not only within the lung but within all of the structures that contribute to the mechanical properties of the respiratory system (Sharp et al., 1967). The temporal nature of transpulmonary and transrespiratory system pressure at constant volume implies that the compliance of the lung and respiratory system are affected by the rate of inflation or the frequency of periodic ventilation. In one study of excised lungs from adult cats, Hildebrandt (1969) found that the viscoelastic properties of the lung cause a frequency dependent increase in lung elastance between 0.01 and 2 Hz. Because the change in elastance was approximately 10 % for a tenfold increase in ventilation frequency, it appeared that lung viscoelasticity contributes little to its dynamic mechanical behavior at normal breathing frequencies. In two previous studies of isolated lungs from newborn piglets (Sullivan and Mortola, 1985) and kittens (Sullivan and Mortola, 1986), we found that dynamic compliance during periodic

ventilation at low frequency was less than the corresponding static compliance obtained by step inflations and considered the possibility that stress relaxation was responsible for the difference. A reduction in dynamic compliance is generally interpreted to be the result of substantial airflow resistance or large regional differences in peripheral flow resistance (Otis et al., 1956). The frequency response of isolated lungs however, did not follow the pattern expected of a mechanism governed by flow resistance (Sullivan and Mortola, 1986) Rather, the difference between static and dynamic compliance was related to the rate of stress relaxation. This relationship suggested that the viscoelastic properties of the lung cause it to stiffen during periodic ventilation and that the magnitude of the change in compliance is greater in the newborn than adult Since the respiratory system also exhibits stress relaxation, its mechanical behavior during periodic ventilation may be similarly affected There are, however, no studies which examinè whether the stress relaxation response of the respiratory system varies with age in the manner suggested from excised lungs or whether changes in the viscoelastic properties of the respiratory system substantially affect its dynamic mechanical behavior. The purpose of this study is to determine the relationship between stress relaxation within the respiratory system and age in young rats between 0 and 40 days old and to establish to what extent the viscoelastic properties of the respiratory system may be related to its compliance during passive mechanical ventilation.

MATERIALS AND METHODS

MEASUREMENTS OF STRESS RELAXATION

21 Sprague Dawley rats were placed into one of three groups according to age: Group I consisted of rats between 0-1 day old, in Group II, were rats between 4-6 days old and, in Group III, between 30-40 days old. Table 4 1 presents the sample size, age and weight distribution of each group. Each rat was anesthetized with pentobarbital sodium (30-35 mg/ kg, i.p), tracheotomized and cannulated and placed inside the plethysmograph as shown in Figure 4 1. One end of a metal tube leading into the plethysmograph was connected to the tracheal cannula while the other end of this tube was attached to a small pneumotachograph and differential pressure transducer for measurements of airflow ($\dot{V}$) Another tube extended along the side of the animal and was adjusted so that its tip was approximately at the middle height of the thorax. This tube was connected to a saline filled fluid transducer (Hewlett Packard, model 1280C) for measurements of mean transrespiratory system pressure, P. When these connections and adjustments were completed, the animal was killed with an overdose of Sodium Pentobarbital (i.p. or i.v.) and the plethysmograph was sealed and filled with saline (0.9 gm %) at room temperature (21-24 ^{O}C)

All signals were amplified with Hewlett Packard Carrier amplifiers and recorded on a multichannel pen recorder (Gould Pen recorder, model

TABLE 4 1 STRESS RELAXATION· PHYSICAL CHARACTERISTICS OF EACH GROUP OF RATS

GROUP	N	AGE (days)	WEIGHT (g)	n	Vs (ml)	Po (cmH_2O)	Vs/Po (ml/cmH_2O)
I	6	0.33 (0 33)	5.8 (0.7)	37	0.05 (0.01)	3.33 (0.42)	0 014 (0 002)
II	7	4.8 (0.5)	12 0 (1.8)	41	0 08 (0 02)	3.81 (0.79)	0.021 (0 004)
III	8	33.4 (3.0)	102.2 (19.1)	44	0.3 (0.1)	4.49 (0.85)	0.065 (0 015)

N is the number of rats n is the total number of stress relaxation curves analyzed. Vs is the volume step and Po is the pressure at zero flow. Vs/Po; respiratory system compliance. Each value is the mean for the group with one standard deviation given in parentheses.

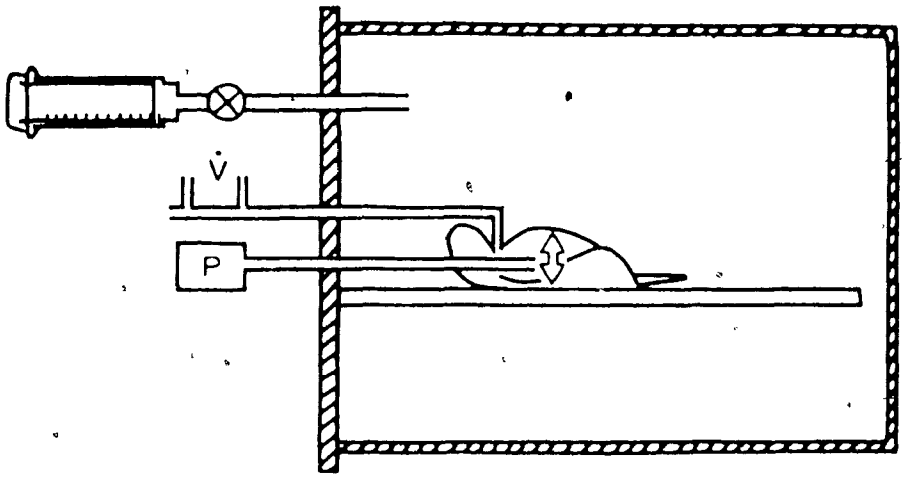

FIGURE 4.1 Schematic of the apparatus used to record transrespiratory system pressure following a step inflation. P, mean transrespiratory system pressure; $\dot{V}$, flow.

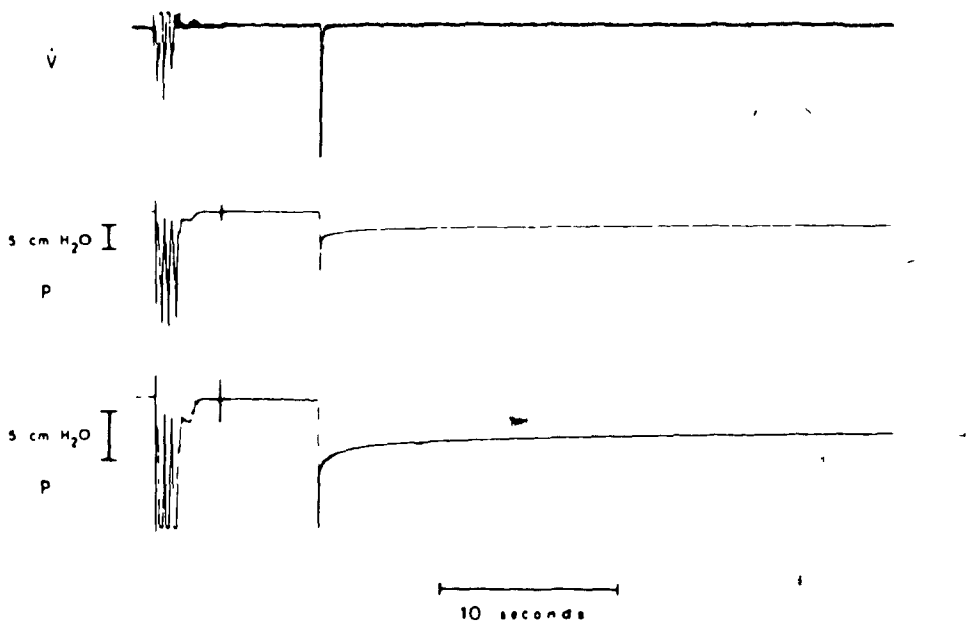

FIGURE 4.2 Stress relaxation response to a step inflation Upper trace shows the duration of airflow, $\dot{V}$, middle and lower traces show the time dependent decay in transrespiratory system pressure P, due to stress relaxation Scale bars provide pressure and time calibrations

260). P was displayed on two channels, one with an increased gain for greater resolution. With the plethysmograph completely filled with saline, P was set to zero (ie. the difference between mid-thoracic pressure and atmospheric pressure) and the lungs were inflated three times to a P of approximately 20-25 cm H_2O then P was returned to zero and the system was allowed to reach thermal equilibrium. During this time the pressure within the plethysmograph is unstable as heat is transferred from the animal to the surrounding saline A steady record of P was obtained usually within 20 minutes after which volume history was standardized by three inflations to 20-25 cm H_2O. Since P was set to zero, the initial volume of the respiratory system within the saline filled plethysmograph was equal to its resting volume. From this initial volume, the lung was rapidly inflated to a constant volume by withdrawing saline from the plethysmograph with the syringe and changes in P due to stress relaxation were recorded for 30 seconds (Figure 4 2). The size of the volume step (Vs) was selected to produce a change in P of 2-8 cm H_2O at the instant of zero airflow which occurred within approximately 200 ms in all experiments. For each rat, stress relaxation responses were obtained for three or more volume increments and each step inflation was preceded by three inflations to a P of 20-25 cm H_2O. The duration of each experiment, from the moment the anesthetic was administered to the end, was about 2.5 hours.

To determine whether the viscoelastic properties of the plethysmograph contribute to the response curves obtained from rats, 5

ml of air was introduced in the saline filled plethysmograph and rapidly expanded by withdrawing saline. Because of the rate of expansion, the pressure-volume transformation is nearly adiabatic (cf. Figure A2.1) but becomes isothermal as heat is exchanged with the surrounding saline. The conversion from primarily adiabatic to isothermal conditions caused a time dependent decay (i.e., towards atmospheric pressure) in plethysmograph pressure during the initial 100-200 ms after which pressure remained constant for at least 2 minutes. Since no change in pressure occurred during this time we concluded that the viscoelastic properties of the plethysmograph are negligible and do not affect the stress relaxation curves obtained from rats.

ANALYSIS OF STRESS RELAXATION CURVES

The record of the change in P with time following a volume step was digitized continuously by hand from t=0 until t=30 s on a Graphics Tablet (Hewlett Packard, model 9111A) and the data stored in a microcomputer (Hewlett Packard, model 85) for statistical analysis and graphic presentation. From t=0 until t=6 seconds following the volume step the value of P was recorded every 200 milliseconds and, from t=6 until t=10 seconds, every 500 milliseconds. Between t=10 and t=30 seconds P was recorded at 5 second intervals. To reduce the error associated in hand digitizing the relaxation response, each curve was digitized five times to obtain a mean value for every point in the curve. The coefficient of variation about the mean value of each time

point obtained in this manner was less than 5 per cent. A measure of the rate of stress relaxation was obtained from linear regression analysis of the normalized decay in pressure over the natural logarithm of time. Differences in the slope (R) between groups were tested using the one way analysis of variance (ANOVA) and the modified t-test described by Rosner (1982) for comparison of specific groups within ANOVA. Differences between groups were considered significant if $P < 0.05$.

MEASUREMENTS OF QUASI-STATIC AND DYNAMIC COMPLIANCE

The static (Cstat) and dynamic (Cdyn) compliances of the rat respiratory system were determined using rats similar in age to the three groups used in the study of stress relaxation. Table 4.3 presents the sample size, age and weight distribution of each group of rats used in this part of the study. Each rat was anesthetized with pentobarbital sodium, tracheostomized and cannulated. Changes in P were obtained from changes in tracheal pressure using a pressure transducer connected to a side port of the cannula. Flow was obtained using a small pneumotachograph (Mortola and Noworaj, 1983) and differential pressure transducer (Validyne, model DP45-16). During periodic ventilation the change in lung volume was derived from electrical integration of the flow signal (Hewlett Packard Integrator, model 8815A). Because of the comparatively large gas volume of the flow recording apparatus, the integrated volume changes overestimated actual changes in lung volume

and had to be corrected for gas compression within the apparatus. The procedure used to correct the change in volume is described in APPENDIX 2. After connecting the tracheal cannula to the pneumotachograph and recording apparatus, the rat was killed with an injection of pentobarbital sodium (i.p. or i.v.), volume history was standarized by three inflations to a P of 20-25 cm H_2O and the lung was ventilated at about 100 cycles per minute (cpm) with an end-inflation P of 5 cm H_2O using a small animal ventilator (Harvard Apparatus, model 380)

To determine the effect of ventilation frequency, Cdyn was determined at frequencies between approximately 10 and 100 cpm. The change in lung volume at 100 cpm for an end-inflation P of 5 cm H_2O provided a reference volume which was subsequently maintained constant at frequencies below 100 cpm by adjusting the stroke volume of the ventilator. At each frequency of ventilation, volume history was first standardized by three inflations to a P of between 20-25 cm H_2O. Cdyn was calculated as the ratio of the change in lung volume to the change in P between instants of zero flow during inflation. A mean value of Cdyn at each frequency was obtained from five consecutive cycles of ventilation.

To determine the quasi-static pressure volume (P-V) characteristics of the respiratory system, an airtight, calibrated syringe was connected to the tracheal cannula and the lung was inflated in steps beginning each step at the resting volume of the respiratory system. For each volume step, the lung was inflated four consecutive

times and, at the end of the fourth inflation, lung volume was held constant for 15 seconds at which time the corresponding change in P was recorded. The change in lung volume was derived from the volume read directly off the syringe and corrected for gas compression within the apparatus. Three static inflation P-V curves were constructed for each rat and for each curve, volume history was first standardized by three inflations to a P of 20-25 cm H_2O. Cstat was calculated as the ratio of the change in lung volume to the change in P for the same volume change used to calculate Cdyn. The average duration of each experiment was 70 minutes.

All variables were recorded on a pen recorder and digitized by hand on a graphics tablet. Within groups differences were tested using the t-test for paired comparisons whereas groups differences in Cdyn/Cstat were tested using the one way ANOVA and modified t-test. Values of $P < 0.05$ were considered significant.

RESULTS

STRESS RELAXATION

The mean volume step, the peak change in transrespiratory system pressure at zero flow (Po) and the corresponding respiratory system compliance for each group of rats are presented in Table 4.1. A scatter plot of stress relaxation following volume steps of 0.04, 0.05 and 0.06

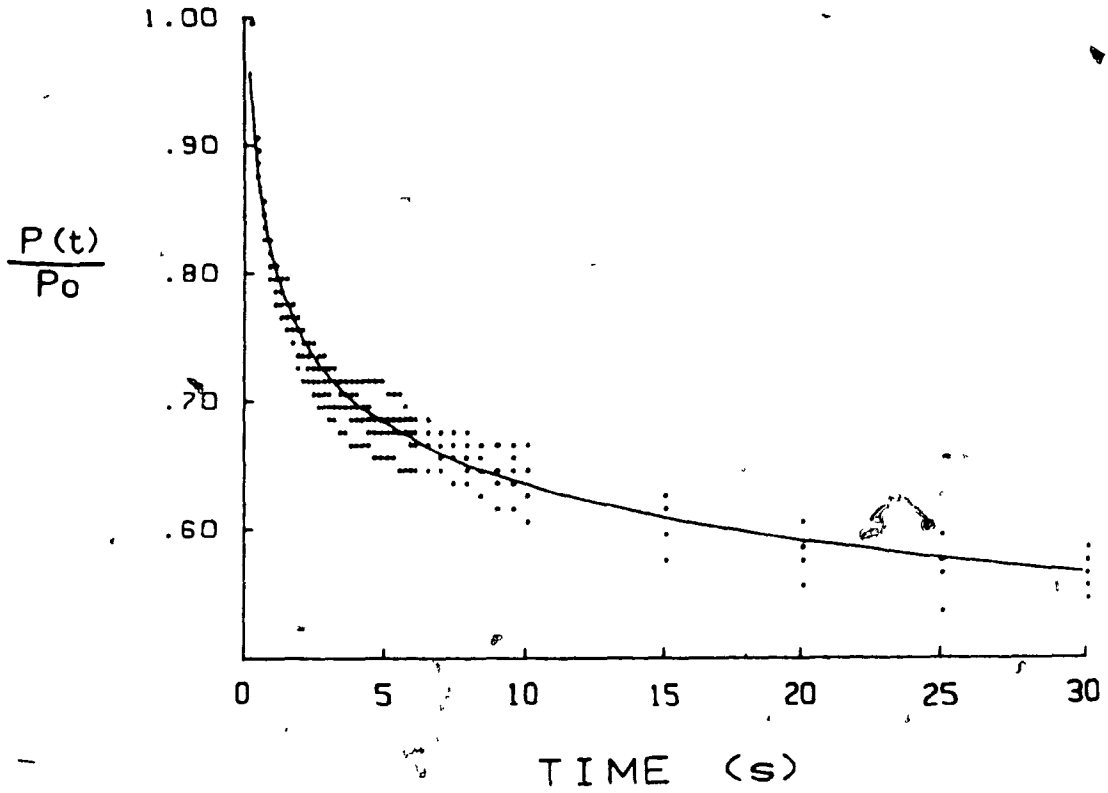

FIGURE 4.3 Scatter plot of the stress relaxation response obtained from one rat, 6 hours old. The points are the results of six volume steps of 0.04, 0.04, 0.05, 0.05, 0.06 and 0.06 ml. P(t)/Po, represents the normalized change in mean transrespiratory system pressure.

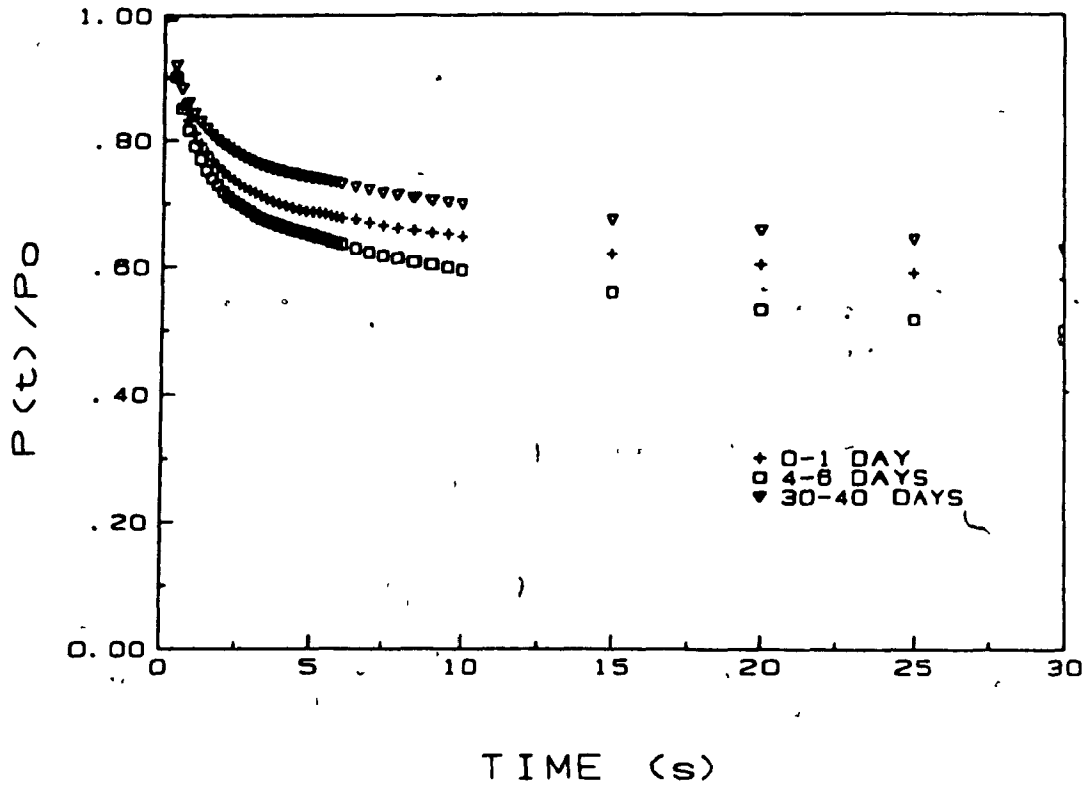

FIGURE 4.4 Mean stress relaxation curves from each group of rats. P(t)/Po, normalized change in mean transrespiratory system pressure. Differences in the rate of stress relaxation are apparent from the fraction of transrespiratory system pressure remaining at t = 30 s following the volume step.

ml obtained from a six hour old rat is shown in Figure 4.3. Each volume step was repeated once and the solid curve is approximately the average relaxation response of six trials. The data for each rat were combined to obtain mean relaxation curves for each group (Figure 4.4) At 30 seconds following the step, transrespiratory system pressure has decayed more than 30% of the initial value in all three groups with the greatest drop in pressure occurring in Group II (4-6 days) and the least change found in Group III (30-40 days). In the youngest rats (Group I), the magnitude of the decay in pressure at 30 s is between the changes found in the other two groups. When the mean relaxation curves for each group are plotted against the natural logarithm of time (Figure 4.5), the relationship of the change in transrespiratory system pressure to time is approximately linear and may be described by the function:

$$P(t)/Po = A - R*\ln(t) \qquad [4.1]$$

where P(t)/Po is the normalized change in pressure, A is an arbitrary constant and R is the slope of the curve and defines the rate of stress relaxation. Changes in the rate of relaxation in the respiratory system of rats of different ages are apparent in the differences in the slope of these curves. Note that the stress relaxation response of the respiratory system deviates slightly from the best fit solution of Equation 4.1, particularly in rats between 4 to 6 days old. This behavior suggests that stress relaxation within the respiratory system is curvilinear for a long interval of relaxation, similar to the

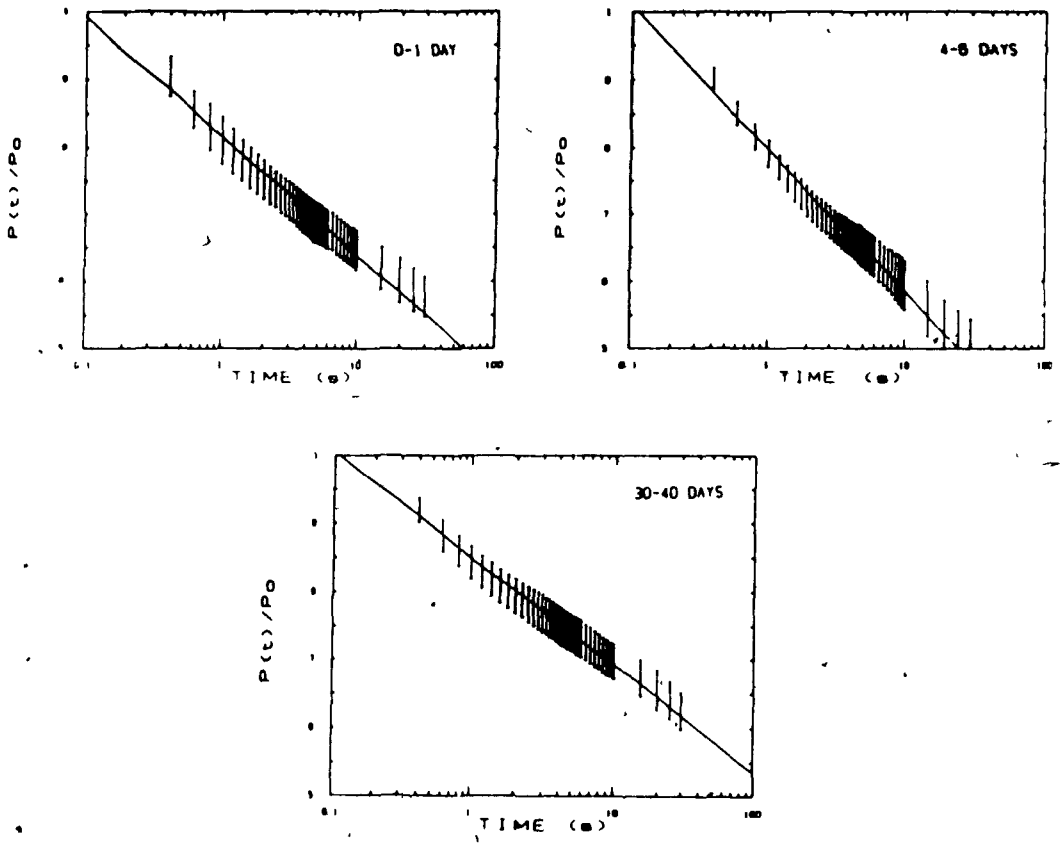

FIGURE 4.5 Stress relaxation curves from each group of rats plotted against the natural logarithm of time. Bars are one S.D. For each group, the decay in P(t)/Po is approximately linear between 0.2 and 30 seconds. The solid line represents the solution of Equation [4.1].

TABLE 4.2 AVERAGE RATES OF STRESS RELAXATION FOR EACH RAT

#	GROUP I		GROUP II		GROUP III	
	R	r	R	r	R	r
1	0.085 (0.006)	0.94 (0.02)	0.099 (0.004)	0.99 (0.01)	0.070 (0.005)	0.95 (0.04)
2	0.074 (0.005)	0.93 (0.03)	0.096 (0.004)	0.99 (0.01)	0.065 (0.005)	0.98 (0.02)
3	0.082 (0.003)	0.97 (0.01)	0.110 (0.004)	0.99 (0.00)	0.063 (0.003)	0.96 (0.03)
4	0.076 (0.004)	0.96 (0.01)	0.080 (0.004)	0.97 (0.01)	0.065 (0.005)	0.97 (0.03)
5	0.071 (0.004)	0.95 (0.04)	0.086 (0.009)	0.97 (0.02)	0.071 (0.008)	0.98 (0.01)
6	0.075 (0.010)	0.97 (0.03)	0.082 (0.009)	0.94 (0.05)	0.069 (0.006)	0.98 (0.00)
7			0.092 (0.006)	0.97 (0.01)	0.064 (0.005)	0.99 (0.01)
8					0.075 (0.008)	0.99 (0.01)
Mean	0.077	0.95	0.092	0.97	0.068	0.98
S.D	0.005	0.02	0.011	0.02	0.004	0.01

Values of the rate of stress relaxation, R, obtained from each rat. r^2 is the coefficient of determination. Values are means with one standard deviation in parentheses. Group means are presented at the bottom of the table. The mean rate of stress relaxation within each group is significantly different from the others ($P<0.05$).

response of many biological tissues (Tanaka and Fung, 1974). If so, then the straight line estimation of the rate of stess relaxation may apply only to the interval between 0.2 and 30 seconds.

To compare rates of stress relaxation between groups, mean values of R were obtained for each rat. These are presented in Table 4.2 along with the corresponding mean coefficient of determination (r^2). Values of r^2 varied between 0.93 and 0.97 for all rats studied. Mean rates of stress relaxation for each group of rats are presented at the bottom of the bottom of the table. The rate of stress relaxation for each age group is significantly different from the other two indicating that the viscoelastic properties of the respiratory system change with age. The fastest rate of stress relaxation occurs in rats between 4-6 days old whereas the slowest rate occurs in the 30-40 day old rat.

DYNAMIC AND STATIC COMPLIANCE

Table 4.3 presents mean values of static (Cstat) and dynamic (Cdyn) compliance for each age group of rats used in the second part of the study. In each group, Cdyn at all frequencies of ventilation is significantly less than Cstat. This relationship is illustrated in figure 4.6 where the ratio Cdyn/Cstat is plotted against the frequency of ventilation. To compare values of Cdyn/Cstat between groups, a preliminary analysis was performed to determine whether Cdyn varied with frequency within each group. The results are shown in Table 4.4. In the youngest (GP 1) and oldest (GP 3) rats, Cdyn remained constant up

TABLE 4.3 STATIC AND DYNAMIC MEASUREMENTS OF COMPLIANCE: PHYSICAL CHARACTERISTICS OF EACH GROUP OF RATS

					FREQUENCY (cpm)				
					16 (1)	36 (2)	59 (1)	83 (0)	107 (1)
GROUP	N	AGE (days)	WEIGHT (g)	Cstat (ul/cmH_2O)	Cdyn (ul/cmH_2O)				
I	4	0.4 (0.2)	5.5 (0.4)	9.4 (1.5)	7.1 (1.3)	7.6 (1.4)	6.8 (1.7)	7.4 (1.4)	6.2 (1.4)
II	5	4.6 (0.5)	9.5 (0.7)	28.4 (4.5)	20.4 (3.5)	20.7 (4.3)	19.5 (3.3)	18.5 (3.2)	21.4 (6.2)
III	4	37 (0.5)	116 (5)	103 (13)	88 (9)	89 (7)	85 (7)	82 (8)	78 (4)

Mean values ($\pm$1 S.D.) of static (Cstat) and dynamic (Cdyn) compliance for each group of rats. N, number of rats in each group. In all three groups, Cdyn is significantly less than Cstat ($P<0.05$)

TABLE 4.4 FREQUENCY DEPENDENT VARIATION IN THE COMPLIANCE OF THE RAT RESPIRATORY SYSTEM

	FREQUENCY (cpm)				
	16 (1)	36 (2)	59 (1)	83 (0)	107 (1)
GROUP	Cdyn/Cdyn (f=16cpm)				
1	1 0	0 99 (0 10)	0 94 (0 08)	0 96 (0 07)	0 86 * (0 05)
2	1 0	1 01 (0 06)	0 96 (0.05)	0 91 * (0 06)	0 87 * (0 05)
3	1 0	1 02 (0.05)	0 98 (0.06)	0 94 (0 12)	0.89 * (0.06)

Values of Cdyn at each frequency of ventilation are presented as a fraction of Cdyn at the lowest frequency (i.e. at approximately 16 cpm). *, Cdyn is significantly less than Cdyn at 16 cpm ($P<0.05$).

to 83 cpm whereas for rats between 4 and 5 days old Cdyn fell after 59 cpm The fall in Cdyn at frequencies of ventilation roughly 5 to 7 times the lowest frequency is consistent with the effect of viscoelasticity but may also be due to mechanisms involving flow resistance (Otis et al , 1956) Since it is not possible to distinguish between the two from the data, group differences were evaluated at the lowest frequency of ventilation where the contribution of air flow resistance is minimal and differences between static and dynamic compliance may be assumed to due primarily to the viscoelasticity of the respiratory system Significant differences in Cdyn/Cstat were found between 0-1 and 37 day old rats The difference between 0-1 and 4-6 day old rats was not significant Figure 4 7 shows the relationship between changes in the rate of stress relaxation and the difference between Cstat and Cdyn at the lowest frequency of ventilation Between 0 and approximately 40 days, the difference between Cstat and Cdyn varies with the degree of stress relaxation

DISCUSSION

SOURCES OF RESPIRATORY SYSTEM VISCOELASTICITY

Stress relaxation within the respiratory system reflects the combined viscoelastic properties of the lung and chest wall. Few studies, however, have examined the extent to which each structure contributes to the overall viscoelastic nature of the respiratory system. Sharp et al., (1967)

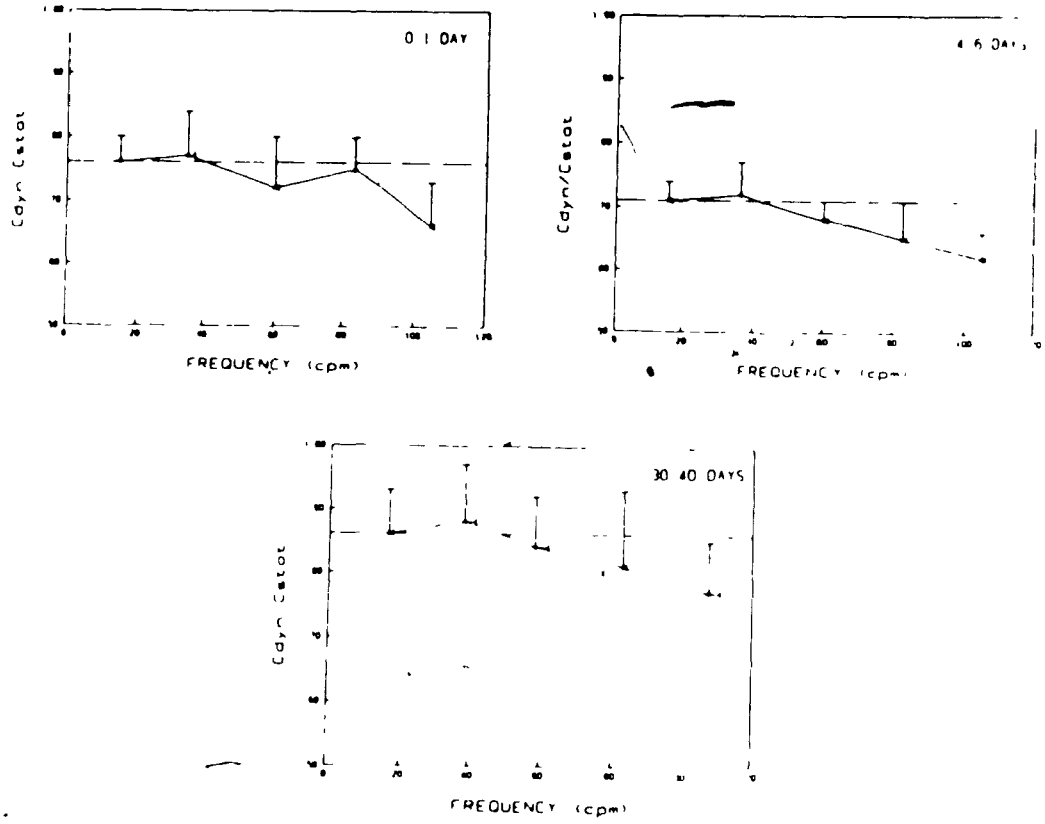

FIGURE 4 6 Frequency response of normalized Cdyn for each groups of rats. Values of Cdyn at each frequency are presented as a fraction of Cstat. Points are the mean ratio of Cdyn/Cstat and bars represent one standard deviation (S.D).

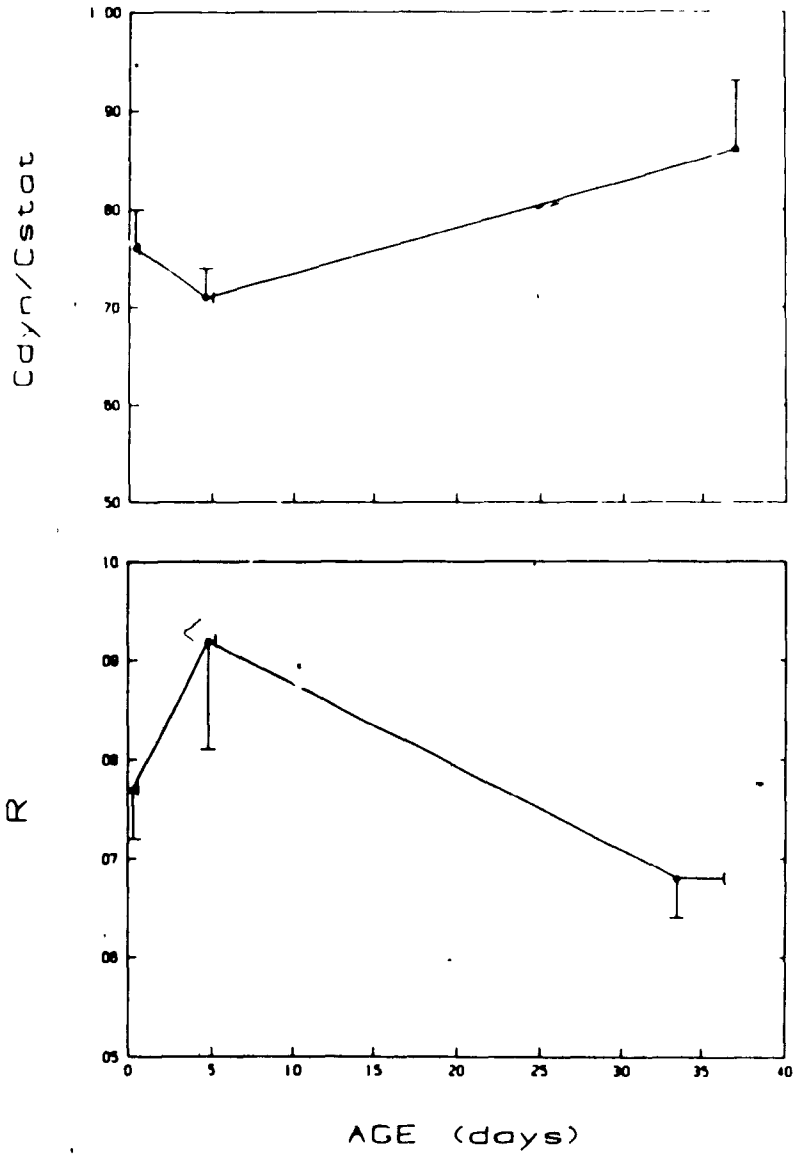

FIGURE 4.7 Relationship between the rate of stress relaxation R, and Cdyn/Cstat for each age group of rats. Bars represent one standard deviation.

examined the relative contributions of the lung and chest wall to the viscoelasticity of the respiratory system in paralyzed, mechanically ventilated subjects and observed that stress relaxation and hysteresis were generally greater in the lung than chest wall. In contrast, Butler (1957) reported that hysteresis was greater in the chest wall than lung However, his observations were based upon area measurements of open pressure-volume curves obtained without preinflations to standardize volume history. Horie and Hildebrandt (1973) subsequently demonstrated that the apparent hysteresis in open curves obtained from excised lungs of adult cats is greater than the steady state hysteresis present after several cycles Van de Woestijne (1967) examined volume creep within the lungs and thorax of adult dogs and observed that both chest wall and lungs contribute to creep within the respiratory system but that variations in creep accompanying forced inflations are more pronounced in the lungs.

Though it is not possible to assess the relative contribution of the chest wall and lung in this study, there is evidence to suggest that the lung contributes to the age related changes in the viscoelastic properties of the rat respiratory system. Developmental changes in the mechanical properties of the saline filled lungs of rats between 4 and 40 days of age include a rapid decrease in the hysteresis ratio and stress relaxation between 4 and 12 days followed by little additional changes up to 40 days (Nardel and Brody, 1982). The coincidence of a decrease in lung stress relaxation with similar changes in the rate of stress relaxation within the respiratory system over the same interval of time suggests that at least

part of the difference we observed is due to changes in the viscoelasticity of the lung parenchyma. It is of interest to note that although the viscoelastic properties of the saline filled lung appear to stabilize within 40 days, stress relaxation and hysteresis in isolated strips of alveolar walls from rats decrease progressively with increasing age between 1 and 28 months (Martin et al., 1977). The discrepancy between time dependent changes in the saline filled lung and isolated tissue strips suggests that the mechanical properties of the lung parenchyma determined from measurements of transpulmonary pressure and volume depends not only upon the viscoelastic characteristics of the alveolar wall but also upon the structure and organization of the alveoli and airspaces. If lung viscoelasticity is affected in this manner then it is conceivable that the extensive morphological changes occurring within the lung during the first month of life (Burri et al., 1974) may be one source of age related variation in respiratory system viscoelasticity.

The viscoelastic properties of the lung are also determined by surface active material that lines the peripheral airspaces. Extracts of lung surfactant exhibit characteritics of viscoelasticity whether spread over a planer surface as in a Wilhelmy balance (Bienkowski and Skolnick, 1972) or deposited over the surface of a gas bubble (Horn and Davis, 1975). The contribution of the surface component to lung viscoelasticity was estimated from the change in the magnitude of stress adaptation caused by filling excised lungs of adult cats with saline (Horie and Hildebrandt, 1971). Abolishing the surface active layer in this manner substantially reduced

stress relaxation within the lung, indicating that the surface component is the major source of lung viscoelasticity. Similar observations were made on excised lungs of adult rats (Lorino et.al., 1982). The dominant influence of the surface component upon the viscoelastic characteristics of the excised lung suggests that it plays an important role in the stress relaxation response of the respiratory system. In a recent study, Barrow (1986) measured the hysteresis area of pressure volume curves obtained from excised lungs and lung-ribcage preparations from adult rabbits before and after filling the lung with a THAM-HCL (Tris-Hydroxymethylaminomethane Hydrochloride) solution. Filling the excised lung with THAM-HCL reduced the hysteresis area to 23 % of the air-filled control value, confirming the results of previous studies on saline-filled lungs. Hysteresis in the unrestrained lung-ribcage preparation however, was reduced to 46 % of the control value, indicating that the surface component contributes less in the lung-ribcage preparation than in the excised lung. Barrow concluded that the tissue component of pressure-volume hysteresis was greater in the lung-ribcage preparation but that it was not clear what tissues were responsible. In view of the observations of Sharp et al., (1967) it appears likely that part of the augmented tissue component is due to the viscoelastic properties of the ribcage.

Skeletal muscle (Abbott, 1957), cartilage (Fung, 1981) and bone (McElhaney, 1966) are viscoelastic and since they form the major components of the chest wall, are likely responsible for its viscoelasticity. During fetal development the ribcage develops as cartilage and is transformed into

bone through a process that continues after birth. Because the viscoelastic properties of bone and cartilage generally differ, a change in the relative proportion of these tissues within the chest wall may be a source of variation in the rate of stress relaxation.

STRESS RELAXATION AND MECHANICAL VENTILATION

By virtue of their viscoelastic nature, the dynamic mechanical behavior of many biological tissues is characterized by frequency dependent elastic modulus and hysteresis In general however, the effect of frequency upon elastance and hysteresis is slight and is only apparent over a wide range of frequency (Fung, 1981). Stress-strain hysteresis in isolated strips of lung tissue appears sensibly constant within one decade of frequency (Sugihara et al., 1971) whereas the peak tension developed tends to increase with the rate of stretch (Sugihara et al., 1971, Fukaya et al., 1968). Similarly, extracts of lung surfactant exhibit frequency dependent changes in hysteresis and peak tension (Bienkowsky and Skolnick, 1972; Horn and Davis, 1975). The frequency dependent behavior of the separate components of the lung suggests that the dynamic mechanical behavior of the intact lung exhibits similar characteristics. Hildebrandt (1969 a) examined the contribution of viscoelasticity to the dynamic pressure-volume behavior of isolated lungs using a fluid filled plethysmograph. To reduce the contribution of airflow resistance, the trachea was sealed to prevent airflow into and out of the lung and lung volume was varied harmonically by alternatively expanding and compressing the air within it. Under these

conditions, the dynamic elastance of the lung rose slowly with increasing frequency whereas the hysteresis area was relatively unaffected. Using a different technique, Grotberg et al.(1980) assessed the viscoelastic properties of isolated lobes of adult dogs during mechanical ventilation and obtained similar results though in roughly half of the lobes tested, hysteresis area also varied with frequency. These studies indicate that changes in the dynamic mechanical behavior of the intact lung are consistent with the viscoelastic characteristics of the parenchyma and surface active layer.

In two previous studies on isolated lungs from newborn piglets (Sullivan and Mortola, 1985) and kittens (Sullivan and Mortola, 1986) dynamic lung compliance was found to be less than the corresponding static compliance. From the frequency response curve of dynamic compliance it appeared that an abrupt decrease in lung compliance occurs at low frequencies of ventilation, followed by negligible changes up to 110 cpm (Sullivan and Mortola, 1986). In comparison, the frequency response of dynamic compliance obtained from the lungs of adult cats showed a similar pattern at low frequencies but the difference between static and dynamic compliance was less pronounced. The ratio Cdyn/Cstat, at the lowest frequency of ventilation correlated with the rate of stress relaxation in that Cdyn/Cstat was smallest in lungs which exhibited the greatest stress relaxation. Since this relationship is predictable on the basis of linear viscoelasticity, it is apparent that age related differences in lung viscoelasticity are responsible for the smaller value of Cdyn/Cstat in the

newborn. It is of interest to note that the relationship between static and dynamic compliance is not unique to the lung but also applies to the dynamic and static elastic modulus of arteries (Bergel, 1961). Moreover, the difference appears to be greater in arteries which exhibit pronounced stress relaxation (Tanaka and Fung, 1974).

The results of this study indicate that the dynamic mechanical behavior of the respiratory system is similarly afffected by its viscoelasticity. As anticipated from studies on isolated lungs, the magnitude of Cdyn/Cstat during mechanical ventilation correlates with the rate of stress relaxation. Since respiratory system stiffness differs between dynamic and static conditions one may expect that its dynamic mechanical behavior will differ from that predicted on the basis of static or quasi-static maneuvers. This was demonstrated in newborn rats (Mortola et.al., 1985) in which the time course of passive deflation was determined by the duration of the preceding interval of maintained lung inflation. Presumably, while at constant volume, stress relaxation within the respiratory system increases its compliance which, in turn, leads to an increase in the time constant of passive deflation (Sullivan and Mortola, 1986).

In conclusion, age related differences between Cstat and Cdyn are in agreement with that expected due to changes in the viscoelastic proeprties of the respiratory system. The results indicate that the dynamic mechanical properties of the respiratory system, like the lung, differ from those predicted on the basis of static or quasi-static measurements.

CHAPTER 5

STRESS RELAXATION AND RATE DEPENDENT CHANGES IN THE PASSIVE RECOIL PRESSURE OF THE RAT RESPIRATORY SYSTEM

SUMMARY

The viscoelastic properties of the rat respiratory system were analyzed using a linear model of viscoelasticity originally proposed by Fung (1972) to describe the behavior of tissue strips stretched in one dimension. The model was fit to the mean stress relaxation curves obtained from rats of different age and subsequently used to predict rate dependent changes in the passive recoil pressure of the respiratory system for various rates of inflation. Predictions based upon the model were generally larger than mean experimental values, although the average difference between predicted and actual values was only 9.0 $\pm$4.7 % (n=15) of the experimental values. The close correlation between experiment and theory suggests that viscoelastic properties of the respiratory system may cause rate dependent changes in its compliance independently of mechanisms affecting the distribution of ventilation within the lung.

INTRODUCTION

In a recent study of the passive mechanical properties of the rat respiratory system, we observed that the rate of stress relaxation, measured as the time dependent decay in transrespiratory system pressure, was similar among rats of the same age (Sullivan and Mortola, 1987). For rats of different age, the rate of stress relaxation correlated with the difference between static and dynamic compliance, suggesting that rate dependent changes in the compliance of the respiratory system are due to its viscoelastic nature. A difference between static and dynamic compliance, however, may be caused by other mechanisms, notably those involving the distribution of ventilation within the lung (Otis et al., 1956; Mead, 1969, Jackson and Watson, 1982). Furthermore, although stress relaxation and compliance are interrelated (Fung, 1981), it is not clear whether the rate of stress relaxation within the respiratory system is sufficient to cause the observed changes in compliance. To determine the extent to which the compliance of the rat respiratory system may be affected by its relaxation characteristics, the relationship between stress relaxation and compliance was analyzed using a hypothetical model of the respiratory system based upon linear viscoelastic theory. The results are presented in this study. Predictions obtained from the model suggest that rate dependent changes in the compliance of the respiratory system can be accounted for, in part, by its viscoelastic characteristics.

MATERIALS AND METHODS

Stress Relaxation Complete details of the protocol are given in a previous study (Sullivan and Mortola, 1987). .Data were obtained from young rats between 6 hours and 40 days old separated into three groups according to age (Table 5.1). Each rat was killed with an overdose of pentobarbitol sodium (i.v or i.p) tracheotomized, cannulated and placed inside a plethysmograph filled with saline (0.9 gm %) at room temperature (22-24^{o}C). Lung volume was regulated by varying the amount of saline in the plethysmograph with a syringe and changes in mean transrespiratory system pressure (P) were monitored using a saline filled transducer adjusted to measure hydrostatic pressure at the level of the thorax (Figure 5.1, Left). To obtain a single stress relaxation response, volume history was first standardized by three inflations to a P of approximately 20-25 cm H_2O then P was reduced to zero. Because of stress recovery following the three inflations (Sharp et al., 1967), a steady record of P was usually obtained within 2-3 minutes at which time lung volume was abruptly increased by withdrawing saline from the plethysmograph and the decay in P due to stress relaxation was recorded for thirty seconds (Figure 5.1, Right). Each volume step (Vs) began at approximately the resting volume of the respiratory system (i.e P = 0) and the size of the volume step was varied to produce changes in P at the end of inflation of between 2-8 cm H_2O. The duration of inflation for each volume step was approximately 200 ms. The average duration of all experiments, from the moment the anesthetic was administered

TABLE 5.1 PHYSICAL CHARACTERISTICS OF EACH GROUP OF RATS

AGE GROUP	STRESS RELAXATION				COMPLIANCE			
	N	AGE days	WEIGHT g	Vs ml	N	AGE days	WEIGHT g	V/Ti ml/s
0-1	6	0 3	5.8	0 05	4	0 4	5 5	0 20
		(0.3)	(0.7)	(0.01)		(0 2)	(0 5)	(0 04)
4-6	7	4 8	12.0	0 08	5	4 6	9 5	0 38
		(0.5)	(1.8)	(0 02)		(0 5)	(0 7)	(0 07)
30-40	8	33.4	102	0 3	4	37	116	1 92
		(3 3)	(19)	(0 1)		(0 5)	(5)	(0 13)

Physical characteristics of the rats used to determine the stress relaxation response and compliance of the respiratory system at different ages. Vs is the size of the step inflation and V/Ti is the highest rate of inflation during mechanical ventilation Values of age and weight, Vs and V/Ti are group means with one standard deviation in parentheses. N is the number of rats in each group.

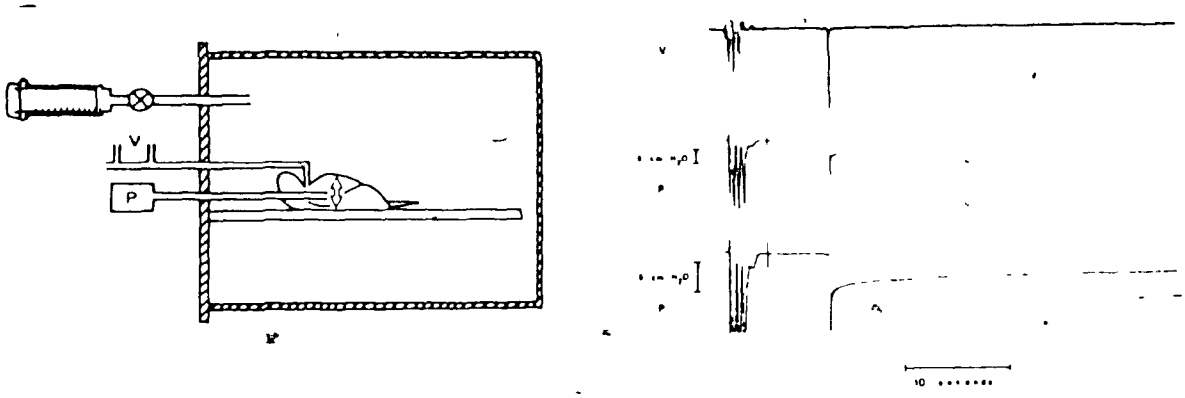

Figure 5.1 Left : Schematic of the saline filled plethysmograph used to determine the stress relaxation response of the rat respiratory system P, transrespiratory system pressure; $\dot{V}$, flow. Further details are provided in the text Right Record of the stress relaxation response following an abrupt inflation Scale bars provide calibration of time and transrespiratory system pressure The interval between the three large inflations and the volume step has been shortened in this illustration

to the end, was approximately 150 minutes.

To analyze the stress relaxation response obtained from a single rat, relaxation curves were digitized at 200 ms intervals between 0 and 6 seconds, at 500 ms intervals between 6 and 10 seconds, and at 5 second intervals between 10 and 30 seconds. Each digitized curve was normalized by dividing the change in P at every time point by the change in P measured at about the instant of zero airflow. Average curves for each group of rats were obtained by computing the group mean of the normalized change in P at each time point From each mean curve, the rate of stress relaxation was computed from the best fit solution of the equation

$$P(t)/Po = A + R*\ln(t)$$

where P(t)/Po is the normalized change in transrespiratory system pressure, R is the rate of stress relaxation, and A is constant

Dynamic and Quasi-static Measurements Of Recoil Pressure The static and dynamic recoil pressures of the respiratory system were determined in another set of rats of similar age (Table 5.1). Each rat was killed with an overdose of pentobarbitol sodium (i.p or i.v), tracheotomized and cannulated with a small pneumotachograph cannula (Mortola and Noworaj, 1983). Volume history was standardized by three inflations to a P of 20-25 cm H_2O and the lung was ventilated at 100 cycles per minute (cpm) with an end inflation P of 5 cm H_2O. The change in P during each cycle of ventilation was obtained from changes in tracheal pressure using a pressure

transducer connected to a side port on the cannula and airflow (V) was obtained from a differential pressure transducer and pneumotachograph-cannula. Changes in lung volume were derived from electrical integration of the flow signal and corrected for gas compresion within the apparatus (see APPENDIX 2)

The frequency response of the rat respiratory system was determined for frequencies of ventilation between 20 and 100 cpm. At each frequency, lung volume history was first standardized by three inflations to a P of between 20-25 cm H20 and the stroke volume of the ventilator was adjusted to provide the same change in lung volume observed at 100 cpm The dynamic recoil pressure of the respiratory system at each frequency of ventilation was measured at the instant of zero airflow at the end of inflation.

The quasi-static pressure volume behavior of the rat respiratory system was determined by connecting a calibrated syringe to the tracheal cannula and inflating the lung in steps, beginning each step at the resting volume of the respiratory system. For each volume increment, the lung was inflated four consecutive times and at the end of the fourth inflation, lung volume was maintained constant for 15 seconds at which time the corresponding change in tracheal pressure was recorded. Lung volume was obtained from the change in syringe volume corrected for gas compression within the apparatus. To compare values of dynamic and quasi-static recoil pressure, the quasi-static recoil pressure of the respiratory system was determined for the same volume change observed during periodic ventilation from the plot of quasi-static pressure against volume. The average duration

of all experiments in this part of the study was 90 minutes from the moment the anesthetic was administered.

THEORETICAL

The response of a linear viscoelastic material to an imposed stretch may be described as a hypothetical combination of separate elastic and viscous components given by

$$F(x,t) = E(x)*G(t), \quad G(0) = 1 \qquad [5\ 1]$$

where $F(x,t)$ is the resulting force, $E(x)$ is the elastic response to an instantaneous stretch, x, and $G(t)$ is the reduced relaxation function (Fung, 1972). If another step stretch is imposed on the material at some time t1 following the initial stretch, then the total force is given by

$$F(t) = E(x)*G(t) + E(x1)*G(t-t1) \qquad [5.2]$$

That is, the total force is the sum of the forces generated by the initial stretch and by the second stretch with the relaxation function having decreased over the interval (t-t1). For an infinitely small time interval the stretch history may be described by the integral

$$F(t) = E\int_0^t G(t-\tau)\,\frac{dx(\tau)}{d\tau}\,d\tau \qquad [5.3]$$

where dx(t)/dt is the rate of stretch.

To establish the extent to which stress relaxation within the rat respiratory system correlates with changes in its recoil pressure, we propose a hypothetical model of the respiratory system based upon linear viscoelastic theory. The recoil pressure of the hypothetical system is determined by the rate it is inflated in the same manner that tension in a strip of viscoelastic material is affected by the rate it is stretched Accordingly, during periodic ventilation, the change in recoil pressure of the respiratory system is given by an adapted form of Equation 5.3, namely

$$P(t) = E\int_0^t G(t-\tau)\,\frac{dV(\tau)}{d\tau}\,d\tau \qquad [5\ 4]$$

where E is the instantaneous elastance of the respiratory system analogous to the elastic response in Equation 5.1 and dV(t)/dt is the rate of volume change. For each cycle of ventilation, the rate of inflation is assumed to be approximately constant or

$$dV(t)\ /\ dt \quad - \quad \Delta V\ /\ Ti \qquad [5\ 5]$$

where ΔV is the change in volume and Ti is the duration of inflation Substituting Equation 5.5 into Equation 5.4, the dynamic recoil pressure (Pd) at the end of inflation becomes

$$Pd(Ti) = \frac{E(\Delta V)}{Ti} \int_0^{Ti} G(u)\,du \qquad [5.6]$$

To compare the response of the hypothetical system to different rates of inflation with its quasi-static behavior, the quasi-static recoil pressure (Ps) following a step inflation may be estimated from

$$Ps(t=15) \simeq E(\Delta V) * G(t=15) \qquad [5.7]$$

where t = 15 seconds is the duration of maintained lung inflation used to determine the quasi-static recoil pressure of the rat respiratory system. If the change in lung volume under both conditions is the same, then the ratio of recoil pressures becomes

$$\frac{Pd}{Ps} = \frac{\frac{1}{Ti}\int_0^{Ti} G(u)\,du}{G(t=15)} \qquad [5.8]$$

Thus, the ratio of recoil pressures is determined entirely by the relaxation function G(t) which describes the stress relaxation characteristics of the respiratory system.

Determination Of The Reduced Relaxation Function The stress relaxation response of the rat respiratory system is approximately linear when plotted against the natural logarithm of time and may be described by a relaxation function which features a continuous distribution of retardation times such as the one proposed by Fung (1972). To characterize the viscous

nature of the rat respiratory system we have adopted Fung's generalized reduced relaxation function which may be stated as

$$G(t) = \frac{1+c\left[E_1\left(\frac{t}{T_2}\right) - E_1\left(\frac{t}{T_1}\right)\right]}{1+c\ln\left(T_2/T_1\right)} \qquad [5.9]$$

where C, T1 and T2 are constants and $E_1(x)$ is the exponential integral

$$E_1(x) = \int_x^\infty \frac{e^{-t}}{t}\, dt \qquad [5\ 10]$$

which is tabulated (Abramowitz and Stegun, 1964) For a long relaxation, Equation 5.9 simplifies to

$$G(\infty) = \frac{1}{1+c\ln\left(\frac{T_2}{T_1}\right)} \qquad [5\ 11]$$

whereas for $T1 << t << T2$

$$G(t) = \frac{1-c\gamma-c\ln\left(\frac{t}{T_2}\right)}{1+c\ln\left(\frac{T_2}{T_1}\right)}, \quad \gamma = 0.57722 \qquad [5.12]$$

Differentiating Equation 5.12 with respect to ln(t) results in

$$\frac{dG(t)}{d\ln t} = \frac{-c}{1+c\ln\left(\frac{T_2}{T_1}\right)} = R \qquad [5.13]$$

where R is the slope of the normalized stress relaxation curves shown in Figure 5.3. To fit the relaxation function to data, initial estimates of the function paramters C, T1 and T2 were calculated using equations 5.11,

5.12 and 5.13 and values of R and G(30) derived from the data (Table 5.2) Optimal values of these parameters were determined using a nonlinear regression analysis program which utilizes a least squares algorithm to minimize the difference between observed and predicted values.

RESULTS

Examples of quasi-static pressure-volume curves from rats of different age are presented in Figure 5.2 to illustrate the approximately linear behavior of the respiratory system for small changes in lung volume. The circled points in these graphs represent the change in transrespiratory system pressure and lung volume at the end of inflation during mechanical ventilation at about 16 cpm. In each case, the increase in recoil pressure that occurs during mechanical ventilation is apparent from the position of these points with respect to the quasi-static pressure volume curve. Figure 5.3 shows the mean stress relaxation curves obtained from each group of rats and the fit (continuous line) of the reduced relaxation function, G(t). The corresponding function parameters are given in Table 5.2. By substituting the values of these parameters into Equation 5.8, predicted ratios of dynamic to static recoil pressures Pd/Ps, were computed for a range of inflation intervals (Ti) (see APPENDIX 4). The results are shown in Figure

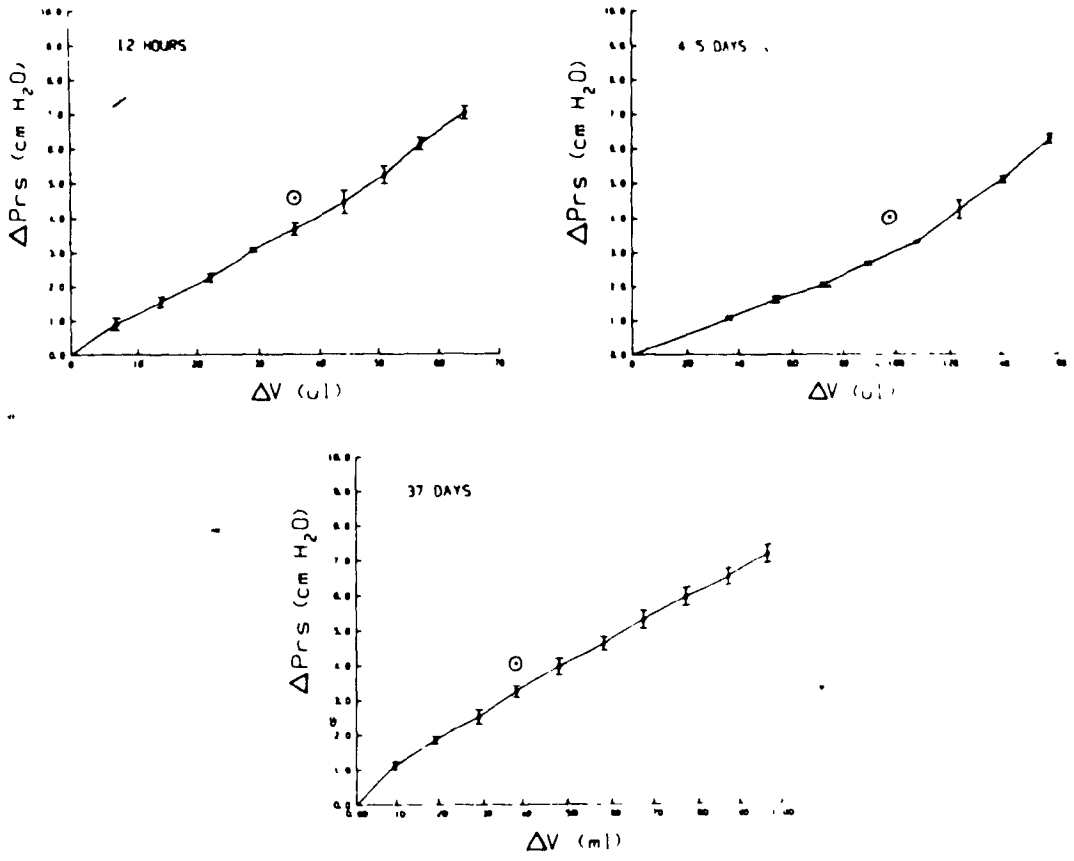

FIGURE 5.2 Quasi-static pressure-volume characteristics of the respiratory system from three rats of different age. ΔP, the change in transrespiratory system pressure; ΔV, the change in lung volume. Each point is the mean of three trials and the bars are standard deviations (± 1 S D) The circled points are the mean values (n= 5 cycles) of P and V at the end of inflation during periodic ventilation at approximately 16 cpm.

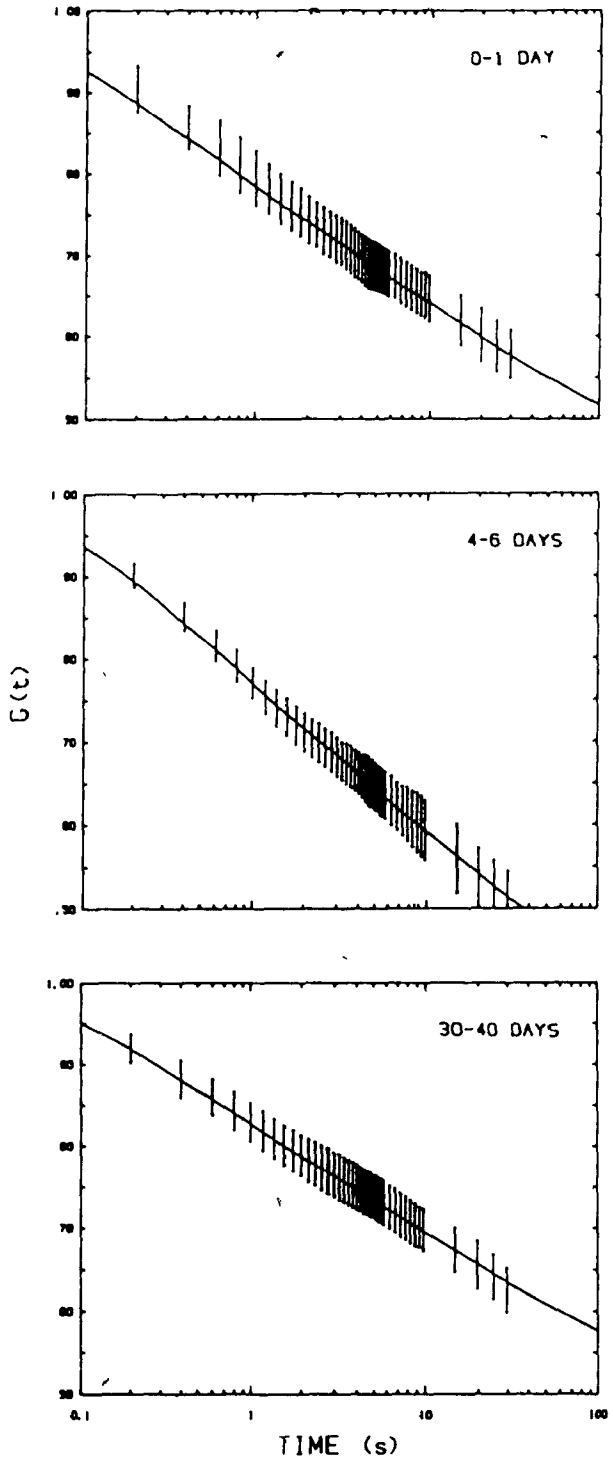

FIGURE 5.3 The fit of the reduced relaxation function G(t), (continuous line), to the mean stress relaxation response from each group of rats. Bars are ±1 S.D..

TABLE 5.2 FUNCTION PARAMETERS FOR EACH GROUP OF RATS

AGE (days)	R	G(30)	C	T1	T2
0 - 1	0.077 (0.005)	0.58 (0.03)	0.133	0.060	210.0
4 - 6	0.092 (0.011)	0.50 (0.05)	0.192	0 099	150.0
30 - 40	0.068 (0.004)	0 62 (0 03)	0.110	0 090	296 0

Values of C, T1 and T2 of the reduced relaxation function for each group of rats. R is the mean slope of the normalized stress relaxation curves with one standard deviation (SD) given in parentheses. G(30) is the fraction of viscoelastic response remaining at 30 seconds following the step inflation

5.4 where the predicted values (continuous line) are plotted along with experimentally determined values. In all three groups predicted values of Pd/Ps are generally larger than the experimentally determined values, although the average difference between the two is only 7 % ($\pm$5 S.D, n = 5) of the experimental value in 0-1 day old rats; 8% ($\pm$4) in 4-6 day old rats and 12% ($\pm$4) in 30 - 40 day old rats. Possible causes of these differences are discussed in the following section. Note that rate dependent changes in the predicted ratio roughly follow the general trend in the experimental values which is indicated by the significantly different values of Pd/Ps between the slowest and fastest rates of inflation.

DISCUSSION

Many biological tissues are viscoelastic and exhibit stress relaxation, creep, stress-strain hysteresis and frequency or rate dependent changes in elastic modulus (Fung, 1981). For structures such as arteries (Peterson et al., 1960), bladders (Remington and Alexander, 1955), and lungs (Hildebrandt, 1969a), the viscoelasticity of the individual tissue components causes time or rate dependent changes in the relationship between transmural or inflating pressure and volume which may be described by empirical models of viscoelasticity. Though models of this sort generally do not reveal the mechanisms responsible for the viscoelastic properties of the organ, they can provide a unifying theory to account for its mechanical behavior under a variety of conditions. In the present study,

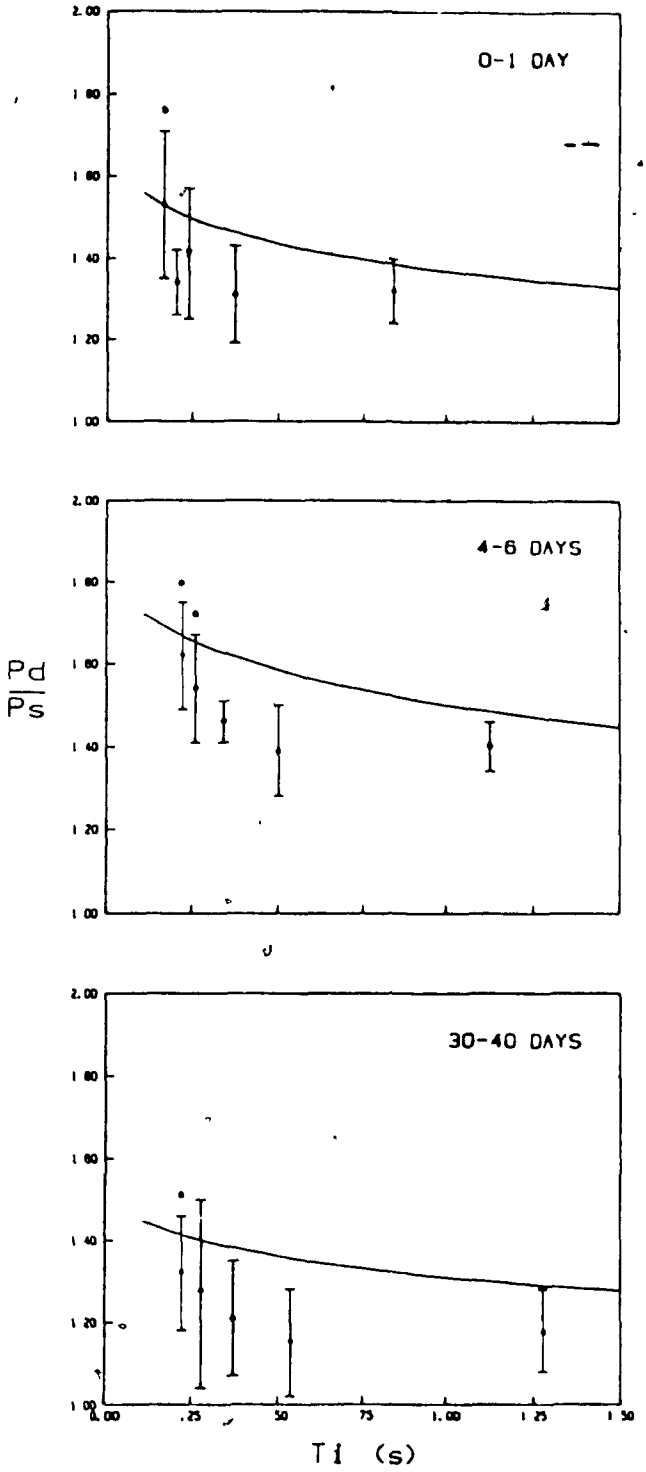

FIGURE 5.4 Ratios of dynamic, Pd, to static Ps, recoil pressures of the rat respiratory system for each age group. Ti is the duration of inflation during periodic ventilation. Each point is the mean ratio and the corresponding bars are ± 1 S.D. Solid line : behavior of the hypothetical respiratory system predicted using equation 5.8 and the average stress relaxation response of the rat respiratory

the passive mechanical behavior of the rat respiratory system was compared to the behavior of a viscoelastic model exhibiting similar relaxation characteristics. Predicted changes in the recoil pressure of the model were close to actual values obtained experimentally, suggesting that rate dependent changes in the passive recoil pressure of the rat respiratory system can be explained, in part, by its viscoelastic nature. The practical significance of these results is that frequency dependent changes in the mechanical properties of the respiratory system can occur independently of mechanisms (Otis et al., 1956; Mead, 1969; Jackson and Watson, 1982) affecting the distribution of ventilation within the lung.

Although some of the variation between the predicted and actual values of Pd/Ps may be attributed to the fact that relaxation rates and values of Pd/Ps were obtained from different sets of rats (Table 5.1), it is apparent from Figure 5.1 that the model systematically over-estimates rate dependent changes in recoil pressure for all three age groups. It is unlikely that the differences are caused by the effect of respiratory system inertance on measurements of compliance (Dosman et al., 1975) because the fastest rates of inflation observed in each group of rats (Table 5.1) are comparable or less than the rates of inflation observed in the spontaneously breathing rat at rest (Mortola, 1984; S. Okubo, personal communication). At these rates of inflation, the contribution of inertia is negligible and the mechanical behavior of the respiratory system may be characterized by its viscoelasticity and airflow resistance (Crosfill and Widdicombe, 1961). Alternatively, the discrepancy between observed and experimental values may

be due to differences in the volume history used to standardize measurements of Pd, Ps and R.

The viscoelastic characteristics of the respiratory system (Van de Woestijne, 1967) and lung (Nagao et al., 1969) are sensitive to the history of volume changes that precede the moment at which these characteristics are measured and reproducible measurements are generally obtained only after volume history has been standardized by repeated inflations to a preset lung volume or transpulmonary pressure. This procedure is analogous to a process known as preconditioning (Fung, 1981) in which an isolated tissue strip is stretched to a preset test length several times before measuring its material properties. In the present study, the rate of stress relaxation was obtained from a single, rapid inflation after a period of time at the resting volume of the respiratory system whereas the corresponding dynamic and static recoil pressures were recorded after several inflation cycles. For strips of alveolar tissue, the rate of stress relaxation following a single, unconditioned stretch is greater than that observed following several stretch cycles (Fukaya et al., 1968; Sugihara et al., 1972) indicating that the viscous component is reduced with cycling. An analogous phenomenon occurs in isolated lungs in which the pressure-volume hysteresis of the first inflation cycle is greater than in subsequent cycles (Horie and Hildebrandt, 1973). Since these characteristics of pulmonary viscoelasticity are also present in the respiratory system (Sharp et al., 1967; Van de Woestijne, 1967), it is likely that the rate of stress relaxation obtained following a single inflation of the respiratory system

is greater than that occurring after several inflation cycles. Consequently, predictions based upon the relaxation response to a single inflation will tend to overestimate the steady state changes in recoil pressure during continuous ventilation.

Another factor which may affect predictions based upon the relaxation response is the non-linear nature of respiratory system viscoelasticity. Most viscoelastic tissues exhibit non-linear material properties which cannot be accounted for by linear viscoelastic theory (Fung, 1981). Among these is the tendency of the rate of stress relaxation to vary over long time intervals (e.g. Tanaka and Fung, 1974). As noted in a previous study (Sullivan and Mortola, 1987), the initial relaxation response of the rat respiratory system deviates slightly from the remaining curve, suggesting that the rate of stress relaxation is not constant but varies with the duration of maintained lung inflation. If so, then the rate of stress relaxation (R) determined over the time interval of 0.2 to 30 seconds following lung inflation may only approximate the viscous characteristics of the respiratory system for shorter time intervals, including its response to rapid inflations. However, it is worth noting that the rate of stress relaxation within isolated lungs of adult cats is approximately linear from 0.1 to 50 seconds following rapid lung expansion (Hildebrandt, 1969a). This suggests that variations in the rate of relaxation within the rat respiratory system may be due to non-linear tissue properties of the chest wall.

Despite age related differences in the rate of stress relaxation, it

is apparent from Figure 5.4 that the dynamic recoil pressure of the respiratory system varies rather slowly with the rate of inflation within each age group. In 4 to 6 day old rats for example, rate dependent changes in the dynamic recoil pressure are greater than those observed in the two other groups, and yet the mean dynamic recoil pressures at the slowest and fastest inflation rates differ by only 13 %. Since these inflation rates correspond roughly to a 7-fold difference in the frequency of ventilation, it is unlikely that the viscoelastic properties of the respiratory system would cause substantial changes in its compliance over the range of breathing frequency observed in the spontaneously breathing rat at rest. On the other hand, the viscoelastic properties of the respiratory system may have an important influence on impedance measurements which generally employ a wide range of ventilation frequencies. In a recent study of respiratory system impedance, Hantos et al. (1986) observed that the effective compliance of the chest wall and respiratory system fell with increasing frequency between 0.25 and 5 Hz. They attributed this behavior to regional differences in tissue properties. In view of the results of this study, it is possible that part of the loss of compliance may be attributed to the effect of tissue viscoelasticity.

The viscoelastic behavior of the respiratory system reflects the combined mechanical properties of the chest wall and lung (Sharp et al., 1967; Van de Woestijne, 1967). Of these, it appears that the lung is the principal source of the viscous component primarily by virtue of its surface active layer at the air interface. Abolishing this interface by filling

the lung with a salt solution not only substantially reduces stress relaxation and pressure-volume hysteresis in isolated lungs (Horie and Hildebrandt, 1971; Lorino et al., 1982) but also reduces hysteresis within intact preparations of the lung, rib cage and diaphragm by about 50% (Barrow, 1986). Several studies (Bachofen, 1968; Hildebrandt, 1969a; Bachofen and Hildebrandt, 1971; Horie and Hildebrandt, 1973) have demonstrated that lung stress relaxation and the pressure-volume hysteresis generally increase with lung volume, indicating that the contribution of the surface active layer varies according to volume. Since surfactant covers most of the internal surface area of the lung, its contribution may more accurately reflect the changes in surface area that accompany changes in lung volume (Forrest, 1970).

To examine how lung morphology varies in comparison to the rate of stress relaxation within the respiratory system, age related changes in the surface to volume ratio of the rat lung obtained from Burri et al. (1974) were plotted along with changes in the rate of stress relaxation in Figure 5.5. Note that the smallest surface to volume ratio occurs at approximately the same age as the fastest rate of stress relaxation, and that variations in the surface to volume ratio in rats between 1 and 21 days old are roughly inversely related to changes in the rate of stress relaxation. The coincidence of changes in stress relaxation with changes in lung morphology suggests that the viscoelastic characteristics of the respiratory system are influenced by the surface to volume ratio of the lung. If so, then it appears that the viscoelastic behavior of the res-

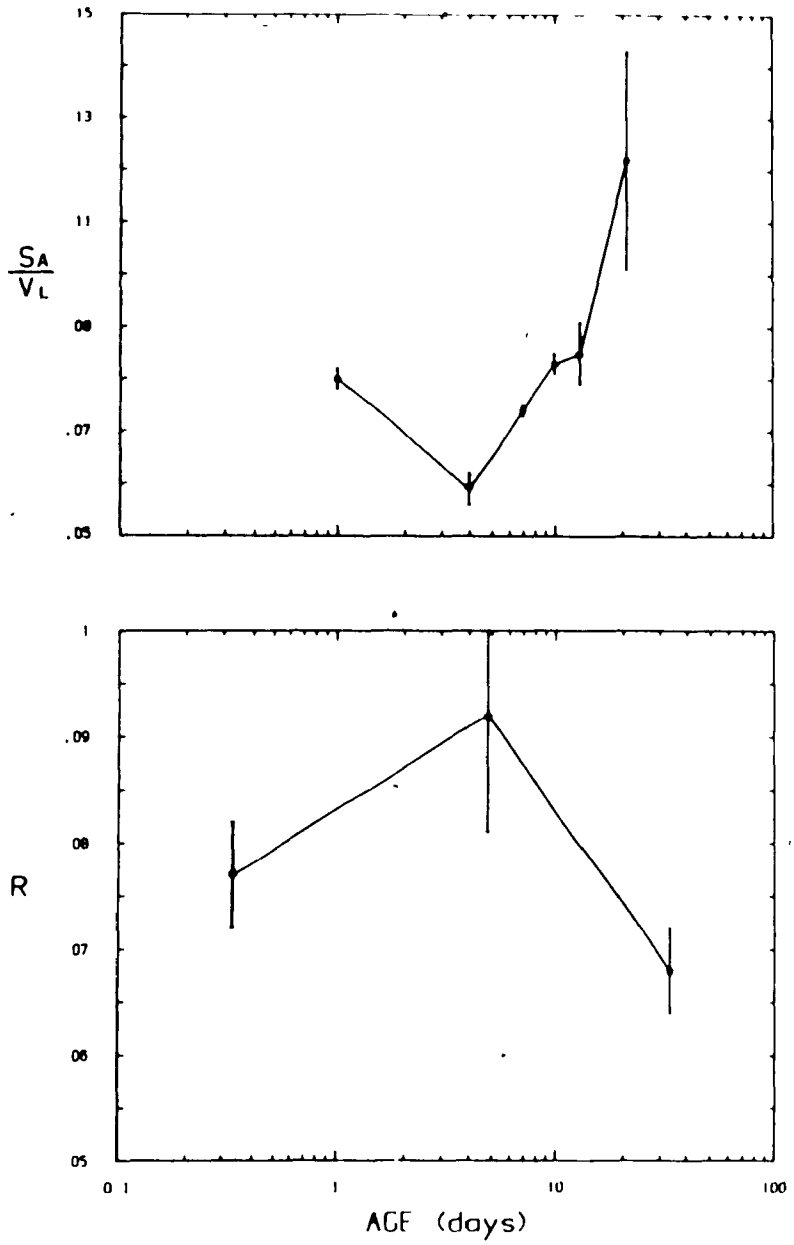

FIGURE 5.5 Comparison of age related changes in the surface to volume ratio, S_A/V_L of the lung with changes in the rate, R, of stress relaxation of the rat respiratory system. Mean values of the surface to volume ratio are from Burri (1974) and the corresponding bars are 1 S.E. Values of R are means $\pm$ 1 S.D.

piratory system and lung is determined not only by the combined viscoelastic properties of the different tissue elements and surface active layer but also by the internal structure of the lung. This may have some bearing on the observations by Haber et al. (1983) that lung distensibility is directly proportional to the mean linear intercept of its airspaces and thus inversely proportional to the surface to volume ratio.

In conclusion, rate dependent changes in the passive recoil pressure of the mechanically ventilated rat respiratory system have been compared to the behavior of a linear viscoelastic model exhibiting similar relaxation characteristics. The close correlation between experiment and theory suggests that frequency dependent changes in the dynamic compliance of the respiratory system can result from its viscoelastic properties rather than mechanisms involving the distribution of ventilation within the lung.

CHAPTER 6

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

The respiratory system of the newborn is characterized by a high chest wall/lung compliance ratio which encourages distortion of the chest during spontaneous breathing. Though there is evidence which suggests that the work of breathing is increased in distorted breathing, the extent to which this increase may be due to changes in the lungs' mechanical properties caused by deformation is not known. Since an analysis of the effect of lung deformation in vivo is complicated by variations in pleural pressure caused by chest wall distortion, the effect of lung deformation upon its quasi-static and dynamic compliance was examined in excised lungs of newborn piglets.

The lungs were deformed by a vertical pleural surface pressure gradient generated by immersing the lungs in saline. Quasi-static compliance was measured from step inflations of the lung, and dynamic compliance was measured between instants of zero-airflow during mechanical ventilation at 20 cycles per minute. Values of compliance obtained from the deformed lung were compared to values obtained for the undeformed lung suspended from its trachea in air.

Quasi-static lung compliance was not affected by deformation indicating that substantial airway closure or atelectasis does not occur in regions of the lungs subjected to low or negative transpulmonary pressure. This behavior is similar to published observations concerning the effect

of lung deformation in adults, and suggests that the lungs of the newborn adjusts to deformation by changing shape with little change in volume. In contrast, dynamic lung compliance was reduced by deformation. The effect of lung deformation upon dynamic compliance may involve changes in the distribution of ventilation caused by regional changes in peripheral flow resistance or compliance, both of which are likely to occur in the deformed lung.

The decrease in the dynamic compliance of the deformed lungs results in an increase in the work (PV) of mechanically ventilating the lungs and suggests that chest wall distortion in the spontaneously breathing newborn may increase the external work (PV) of breathing. Furthermore, since variations in dynamic compliance reflect changes in the distribution of ventilation, deformation may also alter ventilation-perfusion ratios within the lung and contribute to the changes in arterial PO_2 that accompany paradoxical breathing in the newborn infant.

The dynamic compliance of undeformed piglet lungs was also less than its quasi-static compliance although differences between the two were less pronounced than the differences observed in the deformed lungs. One explanation for the differences in compliance involves stress relaxation within the lung. Stress relaxation is a feature of tissue viscoelasticity and refers to the time dependent decay in stress that occurs when a tissue is stretched and held at a constant length. With respect to the lung, stress relaxation within the parenchyma and surface active layer is expressed as the time dependent decay in transpulmonary pressure at constant

volume. Because of the time dependent nature of transpulmonary pressure, lung compliance will vary according to the rate of inflation or the frequency of ventilation.

To examine whether the viscoelastic properties of the newborn lung may contribute to the differences between its quasi-static and dynamic compliances, excised lungs from newborn kittens and adult cats were ventilated at several frequencies between approximately 10 and 110 cycles per minute. Dynamic lung compliance calculated at each frequency of ventilation was significantly less than the corresponding quasi-static compliance in newborn and adult lungs. The mean difference however, was greater for the lungs of the newborn. In both groups, lung compliance appeared to fall rapidly at low ventilation frequencies then remains constant up to frequencies normally occurring in the spontaneously breathing animal at rest. The large decrease in lung compliance at low frequencies differs from the pattern of frequency dependence generally associated with changes in the distribution of ventilation but is similar to the effect of viscoelasticity on tissue stiffness or lung elastance.

In addition, age related changes in the compliance ratio correlated with a decrease in the magnitude of stress relaxation. The relationship between the lung's compliance ratio and stress relaxation indicate that its viscoelastic properties are likely responsible for differences between quasi-static and dynamic compliance and that the pronounced viscous nature of the newborn's lungs causes greater changes in its compliance compared to the adult's.

Lung stress relaxation at constant volume reduces its recoil pressure and thus the driving pressure of the onset of passive deflation. As a result, the time course of deflation may vary according to the duration of preceding lung inflation. To demonstrate how lung viscoelasticity affects the time course of passive deflation, an empirical function relating changes in recoil pressure with the time constant τ, of passive deflation was developed from a simple linear viscoelastic model. The equation predicted that increasing the duration of maintained lung inflation increases the time constant of the subsequent deflation. The magnitude of the change in τ, was governed by the magnitude of stress relaxation such that the more viscous lungs of the newborn showed greater changes in τ than the adult's lungs for the same duration of inflation. Predicted changes in τ due to lung viscoelasticity agree with published observations concerning the passive deflation of the rat respiratory system. This suggests that the viscoelastic properties of the lungs of the newborn cause its dynamic mechanical behavior to differ from predicted behavior based upon quasi-static measurements.

Age related changes in the viscoelastic properties of the lung suggest that similar changes occur in the mechanical properties of the respiratory system. To examine whether stress relaxation within the respiratory system varies with age, rats between birth and 40 days old were tracheotomized, cannulated, and placed inside a saline-filled plethysmograph with the tracheal cannula extending through the wall. Lung volume was abruptly increased by withdrawing saline from the plethysmograph and the resulting

stress relaxation, measured as the time dependent decay in transrespiratory system pressure, was recorded for 30 seconds. The decay in transrespiratory system pressure was approximately linear on ln(t) over this time interval and the rate of stress relaxation was estimated from the slope of the relaxation curve. The mean rate of stress relaxation increased within the first week of life but thereafter decreased. At 30-40 days, the rate of stress relaxation was less than the rate found in rats less than one day old. Changes in the rate of stress relaxation with age correlated with changes in the compliance ratio of the respiratory system, indicating that differences between quasi-static and dynamic compliances at low ventilation frequency are due to its viscoelastic properties.

Rate dependent changes in the passive recoil pressure of the rat respiratory system were predicted from its relaxation characteristics using an empirical model of respiratory system viscoelasticity. The model was based upon the reduced relaxation function originally proposed by Fung (1972) to describe the viscoelastic properties of tissue strips and features a continuous spectrum of retardation times. Prediction based upon the model were close to experimentally determined values, suggesting that rate dependent changes in the dynamic compliance of the rat respiratory system can occur independently of mechanisms involving alterations in the distribution of ventilation.

CLAIMS OF ORIGINALITY

1. Deformation of excised piglet lungs by immersion in saline does not affect its quasi-static compliance, indicating that the lungs of the newborn can resist airway closure and atelectasis under conditions of low or negative transpulmonary pressure.

2. The dynamic compliance of piglet lungs is less than its quasi-static compliance in undeformed and deformed states, but the difference is increased by deformation. This behavior suggests that deformation affects the distribution of ventilation within the lung, leading to an increase in the work (PV) of ventilating the lung and alterations in the ventilation-perfusion ratio.

3. The dynamic compliance of excised lungs from newborn kittens and adult cats are less than their corresponding quasi-static compliances. The relative differences between dynamic and quasi-static compliance, expressed as the compliance ratio (dynamic/static) is greater in the lungs of the newborn than the adult.

4. Lung stress relaxation, defined as the time dependent decay in transpulmonary pressure at constant volume, is greater in the newborn than the adult. The magnitude of stress relaxation in newborns and adults is not affected by the ventilation frequencies between 10 and 110 cycles per minute.

5. Age related changes in the compliance ratio may be explained by changes in the magnitude of stress relaxation within the framework of linear viscoelastic theory. This suggests that the more viscous nature of the newborn's lungs is responsible for the larger differences between dynamic and quasi-static compliances than is observed in the adult lung.

6. An empirical equation describing the effect of maintained lung inflation upon the time course of passive deflation was developed from a simple model of lung viscoelasticity. Predicted changes in the time constant of passive deflation are qualitatively similar to published observations, suggesting that lung stress relaxation at constant volume prolongs the duration of deflation.

7. Stress relaxation within the respiratory system, defined as the time dependent decay in transrespiratory system pressure, is approximately linear on ln(t) up to 30 seconds following a rapid inflation in rats between 1 and 40 days old. The rate of stress relaxation, estimated from the slope of the relaxation curve on ln(t), increases within the first week and thereafter decreases such that at 30-40 days, it is less than the rate of stress relaxation obtained from rats less than one day old.

8. Age related changes in the compliance ratio (dynamic/static) of the rat respiratory system correlate with changes in the rate of stress relaxation, indicating that variation in the viscoelastic properties of the respiratory system are responsible for differences between its quasi-static and dynamic compliance.

9. Rate dependent changes in the dynamic recoil pressure of the rat respiratory system can be predicted from its relaxation characteristics using an empirical model of viscoelasticity based upon the reduced relaxation function proposed by Fung (1972) to describe stress relaxation in tissue strips. This suggests that rate dependent changes in the dynamic compliance of the rat respiratory system can occur independently of mechanisms affecting the distribution of ventilation within the lung.

APPENDIX 1

EVALUATING THE CONTRIBUTION OF AIR COMPRESSIBILITY TO CHANGES IN LUNG VOLUME

SUMMARY

The contribution of gas compression to measurements of pulmonary and respiratory system compliance is examined. For isothermal conditions, the magnitude of the measurement error depends upon the dead space of the recording apparatus, the resting volume of the lung, and the curvilinear nature of the pressure-volume relationship. Because the respiratory parameters of lung volume and compliance are proportional to body mass, the measurement error does not vary greatly for isolated lungs from the newborns of different species However, for the same fractional volume change in the respiratory system, the measurement error increases progressively with increasing mass due to the relatively stiffer chest wall in heavier species The results of the analysis indicate that the error in volume measurement during mechanical ventilation in kittens is about 3 %.

The compressibility of gas, K, is defined as the fractional decrease in volume per unit increase in pressure (Main, 1978) and is given by

$$K = -\frac{V}{P}\frac{dP}{dV} \qquad [A1.1]$$

At room temperature and atmospheric pressure air behaves as a perfect gas and variations of pressure and volume follow

$$PV^{\gamma} = C \qquad [A1\ 2]$$

where c is a constant and γ is the ratio of heat capacities at constant pressure (Cp) and constant volume (Cv) The value of γ depends upon whether air is compressed adiabatically or isothermally. For completely adiabatic compression

$$\gamma = \frac{Cp}{Cv_H} = 1.4 \qquad [A1.3]$$

whereas for completely isothermal compression

$$\gamma = \frac{Cp}{Cv_T} = 1.0 \qquad [A1.4]$$

For intermediate conditions where compression is neither completely adiabatic or isothermal, the value of γ lies between 1 and 1.4 (Bargeton and Barres, 1969)

To demonstrate the relationship between the compressibility of air given by (A1.1) and the ideal gas law given by equation (A1.2) let

$$V^{\gamma} = \frac{c}{P} \qquad [A1\ 5]$$

then

$$V = \left(\frac{C}{P}\right)^{1/\gamma} \qquad [A1.6]$$

and

$$\frac{dV}{dP} = \frac{-V}{\gamma P} \qquad [A1.7]$$

substituting this result into [A1.1] gives

$$K = \frac{1}{\gamma P} \qquad [A1.8]$$

The compressibility of air, therefore, is governed by the mean ambient pressure, P.

To determine the pressure-volume characteristics of a known volume of air in an airtight, highly stiff container, a calibration is performed by adding known amounts or air at ambient pressure to the container and recording the change in pressure. Using this technique we arrive at a linear relationship between the added volume V and resulting pressure P given by

$$P' = -\alpha V \qquad [A1.9]$$

where α is the slope. Alternatively,

$$V = \frac{-P'}{\alpha} \qquad [A1.10]$$

where V is the change in gas volume due to compression caused by the

increase in pressure P. The first partial derivative of V with respect to P is given by

$$\frac{\partial V}{\partial P} = \frac{-1}{\alpha} \qquad [A1.11]$$

substituting equation [A1.7] into equation [A1 11]

$$\frac{1}{\alpha} = \frac{V}{\gamma P} \qquad [A1\ 12]$$

Equation [A1.12] indicates that if the volume of the system and the ambient pressure are known one can predict the volume change due to air compression without a system calibration. The advantage of this relationship is that it allows us to calculate the contribution of air compressibility for any hypothetical system. To show how well values of α^{-1} calculated from [A1.12] compare with experimentally derived values, calibration curves for systems of known volume were obtained. Initially, the volume of the system was made as small as possible by using short connections and a water filled pressure transducer To increase the volume of the apparatus, an air transducer (AT) or a bottle containing 50, 100, 200, and 400 ml of air was added. Pressure-volume calibrations were performed on each system and the slopes of the resulting curves were determined using linear regression analysis. To compare values of α^{-1} predicted from [A1.12] to the regression values, the mean barometric pressure (Patm) was assumed to be 760 mm Hg. Because a water-filled transducer was used and since the volume of air in the bottle was adjusted by displacing air with water at room temperature, the air within the system was saturated with water vapor. At an ambient temperature

of approximately 24° C the pressure exerted by water vapor is 22 mm Hg and therefore the mean ambient pressure is approximately 738 mm Hg. The density of mercury is 13.5951 times the density of water and so the mean ambient pressure, P, is equal to 1003 cm H_2O. Assuming isothermal conditions (γ = 1.0), the slope of the calibration curve was predicted using [A1.12] for each of the system volumes used in the experiment. In Table A1.1 are shown the predicted values of α^{-1} as well as those obtained from the regression analysis of the experimental data. The close correlation between theory and experiment shown in this table indicates that the relationship described by [A1.12] is correct. As the system volume decreases below 200 ml however, there is an increase in the % error between predicted and experimental values. This deviation is caused mainly by three factors: 1) Vo is not included in system volume; 2) the volume of the tube connecting the bottle to the transducer is not included in system volume and 3) the estimated mean ambient pressure may differ from the actual pressure present when the calibrations were performed.

Mechanical Ventilation in Newborns

Having established a method to calculate the change in gas volume due to compression, it remains to apply this method to experiments concerning the effect of gas compression on lung compliance during positive pressure ventilation.

TABLE A.1.1 COMPARISON OF PREDICTED AND EXPERIMENTAL VALUES OF α

System Volume	α cmH_2O/ml	α^{-1} ml/cmH_2O	α^{-1} predicted ml/cmH_2O	% error	volume predicted	% error
Vo	506.589	0 001974	-	-	2	-
AT	28.125	0 0355	-	-	36	-
50	17.897	0.0559	0.050	11	56	12
100	9.404	0.1063	0 100	6	106	6
200	5.095	0 1963	0 200	2	196	2
400	2.593	0 3867	0.394	3	387	

Experimental and predicted values of α^{-1} and volume for each of 4 systems. Vo is the minimal system volume. AT ; air transducer.

To do so, let $\hat{\Delta V}$ be the actual change in lung volume, corrected for the compression of air. Then

$$\hat{\Delta V} = \Delta V + Vc \qquad \text{(A1.13)}$$

where ΔV is the recorded change in volume and Vc is the volume lost due to air compression. From (A1.7)

$$Vc = -\frac{V_T}{\gamma P}\Delta P$$

V_T is the total gas volume of the system and lung at ambient pressure and ΔP is the change in pressure. The total gas volume can be restated as

$$V_T = Vo + Vr + \Delta V \qquad \text{(A1.14)}$$

where Vo is the volume of the apparatus between the pneumotachograph and the trachea, Vr is the resting volume of the lung, and ΔV is the volume of gas to be displaced into the lung. Therefore,

$$\hat{\Delta V} = \Delta V - \frac{(Vo + Vr + \Delta V)\,\Delta P}{\gamma P} \qquad \text{(A1.15)}$$

For any volume step ΔV , the fractional of the change in lung volume that is lost due to the compression of air is given by

$$\frac{\Delta V - \hat{\Delta V}}{\Delta V} = \frac{V_T}{\gamma P} * \frac{\Delta P}{\Delta V} \qquad [A1.16]$$

Let

$$\phi = \frac{\Delta V - \hat{\Delta V}}{\Delta V} \qquad [A1.17]$$

then the fractional change in lung volume under isothermal conditions can be simplified to

$$\phi = \frac{V_T}{P} * \frac{\Delta P}{\Delta V} \quad , \quad \gamma = 1.0 \qquad [A1.18]$$

Note that the value of Phi depends upon the total gas volume, the change in volume ΔV and the corresponding change in pressure. Because all three are interrelated, we will consider the characteristics of Phi under two conditions. For the first condition, the pressure-volume behavior of the respiratory system or lung follows the form

$$\Delta P = K\Delta V \qquad [A1.19]$$

where K is a contant. For the second condition

$$\Delta P = A(e^{B\Delta V} - 1) \qquad [A1.20]$$

where A and B are constants. The principal difference between the two conditions is the nature of lung compliance. In the former, compliance is constant whereas in the latter, it decreases with increasing volume. To

determine how each of these conditions affects Phi, Equation [A1.19] and [A1.20] are substituted into equation [A1.16]. For [A1.19] this results in

$$\phi = \frac{V_T}{P} * K \qquad [A1.21]$$

To illustrate the effect of compliance upon Phi, consider two hypothetical lungs (1 and 2) having the characteristics shown in Table A1.2 Each lung is subjected to the same change in transpulmonary pressure and attains the same final volume. The compliance of the second lung however, is one tenth the compliance of the first lung and the fractional change in lung volume due to air compressibility is ten times greater as a result. Similarly, if both lungs begin at the same initial volume, the effect of air compression is greater in the less compliant lung (1 and 3).

TABLE A1.2 EFFECT OF LUNG COMPLIANCE ON THE VOLUME LOST DUE TO GAS COMPRESSSION

LUNG	K^{-1}	Vi	dP	dV	Vt	%
1	2	10	5	10	20	1
2	0.2	19	5	1	20	10
3	0.2	10	5	1	11	5.5

Effect of lung compliance upon the fractional loss of volume due to air compressibility. K^{-1}, compliance, ml/cmH2O; Vi, inital volume; dP, change in transpulmonary pressure, cm H2O dV, change in lung volume, ml; Vt total lung volume, ml; %, percent of the recorded volume change that is lost due to the compression of air

The effect of compliance on values of Phi in dissimilar lungs is analagous to the effect of changes in compliance with lung volume. Figure A1.1 shows the quasi-static pressure volume curve of the paralyzed respiratory system of an 8 day old puppy (at 35° C, P = 990 cm H_2O). The curve passing through the data represents the best fit solution of equation [A1.20]. Substituting [A1.20] into [A1.16] results in

$$\phi = \frac{V_T}{P} \frac{A(e^{B\Delta V} - 1)}{\Delta V} \qquad [A1.22]$$

Values of Phi calculated using equation 22 are plotted against the change in lung volume is shown in Figure A1.2. From this relationship , the actual change in lung volume was determined and the corrected pressure-volume curve is plotted as a dotted line in Figure A1.1 The results indicate that the contribution of gas compression to volume measurements in the respiratory system of the puppy is small particularly at low lung volume.

In experiments concerning lung viscoelasticity in newborn kittens and adult cats, excised lungs were inflated in steps, beginning each step at a fixed transpulmonary pressure that was slightly above the recoil pressure of the lung at its functional residual capacity (FRC). To estimate the volume lost due to gas compression at each step, the initial gas volume of the lung was estimated using published values of FRC (Fisher and Mortola, 1980) adjusted in proportion to the difference between Pl_{FRC} and the initial transpulmonary pressure of the excised lung. Values of Phi were calculated using A1.21 and recorded changes in lung volume and transpulmonary pressure. Using this approach, the estimated volume lost

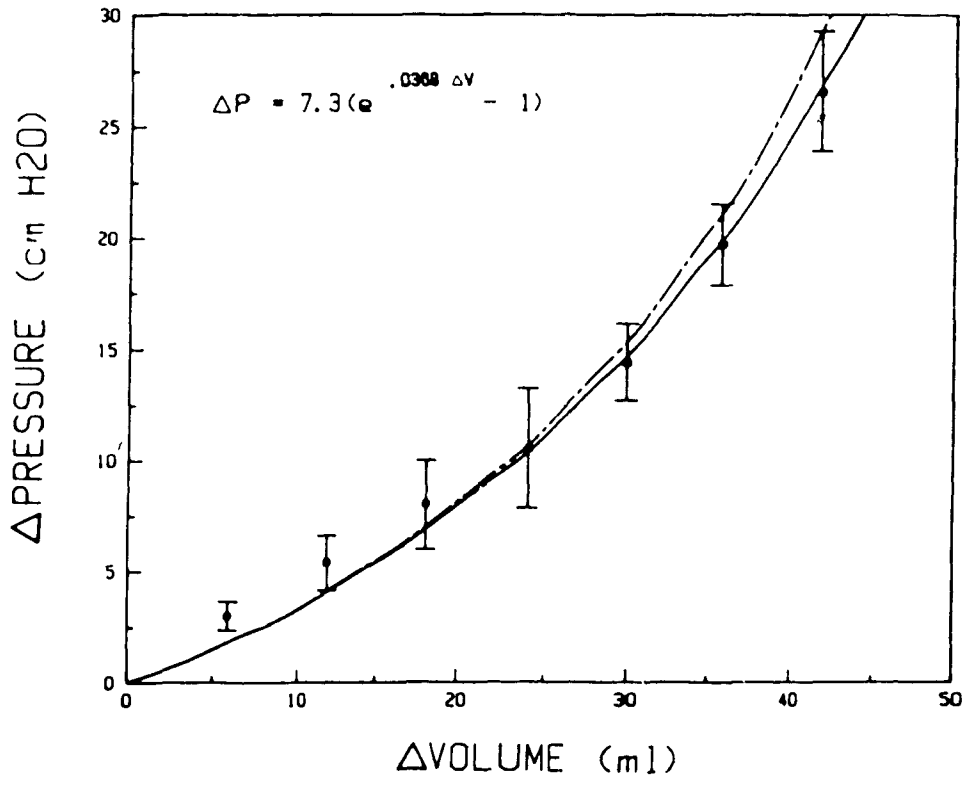

FIGURE A1 1 Quasi-static pressure volume curve of the respiratory system of an 8 day old puppy. Points are the mean of three trials and the corresponding bars are one S.D.. Solid line, best fit of equation (A1.20). Dotted line, the pressure volume curve corrected for gas compression

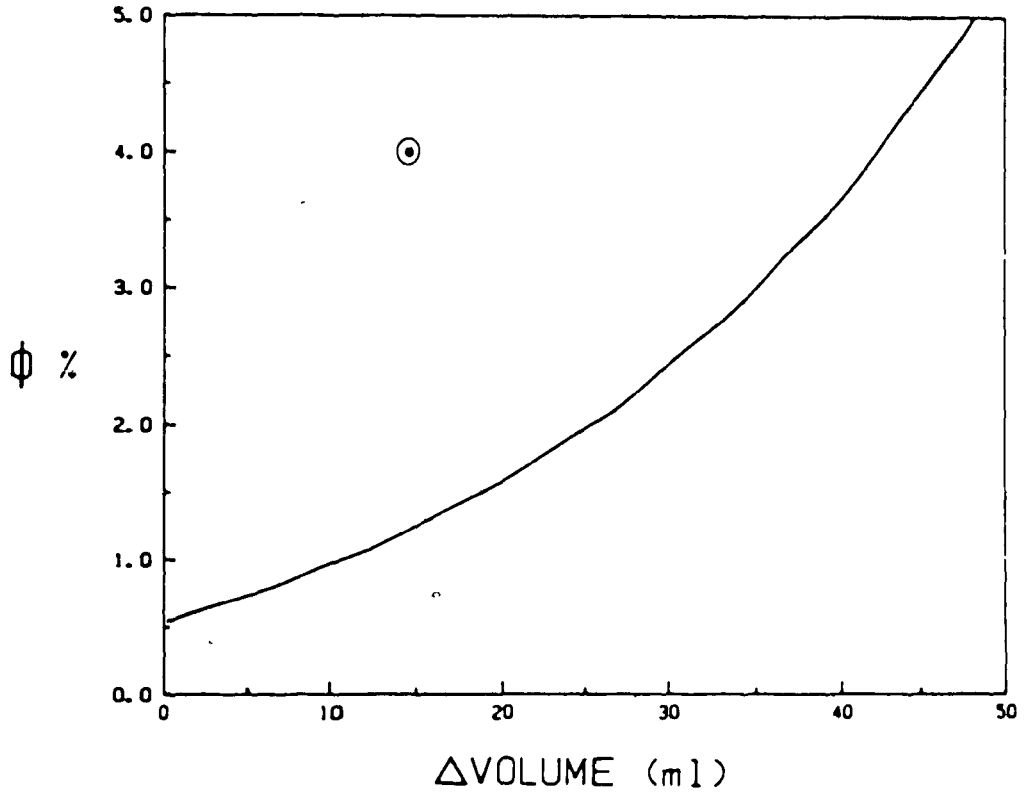

FIGURE A1.2 Variation in the value of Phi for the respiratory system shown in Figure A1.1. The resting gas volume of the lung was estimated from Fisher and Mortola (1980) to be approximately 20 ml. Dotted circle: value of Phi calculated using A1.21 at a transpulmonary pressure of 5 cm H_2O.

due to gas compression was about 3% or less of the recorded volume change.

Basic respiratory paramaters such as lung volume and compliance are proportional to body mass in a large number of species (Spells, 1970/71). The invariance of these parameters with respect to mass indicates dimensional and functional similarity within the respiratory system and lung among different species. Since Phi is a function of lung volume and compliance it follows that it is also proportional to body mass. To demonstrate the relationship between Phi and body mass in newborns, allometric equations concerning the functional residual capacity of the newborn lung and the compliance of the respiratory system and lung derived by Fisher and Mortola (1980) were substituted into equation [A1.8] . For the isolated lung this resulted in

$$\phi = \frac{59.61 * \bar{W}^{0.04} + \Delta P}{P} \simeq \frac{59.61 + \Delta P}{P} \qquad [A1.23]$$

and for the respiratory system

$$\phi = \frac{17.78 * W^{0.107} + \Delta P}{P} \qquad [A1.24]$$

Thus, the magnitude of Phi is relatively independent of body weight for isolated lungs but increases progressively with body weight for the respiratory system. This is due to the fact that the chest wall is relatively stiffer in the newborns of heavier species (Fisher and Mortola, 1981; Mortola, 1983) which causes the compliance of the respiratory system

per unit body weight to decrease with increasing weight. The dotted circle in Figure A1.2 illustrates relationship between values of Phi calculated using body weight and those calculated using equation [A1 20] for an 8 day old puppy.

APPENDIX 2

THE FREQUENCY RESPONSE OF THE APPARATUS USED TO DETERMINE THE DYNAMIC COMPLIANCE OF THE NEWBORN RAT RESPIRATORY SYSTEM DURING MECHANICAL VENTILATION

SUMMARY

The frequency response characteristics of an apparatus used to measure changes in lung volume and transrespiratory system pressure in the newborn rat are presented. During positive pressure ventilation, gas compression within the differential pressure transducer used to measure airflow causes an error in the volume derived by flow integration. The magnitude of the error is reduced by a correction factor which describes the pressure-volume characteristics of the apparatus between the pneumotachograph and the animal. This correction factor differs from that used to correct lung volume obtained from static measurements. Frequency dependent behavior is observed for integrated volumes of the order of 50 ul but is small between 20 and 105 cpm.

In conclusion, pneumotachograph derived measurements in animals the size of a newborn rat are complicated by the fact that the volume of the system may be several orders of magnitude greater than the change in lung volume.

INTRODUCTION

At rest, newborn rats breathe with a tidal volume of roughly 50 ul and at frequencies of up to 120 breathes per minute (P. de Ste Rome, unpublished observations). To record respiratory events of this magnitude in the mechanically ventilated rat, a pneumotachograph designed specifically for small animals (Mortola and Noworaj, 1983) was used as a tracheal cannula. This pneumotachograph consists of a narrow bore, stainless steel tube which serves as the cannula and 3 shorter tubes which are attached to the main tube at 90 degrees These short tubes are used to measure static pressure at different points along the main tube A differential pressure transducer connected to two of the side ports records the pressure drop caused by the flow resistance of the cannula and another pressure transducer connected to the third side port records changes in tracheal pressure. Although the frequency response characteristics of the pneumotachograph have been described, they were obtained at flow rates that exceed those anticipated in this study by at least one order of magnitude. Consequently, it is important to determine the response characteristics of the pneumotachograph at comparable flow rates.

Changes in tracheal pressure during each cycle of ventilation were recorded using a water filled pressure transducer normally used for measurements of blood pressure. The transducer was connected to a side port by a short length of tubing and filled with enough water so that the transducer and about half of the tube were filled. Airway pressure is

transmitted to the pressure sensing diaphragm of the transducer across a meniscus which forms in the tube at the boundary between the water and air. To calibrate the transducer, the air within the pneumotachograph was pressurized with an open end manometer and the sensitivity of the transducer was adjusted accordingly. Because the water filled transducer contains no air, it effectively reduces the gas volume of the system. However, water filled transducers are not normally used to record changes in gas pressure, and so the frequency response of this transducer was also determined

MATERIALS AND METHODS

To assess the frequency response of the pneumotachograph and recording apparatus, a small animal ventilator (Harvard Apparatus, model 380) modified to deliver harmonically varying volume was connected to one end of the pneumotachograph and an airtight jar was attached to the other end. At ventilation frequencies of between 20 and 200 cycles per minute (cpm), the change in volume obtained by electrical integration of the flow signal was maintained at approximately 50 ul by adjusting the stroke volume of the ventilator and the corresponding change in gas volume within the jar was calculated from the change in jar pressure. To eliminate errors in jar volume due to frequency dependent conversion from primarily isothermal to adiabatic conditions (Bargeton and Barres, 1969), shredded aluminum was placed in the jar. The high heat capacity of the aluminum together with its

large surface area, renders pressure-volume transformations primarily isothermal (Greenfield, 1964) (Figure A2.1).

The frequency response of the water filled transducer was assessed by comparing its output to that of a conventional air-filled transducer (Statham model # 15184). Both transducers and the ventilator were connected to an airtight jar. The water filled transducer was attached to the jar using the same connections used to record tracheal pressure in newborn rats. At frequencies between 20 and 200 cpm, the stroke volume of the ventilator was adjusted to maintain a change in pressure within the jar of 5 cm H_2O measured using the air filled transducer while the output of the water filled transducer was simultaneously recorded.

RESULTS

Figure A2.2 shows the frequency response curve of the pneumotachograph in which the integrated volume is presented as a fraction of the change in jar volume. At all frequencies, integrated volume was significantly greater than jar volume, indicating that the pneumotachograph derived volume overestimates the actual change in the volume of gas within the jar. In addition, the integrated volume decreases slightly with increasing frequency, the difference being about 10 % of the total change in volume at 200 cpm.

The frequency response of the water filled transducer is shown in Figure A2.3 where the change in pressure recorded using this transducer is

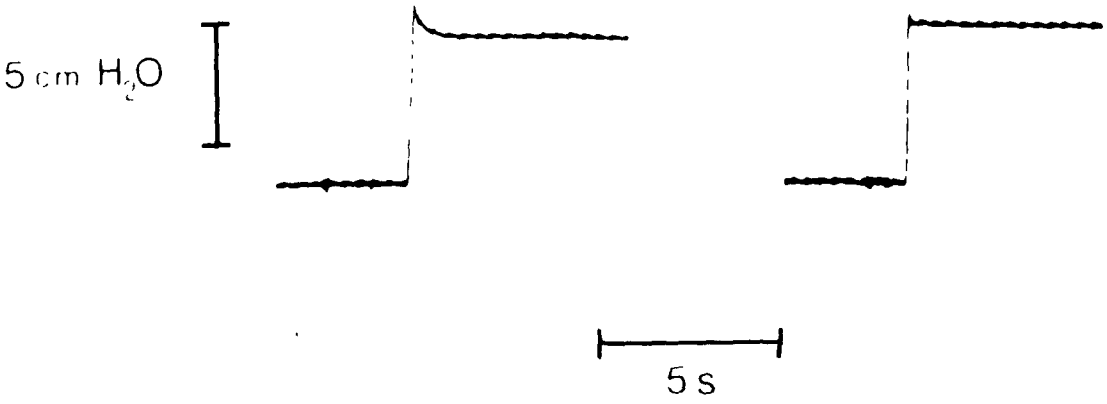

FIGURE A2.1 Left. Change in jar pressure when 0.08 ml air is rapidly injected The peak pressure reflects primarily adiabatic conditions whereas the equilibrium pressure represents isothermal conditions. Right Pressure-volume transformations within the same jar containing shredded aluminum. The volume step is 0 08 ml. The large heat capacity of aluminum causes the temperature of the compressed gas to rapidly approach ambient temperature. Bar provides time scale.

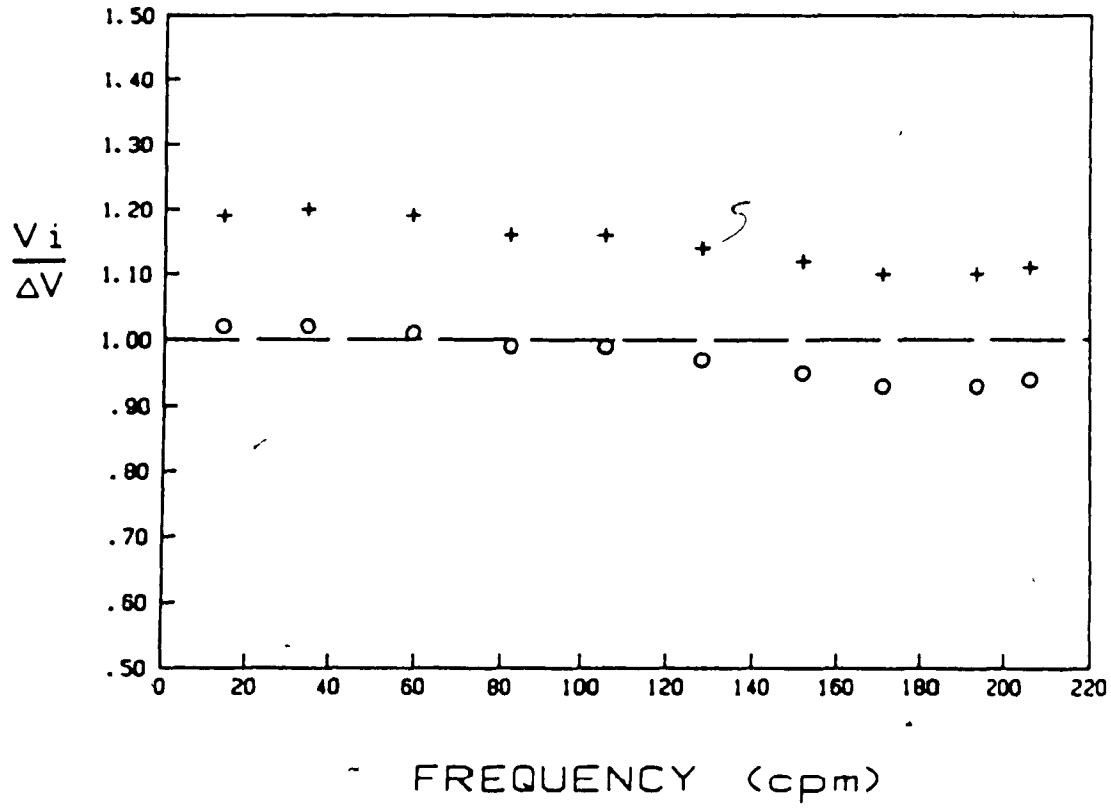

FIGURE A2.2 Frequency response curve of pneumotachograph derived volume. Vi/ΔV; is the ratio of pneumotachograph derived volume to the actual change in gas volume. The crosses are raw data; Circles, data corrected for gas compression within the system. Each point is the mean of 5 cycles.

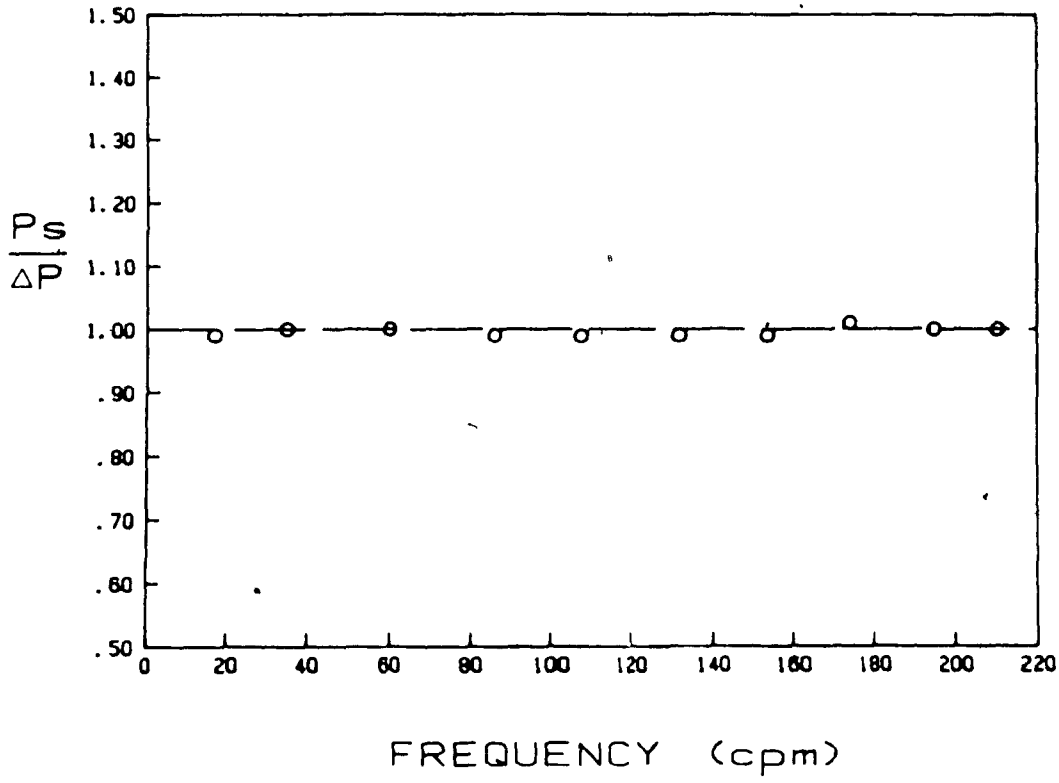

FIGURE A2 3 The frequency response curve of the water filled transducer. Ps/ΔP, is the output of water filled transducer as a fraction of the actual change in jar pressure. Each point is the mean of 5 cycles.

presented as a fraction of the actual pressure change obtained from the Statham transducer. The overall behavior of the transducer between 20 and 100 cpm is good, indicating that the water filled transducer provides a reliable record of change in tracheal pressure.

DISCUSSION

During mechanical ventilation, the pressure within the system increases as air flows into the lung. The increase in pressure compresses the gas within the apparatus and lung which results in a reduction in the original volume of air added to the system. Generally, gas compression within the system is taken into account only for static maneuvers where the actual change in lung volume depends upon the volume of the apparatus For small animals such as newborn rats, however, an additional volume correction must be employed to correct for gas compression during periodic positive pressure ventilation. The reason for this is that the volume of the lung in animals of this size is substantially less than the volume of the apparatus between the pneumotachograph and the animal. Figure A2.4 is a schematic of the apparatus in which each transducer and its connections are presented as a component of total system volume. Note that the volume of the system between the second side port of the pneumotachograph is roughly equal to the

sum of V2 and V3. For simplicity, we will assume that the volume of these two compartments is approximatley half of the total volume of the apparatus or

$$V2 + V3 \approx 1/2\ Vs \qquad A2.1$$

where Vs is the total volume of the apparatus between the valve and the rat The static pressure-volume characteristics of the entire system is given by

$$dP = 270\ dV \qquad A2\ 2$$

where dP is the change in pressure in cm H2O that occurs when a volume of air dV, in ml, is added to the system. From APPENDIX 1

$$\frac{dV}{dP} = -\frac{Vs}{\gamma P} \qquad A2.3$$

where $\gamma = 1.0$ and P is ambient pressure. For half of the system volume

$$\frac{dV}{dP} = -\frac{Vs}{2\gamma P} \qquad A2.4$$

or

$$\Delta Vc \approx -0.0018\ \Delta P \qquad A2.5$$

Equation A2.5 may be interpreted to represent the volume change due to gas compression within the proximal half of the apparatus when the pressure is

altered by dP. The actual change in lung or jar volume after correcting for gas compression within the system is given by

$$V_L = V_I - 0.0018\,\Delta P \qquad \text{A2.6}$$

where V_L is the corrected change in volume and V_I is the integrated volume. It is apparent from A2.6 that as V_I is increased for the same ΔP, the relative size of the correction term is reduced and eventually becomes negligible. This is the case for animals larger in size, and hence in absolute compliance, than the newborn rat. It may also explain why the difference between V_C and V_I was not observed in a previous study of the pneumotachograph (Mortola and Noworaj, 1983), presumably because the compliance of the box was greater than the jar used in this study. For animals that are the size of a newborn rat, however, the effect of gas compression within the system becomes substantial. In the present study, the change in lung volume for an end-inflation transrespiratory pressure of 5 cmH_2O is typically about 0.035 ml in a rat less than one day old. After correcting for gas compression using A2.5, the actual change in lung volume is about 0.026 or roughly 75 % of the change in volume derived from the integrated flow signal.

The correction factor given in A2.5 is based upon the pressure volume characteristics of the entire system and the assumption that the volume of the apparatus between the pneumotachograph and the animal is half of the total volume. Although this derivation served to show the contribution of

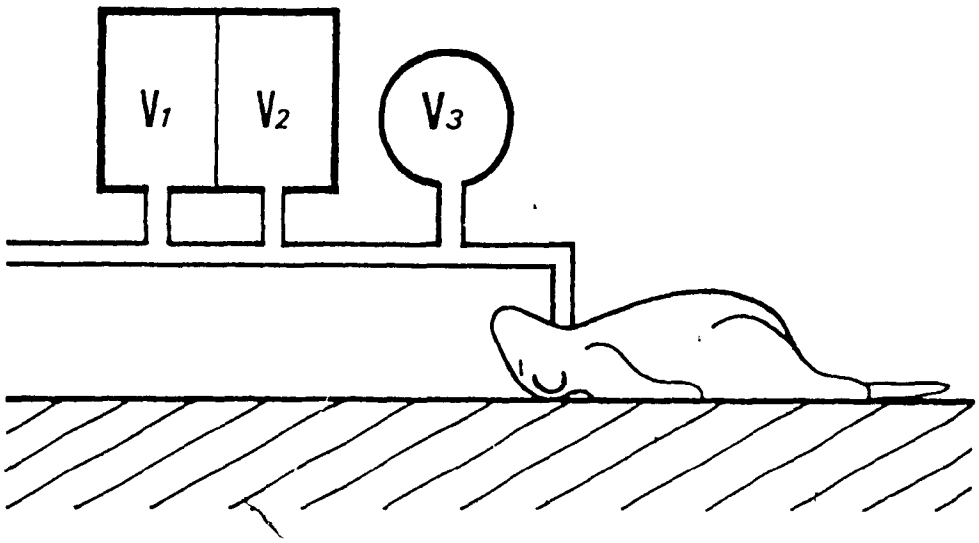

FIGURE A2.4 Schematic of the apparatus used to determine the static and dynamic properties of the rat respiratory system during mechanical ventilation. V1 and V2 represent the differential pressure transducer, and V3 is the saline filled pressure transducer.

gas compression to the error in volume measurements, it is only an estimate. An exact value for a correction factor was determined experimentally in the following manner. The tube at the ventilator end of the pneumotachograph was clamped thereby sealing the system and the remaining volume was calibrated to give

$$\frac{dV}{dP}_{123} = 3.66 \times 10^{-3} \qquad \text{A2.7}$$

The tubes connecting the differential pressure transudcer to the pneumotachograph were then clamped near the side ports to eliminate V1 and V2 from the system. Calibrating the remaining system gave

$$\frac{dV}{dP}_{3} = 7.1 \times 10^{-4} \qquad \text{A2.8}$$

From the results of these two calibrations it appears that the differential pressure transudcer has a volume approximately five times the volume of the remaining system and is, therefore, the principal component of system volume. Subtracting A2.8 from A2.7 one obtains the pressure-volume characteristics of the differential pressure transducer. Because only half of the transducer contributes to volume loss during periodic ventilation, the correction factor was calculated as

$$\frac{dV}{dP} = \frac{dV}{dP}_{3} + \frac{1}{2}\left[\frac{dV}{dP}_{123} - \frac{dV}{dP}_{3}\right] \qquad \text{A2.9}$$

or in terms of the change in lung volume V1

$$V_L = V_1 - 0.00219\,\Delta P \qquad \text{A2 10}$$

Figure A2.2 shows the frequency response curve of the pneumotachograph corrected for gas compression using equation A2.10. The error in integrated volume is reduced to less than 3 % for frequencies of ventilation up to 105 cpm. Since this is also the range of frequencies used to study the mechanical properites of the rat respiratory system, it is reasonable to conclude that pneumotachograph derived volume corrected for gas compression provides an accurate measure of the change in lung volume in newborn rats.

FREQUENCY DEPENDENT EFFECTS

Frequency dependent changes in the output of the pneumotachograph up to 105 cpm are small and may be neglected with practically no loss of accuracy (Figure A2.2). It is of interest to note that frequency dependent characteristics of the pneumotachograph are due to different time constants of the two compartments within the differential pressure transducer. The time constants of each compartment is the product of its compliance and the flow resistance of the connecting tube. When attached to the pneumotachograph, the flow resistance to one compartment is increased by the resistance of the cannula. As a result, the time constants differ and cause

frequency dependent variation in the pressure within the compartments. Since the pressure difference is likely not affected by airway pressure, this behavior is also present when the pneumotachograph is used to record spontaneaous breathing in the anesthetized rat. Like the effect of gas compression, however, the error in the volume signal is constant and becomes negligible for larger values of Vi

APPENDIX 3

THE DERIVATION OF EQUATION 3.6

Upon occlusion at end inflation, stress relaxation of the lung parenchyma and surface active film reduces the recoil pressure of the lung. Assuming stress recovery has a small effect compared with flow resistance upon the time course of deflation, the relationship between lung recoil pressure and the time constant of deflation may be described by equation 3.5. Substituting equation 3.2 for G(t) and rearranging the terms, one obtains

$$\frac{dV}{V} = \frac{-E}{R}\left[Es + (1 - Es)\, e^{-t/T}\right] dt. \qquad [A3.1]$$

which upon integration gives

$$\ln\left(\frac{V(t)}{V_o}\right) = \frac{-E}{R}\left[Es(t' - t) - T(1 - Es)\, e^{-t'/T} * \left(1 - e^{(t'-t)/T}\right)\right] \qquad [A3.2]$$

where Vo is the initial volume of the lung, V(t) is the volume after a period of time, t, following release of the occlusion and t' is the duration of the occlusion. Denoting everything within the square brackets as A and taking the exponential of both sides, the above equation becomes

$$\frac{V(t)}{V} = e^{-\frac{E}{R}A} \qquad [A3.3]$$

The effective time constant of passive deflation, τ, can be expressed according to the formula described by Brody (1954) as

$$\frac{V(t)}{V_o} = e^{(t'-t)/\tau} \quad \text{for } t > t' \qquad [A3.4]$$

Substituting this equation into the preceding equation and rearranging gives

$$\frac{1}{\tau} = \frac{E}{R}\left\{Es + \frac{T(1-Es)}{(t-t')}\, e^{-t'/T} * \left[1 - e^{-(t-t')/T}\right]\right\} \qquad (A3.5)$$

for $(t - t')/T \ll 1$, the term $\mathrm{Exp}(-(t-t')/T)$ can be approximated using

$$e^{-x} = 1 - x + \frac{x^2}{2!} - \frac{x^3}{3!} + \ldots + (-1)^n \frac{x^n}{n!} \qquad [A3.6]$$

or, using only the first two terms on the right hand side,

$$e^{-(t-t')/T} \simeq 1 - (t-t')/T \qquad [A3.7]$$

Substituting into the preceding equation gives

$$\frac{1}{\tau} \simeq \frac{E}{R}(Es) + \frac{E}{R}(1 - Es)\, e^{-t'/T} \qquad [A3.8]$$

As t' approaches zero, the effective time constant approaches the time constant of the unoccluded breath such that

$$\tau = \frac{R}{E} = \tau_o \qquad [A3.9]$$

where τ_o is the time constant of the unoccluded breath. Hence,

$$\tau = \frac{\tau_o}{Es + (1 - Es)\, e^{-t/T}} \qquad [A3.10]$$

APPENDIX 4

NUMERICAL INTEGRATION OF THE REDUCED RELAXATION FUNCTION

To predict changes in the passive recoil pressure of the rat respiratory system for different rates of ventilation, the integral within Equation 5.6 was evaluated using Simpson's Rule. According to this rule, if a function, f(x), is continuous on [a,b] then

$$\int_a^b f(x)dx = \frac{b-a}{n} * [\, f(x_0) + 4f(x_1) + 2f(x_2) + \quad \text{A4.1}$$

$$+ 2f(x_3) + 4f(x_4) + f(xn) \,]$$

where n is an even integer. The function to be integrated is the reduced relaxation function, G(t), which is given by

$$G(t) = \frac{1 + c\left[E_1\left(\frac{t}{T_2}\right) - E_2\left(\frac{t}{T_1}\right)\right]}{1 + c\ln\left(\frac{T_2}{T_1}\right)} \quad \text{A4.2}$$

where El(x) is the exponential integral operator. To compute values of G(t), the exponential integrals within the function were evaluated using the polynomial approximations provided by Abramowitz and Stegun (1964). The computations were performed on a microcomputer (Hewlett Packard model 9816) using the BASIC program listed in this Appendix. Values of C, T1 and T2 are input along with the elastic response E, the change in lung volume V, and the duration of inflation Ti and the program computes the value of the integral and the predicted change in transrespiratory system pressure.

The error in the approximate solution provided by A4.1 decreases with increasing n (Swokowski, 1976). Table A4.1 shows the effect of n on the estimated solution of Equation 5.7. At each value of n, the integral was evaluated for intervals of 0.1,1 and 10 seconds and a measure of the relative error was obtained from the difference between the computed value

and the solution for n = 10,000. It is apparent that the accuracy of the approximation improves little for values of n greater than 100. Accordingly, n =100 was used to calculate the change in transrespiratory pressure predicted by the model.

TABLE A4.1 ERROR IN THE SOLUTION OF EQUATION 6.X FOR DIFFERENT VALUES OF n

n	Ti = 0.1	e	Ti = 1.0	e	Ti = 10	e
25	0.94546	<0.02	0.83333	<0.02	0.69358	<0.02
50	0.95775	<0.0001	0.84381	<0.0001	0.70185	<0.0001
100	0.95774	<0.0001	0.84374	<0.0001	0.70179	<0.0001
200	0.95773	<0.00001	0.84378	<0.0001	0.70180	<0.0001
400	0.95773	<0.00001	0.84377	<0.00001	0.70179	<0.00001
800	0.95773	<0.00001	0.84377	<0.00001	0.70179	<0.00001
1600	0.95772	<0.00001	0.84377	<0.00001	0.70179	<0.00001

Solutions of Equation 5.7 for the different values of n. The constants C, T1 and T2 used in the computation were derived from the stress relaxation response of Group I. The elastic response, E, and the change in lung volume, V, were arbitrarily set to 1. Ti is the duration of inflation in seconds. The letter e represents the difference between the solution for each value of n and that obtained for n = 10,000.

```
10    '  NUMERICAL INTEGRATION OF FUNG'S REDUCED RELAXATION FUNCTI
ON
20    '  ********************************************************
30    '
40    OPTION BASE 0
50    INPUT "INPUT FUNCTION PARAMETERS C, T1 AND T2,",C,T1,T2
60    INPUT "INPUT ELASTIC RESPONSE ,E, VOLUME CHANGE, V, AND DURA
TION T1",E,V,T
1
70    '
80    '  CALCULATE INTEGRAL
90    '
100   N=100      '    # INCREMENTS
110   Nint=0
120   Inc=T1/N
130   F=0
140   M=4
150   S=-1
160   K=0
170   FOR I=1  TO N-1
180       M=M+K
190       X=I*Inc/T1
200       X1=FNT(X)
210       X=I*Inc/T2
220       X2=FNT(X)
230       F1=1+C*(X2-X1)
240       F2=1+C*LOG(T2/T1)
250       F=F+M*F1/F2
260       K=2*S
270       S=-S
280   NEXT I
290   !            FIND END POINTS: LAST POINT  t = T1
300       X=Ti/T1
310       X1=FNT(X)
320       X=Ti/T2
330       X2=FNT(X)
340       F1=1+C*(X2-X1)
350       F2=1+C*LOG(T2/T1)
360       F=F+F1/F2
370   !                                FIRST POINT  t = 0
380   F=F+1
390   Nint=Ti*F/(3*N)
400   '
410   !            COMPUTE PRESSURE RESPONSE
420   !
430       P=E*V*Nint/Ti
440   !
450   X=15/T1
460   X1=FNT(X)
470   X=15/T2
480   X2=FNT(X)
```

```
490   F1=1+C*(X2-X1)
500   F2=1+C*LOG(T2/T1)
510   F15=F1/F2
520   Pd=P/F15
530   !
540   IMAGE AA,3X,DDD.DDD
550   IMAGE 15A,3X,DD.DDD
560   IMAGE 15A,3X,DD.DD
570   IMAGE 20A,3X,DDD.DD
580   PRINT USING 540;"C :",C
590   PRINT USING 540;"T1:",T1
600   PRINT USING 540;"T2:",T2
610   PRINT USING 550;"T1  (s)          ",T1
620   PRINT USING 550;"Vol.(ml)         ",V
630   PRINT USING 560;"RATIO ",Pd
640   PRINT USING 570;"ELASTANCE (cm H2O/ml)",P/V
650   GOTO 60
660   END
670   DEF FNT(X)                  !  EVALUATE EXPONENTIAL INTEGRAL
680         IF X<1 THEN
690               GOSUB 750
700               GOTO 730
710         ELSE
720               GOSUB 840
730         END IF
740   RETURN A
750   A0=-.57721
760   A1=.99999
770   A2=-.24991
780   A3=.05519
790   A4=-.00976
800   A5=.00107
810   A7=A0+A1*X+A2*X^2+A3*X^3+A4*X^4+A5*X^5
820   A=A7-LOG(X)
830   RETURN
840   A1=8.57332
850   A2=18.05901
860   A3=8.63476
870   A4=.26777
880   B1=9.57332
890   B2=25.63295
900   B3=21.09965
910   B4=3.95849
920   A5=X^4+A1*X^3+A2*X^2+A3*X+A4
930   B5=X^4+B1*X^3+B2*X^2+B3*X+B4
940   ON ERROR GOTO 970
950   A=(A5/B5)/(X*EXP(X))
960   GOTO 1020
970   IF ERRN=22 THEN       ! REAL OVERFLOW
980   A=0
990   ELSE
1000  BEEP
1010  END IF
1020  RETURN
1030  FNEND
```

```
10     '  NUMERICAL INTEGRATION OF FUNG'S REDUCED RELAXATION FUNCTI
ON
20     '  ************************************************************
30     '
40     OPTION BASE 0
50     INPUT "INPUT FUNCTION PARAMETERS C, T1 AND T2,",C,T1,T2
60     INPUT "INPUT ELASTIC RESPONSE ,E, VOLUME CHANGE, V, AND DURA
TION T1",E,V,T
1
70     '
80     '  CALCULATE INTEGRAL
90     '
100    N=100        '    # INCREMENTS
110    Nint=0
120    Inc=T1/N
130    F=0
140    M=4
150    S=-1
160    K=0
170    FOR I=1 TO N-1
180        M=M+K
190        X=I*Inc/T1
200        X1=FNT(X)
210        X=I*Inc/T2
220        X2=FNT(X)
230        F1=1+C*(X2-X1)
240        F2=1+C*LOG(T2/T1)
250        F=F+M*F1/F2
260        K=2*S
270        S=-S
280    NEXT I
290    '          FIND END POINTS: LAST POINT  t = T1
300        X=T1/T1
310        X1=FNT(X)
320        X=T1/T2
330        X2=FNT(X)
340        F1=1+C*(X2-X1)
350        F2=1+C*LOG(T2/T1)
360        F=F+F1/F2
370    '                              FIRST POINT  t = 0
380    F=F+1
390    Nint=T1*F/(3*N)
400    '
410    '            COMPUTE PRESSURE RESPONSE
420    '
430        P=E*V*Nint/T1
440    '
450    X=15/T1
460    X1=FNT(X)
470    X=15/T2
480    X2=FNT(X)
```

```
490  F1=1+C*(X2-X1)
500  F2=1+C*LOG(T2/T1)
510  F15=F1/F2
520  Pd=P/F15
530  '
540  IMAGE AA,3X,DDD.DDD
550  IMAGE 15A,3X,DD.DDD
560  IMAGE 15A,3X,DD.DD
570  IMAGE 20A,3X,DDD.DD
580  PRINT USING 540;"C :",C
590  PRINT USING 540;"T1:",T1
600  PRINT USING 540;"T2:",T2
610  PRINT USING 550;"T1   (s)          ",T1
620  PRINT USING 550;"Vol.(ml)          ",V
630  PRINT USING 560;"RATIO ",Pd
640  PRINT USING 570;"ELASTANCE (cm H2O/ml)",P/V
650  GOTO 60
660  END
670  DEF FNT(X)                ' EVALUATE EXPONENTIAL INTEGRAL
680        IF X<1 THEN
690              GOSUB 750
700              GOTO 730
710        ELSE
720              GOSUB 840
730        END IF
740  RETURN A
750  A0=-.57721
760  A1=.99999
770  A2=-.24991
780  A3=.05519
790  A4=-.00976
800  A5=.00107
810  A7=A0+A1*X+A2*X^2+A3*X^3+A4*X^4+A5*X^5
820  A=A7-LOG(X)
830  RETURN
840  A1=8.57332
850  A2=18.05901
860  A3=8.63476
870  A4=.26777
880  B1=9.57332
890  B2=25.63295
900  B3=21.09965
910  B4=3.95849
920  A5=X^4+A1*X^3+A2*X^2+A3*X+A4
930  B5=X^4+B1*X^3+B2*X^2+B3*X+B4
940  ON ERROR GOTO 970
950  A=(A5/B5)/(X*EXP(X))
960  GOTO 1020
970  IF ERRN=22 THEN      ' REAL OVERFLOW
980  A=0
990  ELSE
1000 BEEP
1010 END IF
1020 RETURN
1030 FNEND
```

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