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Engineering aspects of neonatal respiratory augmentation

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ENGINEERING ASPECTS OF NEONATAL RESPIRATORY AUGMENTATION

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INTRODUCTION

Machines providing artificial respiration for paralyzed patients are used extensively by the medical profession. These machines, commonly called respirators, provide the force necessary to move air in and out of the patient's lungs, permitting necessary gas exchange to occur between the blood and the atmosphere.

Despite the common usage of respirators, relatively little is known concerning respiratory assistance in the newborn infant beyond establishing his first breaths. Lack of widespread success in the maintenance of assisted respiration in newborn infants can be attributed in part to the lack of suitable equipment and technique. Few commercial respirators are available or suitable for maintaining or assisting respiration in the newborn infant. The infant's small size presents special problems in the design of the physical apparatus needed and in the method of providing a connection between infant and machine. Design is further complicated by large variations in the respiratory volumes and pressures required for artificial respiration.

This study is an outgrowth of a previous effort to design a suitable device for clinical use in the treatment of the respiratory distress syndrome (RDS). This disease, also called hyaline membrane disease, occurs in newborn infants, particularly those born prematurely. Evaluation of the initial work indicated that a better physiologic matching of the machine characteristics to the infant was desirable. Minimal consideration had been given to optimizing the respirator's output flow contour so as to reduce its interaction with the patient's circulation. Optimizing the clinical application of the respirator requires information about the expected response of

the distressed infant to assisted respiration. Such information is difficult to obtain experimentally. In short, clinical experience with the respirator indicated the need for study of other important facets of the problem of infant respiratory assistance.

The incidence of RDS is relatively high, with an estimated 25,000 deaths occurring yearly in the United States (1). Various sources show respiratory distress to be a leading cause of death of liveborn infants, with RDS accounting for between 30 and 40 per cent of neonatal deaths. Despite great research activity into the cause and treatment of RDS, the death rate due to RDS has remained relatively constant over the past several decades.

Respiratory distress begins to appear in a newborn infant a few hours after birth. Respiration becomes labored, the normally soft chest wall retracting inward with each inspiration due to increased inspiratory effort. Cyanosis usually develops. The respiration rate increases significantly, indicating inefficient breathing resulting from a disturbance in the mechanical characteristics of the lung. Respiratory rates, normally about 40 per minute, often rise to 100 per minute or more.

The underlying cause of respiratory distress is unknown. Often a smooth hyaline-like membrane covering many of the lung alveoli is seen at autopsy. It is known that such a membrane changes the elastic characteristics of the lung, making it stiff and resistant to expansion in response to the intrathoracic pressure variations which occur during respiratory movements. In addition, the presence of the membrane causes an occlusion or atelactesis of many or most of the alveoli. A substantial increase in pulmonary work, as great as 400 per cent, is required to achieve essentially

normal gas flow in and out of the lungs (2). Decreased effective alveolar membrane surface and adverse changes in pulmonary blood flow cause an elevation in the carbon dioxide content of the blood. This in turn affects the acid-base balance of the blood and effects adverse biochemical changes in the body.

Respiratory distress is a self-limiting disease and spontaneously disappears within two to three days if the infant does not succumb to respiratory muscle exhaustion and induced biochemical changes. Treatment is aimed at keeping the infant alive during the critical phase of the disease process. Attempts at treatment have included aerosol therapy to hasten dissolution of the membrane itself, as yet unsuccessful, and chemical control of the blood pH (3) (4). The addition of buffering agents to the blood is a supportive measure, since the change in pH is secondary to the actual cause of distress. A direct approach is respiratory assistance using a respirator. This latter approach seeks to substantially reduce the infant's respiratory work load and to increase the effective quantity of air available in the lungs for gaseous exchange with the blood.

In 1958, Benson et al. reported the successful management of three cases of RDS by employing intermittent positive pressure respiration using a commercially available respirator (5). Colgan et al. report a similar success using respiratory support by means of manual lung inflation with an anesthesia respirator bag (6). Other successes have been reported. However, all have reported some technical difficulties. In all of these reports the procedure described was designed to reduce the respiratory work load performed by the infant. Delivoria-Papadopoulos and Swyer reported that assisted ventilation could result in complete restoration of normal

blood chemical levels in infants with RDS (7). Stahlman and others conclude that death often results from respiratory neuromuscular failure, and that intervention before irreversible biochemical changes occur may achieve survival (8).

To produce adequate pulmonary ventilation by means of a respirator, it is necessary to distend both lungs and thorax to a volume sufficient to achieve the necessary gas exchange. This can be accomplished by means of intermittent negative pressure applied to the outside of the thorax as is done in a tank respirator (an iron lung), or by means of intermittent positive pressure applied at the nose, mouth, or through an endotracheal tube. In a healthy infant, normal inspiratory volumes (tidal volume) of 10 to 15 ml of air are induced by an intrathoracic pressure change of about 5 to 10 cm H_2O. Technical considerations favor the use of intermittent positive pressure. The use of tank type respirators introduces problems of pistoning of the infant about the neck opening, difficulty in achieving an adequate tank seal around the infant's neck, and the difficulty of achieving respiratory rates of 100 per minute or more. These problems are sufficiently severe so as to preclude the use of tank type respirators with newborn infants, particularly premature infants.

In order to be effective in reducing the infant's respiratory work load, a respirator must either completely assume respiratory activity or else synchronously amplify, or augment, it[1]. Synchronous amplification is preferable because of two reasons. First, augmented respiration allows the subject to control the amount of pulmonary ventilation he receives and thus

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[1]One distinguishes between a respirator and a respiratory augmenter. The patient's thorax is completely passive when using a respirator and is active when using a respiratory augmenter.

regulate the concentration of carbon dioxide in his blood. Secondly, and most important in the treatment of RDS, severly distressed infants cannot be sufficiently overventilated to a degree that they will submit to passive ventilation. Benson et al. found it necessary to use curare (muscle relaxent) in order to diminish natural respiratory efforts to a degree that would permit the distressed infant to tolerate the respiratory rhythm of the respirator (5). On the other hand, efficient respiration occurs in the infant under augmented respiration when air is delivered to the lungs in phase with the infant's natural breathing cycle. Positive pressure applied to the face without regard to the timing of the infant's respiratory attempts tends to drive the air down the esophagus into the stomach. Both Donald and Stahlman have reported observations of a "protest" apnea when respiratory assistance was not directly controlled by the patient (9) (10). It is presumed that in protest apnea the epiglottis closes off the trachea, preventing air from entering the lungs.

If positive pressure is applied synchronously with the infant's breathing effort, air takes its intended route to the lungs, providing the necessary pulmonary ventilation. Air delivered by positive pressure into the lungs expands the lungs (analogously to inflating a balloon) and provides most of the work required in respiration, provided the air flow contour, or waveform, is optimum. Grossly incorrect flow patterns can produce the opposite effect, actually increasing the work of respiration. Contraction of the lungs and thorax by natural tissue elasticity suffices to allow expiration and no mechanical assistance is needed.

Certain undesirable physiologic effects can occur in the patient being treated with a respirator or respiratory augmenter. Both thoracic and pul-

monary circulation are embarrassed by positive pressures generated within the chest. If a respirator or respiratory augmenter is to be maximumally effective, it must be designed to minimize the circulatory disturbance.

An intermittent positive pressure respiratory augmenter for the synchronous amplification of inspiratory effort has been designed, constructed, and clinically evaluated. It has been devised primarily for use in the treatment of RDS in premature infants with its design based on a study of the optimal respiratory augmentation process. The optimal process is considered to be that which requires the minimal expenditure of energy by the patient while producing the least circulatory disturbance and maintaining adequate gaseous exchange between the blood and inhaled gases.

Optimization of the augmentation process extends beyond specification of machine parameters. Shunting of pulmonary blood flow around the active regions of the lung prevents adequate carbon dioxide evolution and oxygen uptake by the blood. To compensate for the adverse blood flow, a greater effective alveolar ventilation must be provided. The greater volume, however, creates a greater circulatory disturbance. Using a functional mathematical model of the cardiopulmonary system, predictions are obtained of the respiratory volume required to maintain or achieve normal levels of carbon dioxide in the blood. Supplementary information pertinent to the clinical use of an augmenter is also derived from the mathematical model. For example, data is obtained from the model to show the time required for a change in lung ventilation to be reflected in the arterial blood carbon dioxide level.

This study, then, considers three major facets of respiratory augmentation. The first is a consideration of the mechanical factors influencing

respiratory assistance. The second is the design of equipment. Analysis of how augmentation affects the overall gas exchange process of the cardiopulmonary system is third. A discussion of the clinical results achieved from the use of the respiratory augmenter is also included.

OPTIMIZATION

Introduction

Difficulty is experienced in the quantitative evaluation of the efficiency of respiratory augmentation because the fragility of the subject, particularly the sick premature infant, limits the ability of the investigator to make physiologic measurements. In addition, certain important parameters of respiratory augmentation are not amenable to study by experimental methods. Therefore, a theoretical study employing a model of the pulmonary pneumatic system is the only practical approach to the problem of maximizing the mechanical effectiveness of artificial respiration.

Two different methods are commonly employed to ventilate a patient's lungs. The first is controlled respiration in which the patient is hyperventilated to a point where the concentration of carbon dioxide in the blood is below the threshold of respiratory stimulation, inhibiting the natural respiratory drive. The patient's pulmonary system is then passive to externally induced gas flow. Controlled respiration is commonly used in the administration of gaseous anesthetics.

The second method, augmented respiration, allows the subject to maintain active control of his respiration. A device external to the patient augments, or aids, the respiratory gas flow by providing an additional driving force. Augmented respiration is used in circumstances where it is desirable to reduce, but impossible to eliminate altogether, the patient's respiratory work load due to the impossibility or undesirability of extinguishing his respiratory drive. Infants critically ill from respiratory distress are most easily ventilated by this latter method.

Controlled respiration is optimal when it provides adequate ventilation

of the lungs without impairing circulatory function. The amount of energy expended by the respirator in providing adequate gas movement is not of importance. Augmented respiration is optimum when it allows the patient to exert the least possible effort in obtaining and regulating adequate ventilation without impairing circulation. The added variable of the patient's contribution to the total respiratory effort in augmented respiration complicates the analysis of this type of externally induced ventilation.

All respirators and respiratory augmenters of the intermittent positive pressure (IPP) type employ some means of restricting the flow of air to the lungs. The air source may be volume limited, or its output flow may be restricted by means of a needle valve or other resistance to give it a constant flow characteristic (a needle valve limits flow by presenting a high resistance to a pressure source, analogous to the infinite resistance of an electrical constant current generator).

Positive pressure respirators suitable for pulmonary ventilation of an infant are of two types. One is designed to deliver a fixed, but adjustable, volume of gas. The other provides an inspiratory phase which is terminated when a preset pressure is reached. The advantage of the pressure cycled type is that no explicit knowledge of the appropriate respiratory volume is required. The pressure achieved and the volume delivered depend on the interaction of the respirator with the patient's pulmonary system. Too high a pressure cutoff may cause rupture of alveoli, while too low a pressure cutoff may prevent adequate volume delivery. The pressure cycled device has an advantage in that it automatically compensates for leaks at the patient-respirator interconnection since any air that escapes does not contribute to pressure buildup. The volume limited type is usually

piston driven to provide a preset volume, and has a pressure limiting device to prevent excessive pressure in the event of a block or constriction in the patient's airway or lungs. The duration of the inspiratory phase is fixed by the flow rate.

Commercial intermittent positive pressure respirators can be found that are neither constant flow or constant pressure generators. The Bennet respirator is an example of a hybrid instrument (11). Its output flow is greatest at the beginning of the inspiratory cycle and falls to zero at the end of the cycle. Its output is intended to coincide roughly with the patient's natural flow pattern. Certain other machines are time cycled. That is, they apply a constant pressure for a fixed time interval. Most respirators available commercially have a flow characteristic dictated by design expediency.

Many respirators can also be used as respiratory augmenters particularly suited for use with older infants and adults. They are designed so that the flow and pressure cutoff may be varied over a wide range. However, little information is available concerning the optimum settings for various pulmonary disorders. These devices are primarily intended to improve unequal ventilation by increasing the depth of inspiration and slowing the respiratory rate. They do not directly relieve the patient's respiratory work load, but rather increase the depth of respiration to promote a more effective respiratory pattern.

Little information is available in the literature describing optimization of augmented respiration. Several reports deal with controlled respiration and the characteristics of respirators designed to provide this type of artificial respiration. Mushin et al. analyze the ventilation to

be expected from the constant flow, pressure cutoff type respirator by using a simplified pulmonary analog consisting of a series RC network (11). They also consider the type of respirator which provides a constant pressure for a fixed time interval. Both methods, of course, assume a passive respiratory system. The resulting analyses are strongly dependent upon the parameters of the particular patient. Whittenburger describes a linearized mathematical treatment of the operation of several types of respirators and derives an equation for the pulmonary ventilation to be expected from each (12).

Intermittent positive pressure ventilation is not without adverse physiological effects. Most important is its effect upon the circulation of blood within the thorax. Since the heart and great vessels are contained in the thorax, they are subject to the same pressures as the lungs. Normal respiration generates a slight negative pressure which aids venous return and cardiac filling. Intermittent positive pressure ventilation produces a positive pressure in the thorax which, according to Maloney and Whittenburger, causes a slight decrease in cardiac output, an increase in peripheral vascular resistance, and an increase of blood volume in the peripheral circulation (13). Avery points out that these effects can be deleterious in the event of shock, or any other condition which interferes with peripheral circulatory adjustments (1). "In the newborn infant with peripheral vascular instability, and in the distressed infant in shock, circulatory embarrassment may be lethal when positive pressure breathing is instituted." Pulmonary blood pressure is normally low. Therefore, little excess positive pressure is required to collapse alveolar capillaries, thus shunting blood away from areas of possible gas exchange. Critical

closing pressures are as small as 5 or 6 mm Hg.

Adverse circulatory effects of positive pressure respiration can be minimized if the mean applied pressure is low. Cournand et al. report that in normal adults if expiration occupied at least 50 per cent of the respiratory cycle and if expiratory mask pressures were close to atmospheric pressure, there were no significant adverse circulatory effects (14). A mean pressure at the face mask of 7 to 10 mm Hg caused cardiac output to fall about 15 per cent. Mushin et al. argue for a minimal mean intrapulmonary pressure by saying that it is unlikely that important additional gaseous exchange occurs once the alveoli have expanded during inspiration (11).

The increase of functional dead space is another important physiological effect of positive pressure respiratory assistance[1]. The increase is proportional to the peak pressure and independent of the time course of pressure buildup (15) (16). The elastic nature of the airway and the cheeks permits expansion under pressure, increasing their contribution to the total dead space in the patient-respirator system. This necessitates a greater volume of air per breath than in unaided inspiration. Respiratory dead space is normally large in distressed infants, the ratio $V_{\text{dead space}}$ to $V_{\text{tidal volume}}$ equaling 0.5 to 0.6. Watson found an increase in this ratio (normally 0.2) of 50 per cent when the peak inspiratory pressure was doubled in paralyzed adults (15). When negative pressures were applied during the expiratory phase to assist expiration, this ratio also doubled, presumably because of the collapse of some alveoli and their subsequent

[1]Dead space is that part of the inhaled volume that does not participate in gaseous exchange. In a respirator, it is that excess volume that does not flow into the infant.

failure to reopen during the next breath. No similar numerical data is available for newborn infants.

It is generally agreed that all devices aiding respiration should be limited with respect to the maximum pressure that they can deliver. A greater maximum "safe" pressure allows a proportional increase in the volume of air that can be introduced into the lungs. A dilemma occurs in treating very sick infants; those who need respiratory assistance the most have the least compliant lungs, necessitating delivery pressures higher than can be sustained without danger of rupture. Excised lungs of infants usually tolerate 35 cm H_2O positive pressure without rupturing, according to Gribetz (17). Avery reports sustaining 50 cm H_2O across excised lungs without rupture (18). It should be noted that the pressures referred to here are intrapulmonary pressures and not the pressures normally produced at the face.

The Pulmonary Analog

Anatomically, the lung is a system of millions of air passages and capillaries contained in an elastic tissue substance. In the human the several subdivisions or lobes are connected together by air passages, the bronchial system, whose air passages combine together to form a common duct, or trachea, to the atmosphere. The lungs share the thoracic cavity with the heart and great blood vessels and are held firmly to the parietal pleural (or wall) surfaces by surface tension. The lungs can be most simply thought of as a balloon or bellows suspended in the thoracic cavity and held in a state of partial inflation by a negative pressure between the balloon and the thorax. Its natural elasticity limits the expansion in the resting state.

A change in thoracic volume produces a corresponding change in the volume of air in the lungs. Contraction of the diaphragm and the external intercostal muscles enlarges the thoracic and lung volumes, while their relaxation and the elasticity of the chest wall and lungs serve to decrease the lung volume.

Figure 1 shows a simple mechanical analog of the thorax and lung compartments. The thorax is represented by a "concertina" type bellows. Suspended inside is another bellows, the inside of which communicates with the atmosphere through the airway. The compliance of the relaxed thorax and lung bellows (defined as $\Delta V/\Delta P = C$, with ΔV and ΔP representing changes in volume and pressure respectively) are noted as C_t and C_l respectively. A constriction in the airway represents laminar and turbulant flow resistance to moving air and is designated R_a. M_a represents the mass of a cylindrical volume whose length is that of the effective length of the airway. M_a is associated with the inertial forces produced by air flow into and out of the lungs.

F represents the effective muscle force applied to the thorax compartment during inspiration. Force F is directed in the opposite direction in the event of an active expiration (normally expiration is passive). The muscle system providing this force is a complex combination of agonist and antagonist (action and reaction) muscles acting through a lever system defying description. Both the muscles providng inspiratory effort and those providing expiratory effort are in some degree of contraction throughout the respiratory cycle.

An electrical analog of the pulmonary system is shown in Figure 2 together with the appropriate values for the analog elements. The electrical

analog model is useful in this study because pulmonary parameters are evaluated as lumped components and are therefore easily described as electrical analogs. All components are assumed to be linear. Deviations from linearity are relatively minor and are discussed below. The assumption of linearity allows the use of the principle of superposition in a mathematical analysis. Certain elements of the analog, such as viscous effects of the thorax tissue, which produces second order effects, are omitted to keep the model as simple as practical while still preserving its usefulness in describing the functional properties of the lung and thorax. Additional components such as the naso-pharyngeal region compliance are included in this model in addition to those shown in Figure 1. Figure 3 shows a variation of the basic analog in which the differences in the values of compliance and airway resistance between different lobes are included. The differences are inconspicuous in a healthy lung, but in an atelectic lung the variation from lobe to lobe can be appreciable. This effect leads to differences in the time constant of filling (R_1C_1) so that a short inspiratory interval leads to unequal filling of the lobes and a short expiratory interval causes unequal emptying. Time constant variations between lobes can be as great as 200 per cent.

Data for the evaluation of the analog parameters were obtained by measuring 6 healthy (0 to 3 days old) and 3 distressed newborn infants (one was preterminal). Some of the parameters have been previously reported in the literature, but those reported were obtained during spontaneous respiration, rather than when respiration was augmented (19). Lung compliance, C_1, and airway resistance, R_a, were measured by the method of Cook et al. (20). A water filled plastic feeding tube was inserted into the esophagus

and the pressures were measured. These readings were considered to accurately represent intrathoracic pressures. Air flow was measured simultaneously by means of a pneumotachograph. The flow record was manually integrated at selected points to provide simultaneous volume measurement. Pressure in excess of that needed to fill a linear lung volume was attributed to the airway resistance, R_a, pressure drop. Viscous resistance of the lung tissue is necessarily included into R_a by this method. C_a, the compliance of the alveolar air is computed from the ideal gas law, PV = constant.

$$C_a = \frac{\Delta V}{\Delta P} = \frac{1000}{990} = 1.0 \text{ ml per cm } H_2O \text{ per liter} \qquad (2\text{-}1)$$

C_t, the thorax compliance, cannot be measured during spontaneous respiration because the contribution of the respiratory muscles to the total pleural pressure, P_{pl}, cannot be directly determined. C_t is defined as

$$C_t = \frac{\Delta V_{thorax}}{\Delta P_{thorax}} = \frac{V_t}{\Delta P_{pl \text{ no flow}}} \qquad (2\text{-}2)$$

where

V_t = tidal volume

$P_{pl \text{ no flow}}$ = pressure difference between beginning and end of inspiration

In fact, C_t has no meaning except when the state of the thorax muscle tone is specified. These muscles, the diaphragm and intercostals, are normally in a state of partial contraction in their role of controlling posture (21). Attempts have been made at evaluating C_t by having subjects voluntarily relax. These measurements, of course, conflict with others taken in totally paralyzed subjects.

To be useful in the evaluation of assisted respiration, the value of

C_t should be determined during active respiration. C_t then represents the elasticity of the chest muscles, with their normal degree of tone, and associated connective tissue. In the mechanical analog C_t may be thought of as the elasticity of a spring in series with the force F, which pulls on the bellows representing the chest. C_t is not the elasticity of the bellows itself. The assumption is made that the muscle source is of low impedance, that is to say, external forces can do little to influence its pattern of output. C_t, as shown in the electrical analog, is the total internal impedance of the muscle source.

C_t is estimated in the active infant by noting the change in the pressure, P_{pl}, created by inspiratory volume which is generated by a constant flow augmenter connected to the infant. Values of C_t typically found are in the range of 4 to 5 ml per cm H_2O pressure. As a check on this method, C_t can be evaluated by an alternate procedure. C_l, the lung compliance, is estimated as described above during spontaneous breathing. Lung compliance is not affected by muscle tone and is assumed constant. Then

$$C_t = \frac{V_{insp}}{P_{m_{peak}} - V_{insp}/Cl} \qquad (2\text{-}3)$$

where

V_{insp} = volume of air delivered by augmenter

$P_{m_{peak}}$ = peak pressure at mouth during augmenter respiration

At the end of inspiration, flow ceases and the pressure drop across R_a, the airway resistance, disappears. The end point pressure corresponds to peak pressure. The values obtained by both methods are in close agreement. Data published on the measurement of C_t in apneic, paralyzed infants 5 to 75 days of age is considerably higher, as might be expected (22).

L_a, the analog of the air mass being accelerated in the airway, is estimated to be equivalent to a mass of air 10 cm long and 0.6 cm^2 cross section. The equivalent of the air mass converted to appropriate units is 0.013 cm H_2O per liter per sec^2. L_t, the thorax mass equivalent, is negligible in comparison to the elasticity of the thorax and is ignored in subsequent use of the analog model (23). Since the infant and respirator must be considered as an integrated system, those properties of the respirator known to be invariant with respect to design are included in the model. The compliance of the tubing connecting the augmenter to the infant together with the air contained therein, termed C_r, is 0.4 ml per cm H_2O, assuming a total tubing length of 10 feet of ½ inch inside diameter Tygon tubing.

Figure 4A shows the exponential shape of P_{pl} during spontaneous respiration. Although P_{pl} is generated by the muscle source and subsequently modified by the action of C_t, the muscle source itself is assumed to have an exponential output waveshape. This assumption deviates slightly from the actual situation but creates only a small error in the analysis. Figure 4B shows the same subject's pressure in the upper airway immediately after the airway is sealed from the atmosphere. It represents approximately the pressure created directly by the muscle source. This action is analogous in an electrical circuit to disconnecting the load to obtain the equivalent voltage source of a Thevenin equivalent circuit. The analog model to be used subsequently will contain a perfect voltage generator to represent the respiratory muscle activity.

Optimization Criteria

Specifically, a respiratory augmenter should expand the chest and lungs of a patient in such a way as to minimize the patient's respiratory muscle work with minimum circulatory embarrassment. The ideal augmenter should thus:

1. Produce a positive pleural pressure, P_{pl}, throughout the inspiratory phase.
2. Create minimum resistance to expiratory air flow.
3. Produce a minimum mean pressure in the lungs, P_l, and thorax, P_{pl}, during the inspiratory phase.
4. Produce an air flow sufficient to stimulate adaptation, but small enough to minimize facial mask pressure.

The first requirement assures that the augmenter will always aid the patient's respiratory effort. Positive pressure in the pleural cavity indicates that the augmenter output is working against the musculature. Negative pressure indicates that the infant is trying to inspire against the action of the respirator; with a limited flow device this attempt is futile.

Minimum resistance to expiratory flow assures that the patient is doing the least work necessary for expiration. The energy required to expire passively is stored in the elastic tissues during inspiration. In addition, minimal expiratory resistance promotes quick emptying of the lungs, permitting lower mean intrathoracic pressure. Since the lungs and thorax are effectively in series with respect to air flow, the conditions of minimal P_l and P_{pl} are simultaneously satisfied. An analogous situation is that of two capacitors in series in an electrical circuit. The

voltage across one is always proportional to the voltage across the other.

Experimental observations of infants and laboratory animals indicate the occurrence of adaptation to the inspiratory force of the respiratory augmenter. Presumably the adaptation is mediated through the Hering-Brewer reflex[1]. Initially, augmentation does not affect the subject's inspiratory effort, as evidenced by the intrathoracic pressure shown in Figure 5A. The augmenter, a constant flow device in this case, is delivering slightly more than normal tidal volume. Note that the augmenter output is superimposed upon the normal exponential P_{pl} waveform. Figure 5B shows a change in P_{pl} when the augmenter is delivering twice the normal tidal volume. Notice the reduction in the negative amplitude, indicating the animal's adaptation to the device, i.e., the reduction of his respiratory effort. Hyperventilation is not the cause of the reduction in the respiratory effort in this case. In Figure 5C, P_{pl} is shown to be normal immediately after the augmenter is disconnected. Carbon dioxide concentrations in the blood cannot change instantaneously to effect such a change in respiratory effort. Simultaneous measurements of blood pCO_2 before, during, and after augmentation as shown in Figures 5A, B, and C indicate no significant change.

Figure 6 also documents the adaptation effect in an experimental animal. Notice a significant reduction in inspiratory duration when the tidal volume is increased to 24 ml, twice the normal tidal volume for this animal. (The ripple artifact present in many of the P_{pl} tracings is due to heart beat changing the volume of the thoracic cavity.) Cross et al. document the adaptation effect in newborn infants by noting that a threshold of

[1]The Hering-Brewer reflex causes slowing of inspiration or apnea upon forced inflation of the chest.

forced inspiratory volume exists, above which a transient apnea occurs (24). They state the transient apnea is particularly pronounced immediately after birth, decreasing somewhat with age. Clinical observations of newborn infants, made as a part of this study, indicate a rapid adaptation to an augmenter. A mildly distressed infant's respiratory pattern will change from labored inspiration to one compatible with relaxed sleep. On the basis of the observations discussed, the assumption is made that twice normal tidal volume is sufficient to induce adaptation.

Once the infant has sufficiently adapted, optimum agumentation is that which produces adequate ventilation while minimizing circulatory disturbance. In very sick infants the blood pCO_2 is so elevated and the respiratory drive so intense that adaptation is slight regardless of the volume inspired. As respiratory distress becomes more severe and then recedes the infant goes through a period of non-adaptation of varying intensity. Thus, the augmenter characteristics must be the best compromise for both conditions.

Air flow must be great enough to prevent a negative P_{pl}, but low enough to prevent development of excessive pressure at the mask. Increasing flow increases the pressure drop across the airway resistance. Flow ceases to be laminar at a velocity of about 150 ml per sec, assuming a uniform cylindrical airway of 0.6 cm diameter. High mask pressure increases leakage from around the mask and also forces air down the esophagus, distending the stomach and small intestine.

Non-linearity

Linearity is assumed for each of the components in the respiratory

analog. Pressure-volume curves of both the lungs and thorax are found to be "S" shaped in adults. It was therefore deemed necessary to investigate the linearity of these compliant components in infants to assure that the assumption of linearity was valid.

Figure 7 shows the pressure-volume relationship for the lungs and thorax for two sick infants as well as for two healthy ones. Note that the diseased lungs show a more linear relationship than the healthy ones. Figure 8 indicates the degree of non-linearity of total compliance (lungs and thorax combined) as a function of the rate of filling. Unequal time constants of two or more lung subunits can produce the time dependent non-linearity. Presumably this effect is small enough to be ignored since it is of smaller magnitude than subject to subject variations.

Data for Figures 7 and 8 were obtained while the subject was being ventilated by a constant flow augmenter. The augmenter volume output was varied to produce data on various degrees of filling. The difference between the nasal pressures observed at the beginning and conclusion of inspiratory flow was considered to be the actual change of pressure occurring across the series combination of the lungs and thorax. This method adds air compression and upper airway compliance to the value of compliance encountered. Upper airway compliance cannot be measured directly in the uncooperative subject. Measurement of the upper airway compliance in an adult showed that the compliance is linear within the limitation of a rather large possible experimental error[1].

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[1]The cooperating subject closed off his trachea by straining as during defecation. Simultaneous pressure and volume measurements were made using a stiff face mask connected to the subject.

Airway resistance is inherently non-linear because of two effects. First, as air velocity increases, laminar flow turns to turbulent flow. The pressure drop across a resistance is proportional to the second power of flow when flow is turbulent. Secondly, the airway is compliant, expanding as flow increases, tending to counteract the first effect. Fortunately, R_a does not enter directly into the analysis of devices delivering flow from a limited flow source. R_a is sufficiently linear to permit its use as a constant in the analysis of a constant flow pressure source.

Optimization

An augmenter can be designed to produce any of an infinite variety of possible inspiratory flow waveforms. In the analysis to follow five waveforms, each representing a distinct type of output, will be considered. Each type represents the output possible from a particular design philosophy. The five flow waveforms are:

1. Constant flow
2. Exponential flow (decaying exponential)
3. Ramp flow (increasing with time)
4. Sine waveform flow
5. Reverse ramp flow (decreasing with time)

Most other waveforms can be considered to be simple deviations of the five considered.

A series circuit consisting of R_a, C_1, and C_t has a response, in terms of the voltages across C_1 and C_t, equivalent to that of the analog model shown in Figure 3. The deviations in response between the two remain

within a few per cent, as verified experimentally. Therefore, in the following analysis the simple R_a-C_l-C_t series circuit analog will be used.

Consider first the case of the respiratory muscles being inactive, as in apnea or adaptation to the augmenter. The mean pressure across C_t, analogous to the average voltage across C_t in the electrical circuit, is given by

$$P_{mean} = \frac{1}{C_t T_o} \int_o^{T_o} \int_o^t f(t)dt\ dt \qquad (2\text{-}4)$$

where

T_o, the inspiratory duration is defined by

$V_t = \int_o^{T_o} f(t)dt$, the tidal volume

and

$f(t)$ = air flow, in ml per sec

From Figure 9 it can be seen intuitively that P_{mean} is a minimum when $f(t) = at^n$, when n approaches infinity. The flow, f(t), is then an impulse function. This function is not physically realizable and so need not be considered further. Computing the mean pressure during inspiration as a function of V_t, for a given T_o, for the five types of flow considered, one obtains the following:

1. When f(t) is a constant flow, $f(t) = a$,

$$P_{mean} = \frac{1}{C_t T_o} \int_o^{T_o} \int_o^t a\ dt\ dt = \frac{a\ T_o}{2\ C_t}, \qquad (2\text{-}5)$$

and

$$V_t = \int_o^{T_o} a\,dt = a\ T_o \qquad (2\text{-}6)$$

so

$$P_{mean} = \frac{.5\ V_t}{C_t} \tag{2-7}$$

2. When f(t) is a ramp, f(t) = at,

$$P_{mean} = \frac{1}{C_t T_o} \int_o^{T_o} \int_o^t at\ dt\ dt = \frac{a\ T_o^2}{6\ C_t}\ , \tag{2-8}$$

and

$$V_t = \int_o^{T_o} atdt = \frac{a\ T_o^2}{2} \tag{2-9}$$

so

$$P_{mean} = \frac{.33\ V_t}{C_t} \tag{2-10}$$

3. When f(t) is exponential, stemming from a constant pressure P_o applied to the face, $f(t) = (P_o/R_a)e^{-t/R_aC}$,

$$P_{mean} = \frac{1}{C_t T_o} \int_o^{T_o} \int_o^t \frac{P_o}{R_a} e^{-t/R_aC}\ dt\ dt$$

$$= \frac{P_o C}{C_t T_o} \left[T_o - R_a C\ (1 - e^{-T_o/R_aC})\right]\ , \tag{2-11}$$

and

$$V_t = \int_o^{T_o} \frac{P_o}{R} e^{-t/R_aC}\ dt = P_o C\ (1 - e^{-T_o/R_aC}) \tag{2-12}$$

so

$$P_{mean} = \frac{V_t}{C_t\ (1 - e^{-T_o/R_aC})} - \frac{V_t R_a C}{C_t T_o} \tag{2-13}$$

In this case R_a, the airway resistance, and C, the total compliance $(C_t C_1/C_t+C_1)$, influence the mean pressure by determining the filling time. Assuming typical values of $R_a = 0.03$, $C = 2.0$, and $T_o = 0.5$,

$$P_{mean} = \frac{.9\ V_t}{C_t} \quad \text{approximately} \tag{2-14}$$

The lower bound of $P_{mean} = .5\ V_t/C_t$ occurs when RC approaches infinity, the exponential degenerating into a ramp.

4. When f(t) is a sine waveform, $f(t) = a\ (1 - \cos \frac{\pi}{T_o} t)$,

$$P_{mean} = \frac{1}{C_t T_o} \int_o^{T_o} \int_o^t a\ (1 - \cos \frac{\pi}{T_o} t)\ dt\ dt$$

$$= \frac{a\ T_o}{2\ C_t} - \frac{2a\ T_o}{\pi^2\ C_t}, \tag{2-15}$$

and

$$V_t = \int_o^{T_o} a\ (1 - \cos \frac{\pi}{T_o} t)\ dt = a\ T_o \tag{2-16}$$

so

$$P_{mean} = \frac{.31\ V_t}{C_t} \tag{2-17}$$

5. When f(t) is a reverse ramp, $f(t) = a\ (1 - t/T_o)$,

$$P_{mean} = \frac{1}{C_t T_o} \int_o^{T_o} \int_o^t a\ (1 - t/T_o)\ dt\ dt = \frac{a\ T_o}{3\ C_t} \tag{2-18}$$

and

$$V_t = \int_o^{T_o} a\ (1 - t/T_o)\ dt = \frac{a\ T_o}{2} \tag{2-19}$$

so

$$P_{mean} = \frac{.66\ V_t}{C_t} \tag{2-20}$$

Figure 10 shows the volumes produced by the five types of flows as a function of time. P_{mean} is proportional to the area under each curve, since pleural pressure is equal to the increase in thoracic volume divided

by C_t at any instant of time. Subject to the constraint of minimal circulatory disturbance, a constant pressure device producing an exponential flow is shown to be the poorest and a device producing a sine waveform flow the best. These results can be extrapolated to show that a parabolic shaped flow pattern is slightly better than ramp flow, etc.

Next, consider the situation where the respiratory muscles are active, that is, adaptation has not occurred. It is assumed that the pulmonary system is linear, and further, that the muscles could be represented as a perfect pressure source. Regardless of the volume forced into the thoracic cavity, the pressure waveshape and amplitude remain constant. Only because of these assumptions, the principle of superposition is valid. P_{pl}, then, is the algebraic sum of the pressure produced across C_t by the respiratory augmenter and that produced by the respiratory muscles.

Mean pressures computed for no respiratory muscle activity also apply when the muscles are active. Spontaneous inspiratory attempts always produce negative pressures in the thorax. Then, because the principle of superposition is valid,

$$P_{pl}(\text{active}) = P_{pl}(\text{inactive}) - P_{pl}(\text{muscle source}) \tag{2-21}$$

or

$$P_{pl\ \text{mean}}(\text{active}) = P_{pl\ \text{mean}}(\text{inactive}) - \frac{1}{T_o}\int_o^{T_o} P_{pl}(\text{musc})\, dt \tag{2-22}$$

where

$$\int_o^{T_o} P_{pl}(\text{musc})\, dt = \text{a constant, the mean } P_{pl} \text{ from muscle activity.}$$

Thus choosing a f(t) based on no respiratory muscle activity is also valid for the situation where the respiratory muscles are active.

A positive pressure P_{pl} in the thorax during inspiration is contributing to the inspiratory act by providing some or all of the energy necessary to inspire. In addition, the positive pressure stimulates the pulmonary stretch receptors to inhibit further inspiratory activity for that particular breath. Figure 10 shows a comparison of net pleural pressures expected from each of the five flow waveforms. To facilitate comparison, each flow waveform is of the correct amplitude to produce a final pressure of $P_{pl} = 2V_t/C_t$ for an inspiratory duration of T_o. The shaded areas show the duration of negative pressure for each flow waveform. During the periods of negative pressure the patient is working against the action of the augmenter. P_{pl} generated by each of the flow waveforms can be expressed as,

$$P_{pl}(t) = \int_o^t f(t)dt - P_{pl}(t)\text{spontaneous} \qquad (2\text{-}23)$$

The pressure created by the action of the respiratory muscles, $P_{pl\ \text{spontaneous}}$ is represented by the equation 2-24.

$$P_{pl} = -P_o\ (1 - e^{-at}) \qquad (2\text{-}24)$$

P_o and a are experimentally determined parameters. Examination of P_{pl} recordings produced during spontaneous inspiration in six subjects (two with respiratory distress) shows that P_{pl} terminates at about 90 per cent (+ 5 per cent, - 8 per cent) of its ultimate value if a simple exponential curve fit is assumed. This appears to be true in newborn infants irrespective of the range of T_o encountered. Thus a representative model of P_{pl} is a simple exponential curve with duration of two time constants (87 per cent of ultimate value).

Figure 11 shows graphically how the curves of P_{pl} shown in Figure 10

are obtained. This particular representation is for constant flow. Note that regions of negative pressure occur when the flow rate is too high or too low. In order to deliver two tidal volumes in the normal inspiratory interval T_o, the optimal flow rate for constant flow waveshape can be derived as follows:

subject's maximal flow = initial flow (spontaneous respiration)

$$f(t) = b_1 e^{-t/b_2} \tag{2-25}$$

and

$$V_t = b_1 b_2 (1 - e^{-t/b_2}) \tag{2-26}$$

where b_1 and b_2 are parameters of the pulmonary system

subject breathes V_t in two time constants, or $T_o = 2b_2$

then

$$f_{initial} = \frac{2\ V_t}{.87\ T_o} = \frac{2.3\ V_t}{T_o} \tag{2-27}$$

optimum augmenter flow = subject's initial flow

$$a = \frac{2.3\ V_t}{T_o} \tag{2-28}$$

where a = augmenter flow, in ml per sec

average T_o for sick infants = .35 sec and V_t = 12 ml

therefore

a = 78 ml per sec for distressed infants

average T_o for healthy infants = 0.6 sec and V_t = 15 ml

therefore

a = 57 ml per sec for healthy infants

These values form the lower limits for the augmenter flow output because of the assumption that the augmenter inspiratory interval, T_o, is equal to the infant's inspiratory interval. For the conditions assumed above the infant

would receive 2.3 V_t rather than the 2.0 V_t assumed necessary. In the case of the reverse ramp and exponential flows, the initial flow is always greater than that demanded by the infant.

Constant flow and reverse ramp flow waveforms are acceptable on the basis of the mean pressures that they produce as well as their initial flow rates. Ramp flow and sine waveform flow have insufficient initial flow rates. The exponential flow waveform has an ideal initial flow rate but produces excessive mean pressure. Constant flow is therefore the best choice because of its low mean pressure generation. In addition, it has the advantage in that the initial flow is one-half that of the reverse ramp and thus the airway pressure drop is less than one-half that caused by the reverse ramp flow (turbulent flow pressure drop is proportional to $flow^2$). This means lower face mask pressures and consequently less air is lost to leakage and to abdominal distention. It is therefore concluded that an optimal augmenter output characteristic should be constant flow of approximately 75 ml per sec.

AUGMENTER

Cook et al. in a recent review of current treatment of respiratory distress say that "...only some form of assisted respiration can aid in carbon dioxide removal by actually increasing the alveolar ventilation and supplementing the infant's own strenuous respiratory efforts. Practical devices, whether the positive pressure or tank type, are needed to treat this disease. It is apparent at present that a successful device depends upon interested and highly skilled personnel. The apparatus seems too necessarily complex to allow general use. If a device, however complicated, is marketed, those fetuses with the greatest chance of developing respiratory distress may be recognized before delivery and cared for in appropriate centers" (19). One objective of this study was the development of a practical respiratory augmenter which would be successful from a treatment standpoint and at the same time be simple enough to be used by medical personnel not highly skilled in the use of respiratory augmenters.

Previous attempts at developing a satisfactory device to synchronously augment respiration have enjoyed only limited success. Donald devised a machine which utilized the infant's inspiratory efforts to trigger an input of air from a high pressure source through a reduction valve (25). Technical difficulties included the mask, which by description must have had too much dead space, insufficient positive pressure, and lack of a volume limiting control. His results did indicate temporary benefit. Melville and Hodder developed an augmenter using negative pressure external to the chest, a tank type machine, to expand the chest and thus move air into the lungs (26). The enclosure surrounding the body was necessarily large and air movements into and out of the enclosure were slow, especially with

respect to the breathing rate of premature infants. Again, dead space was not controlled. These and other attempts to develop an infant respirator were not satisfactory because of poor speed and phase response, together with too much dead space in the air passages[1].

Design Requirements

A respiratory augmenter must provide the following functions to be successful:

1. Accurately sense the beginning of the inspiratory cycle.
2. Meter and deliver a predetermined volume of air or gas mixture to the subject, preferably at a constant flow of 75 ml per sec.
3. Provide a satisfactory machine-patient connection which can be left in place for periods of 48 to 72 hours.
4. Provide adequate supervisory control so that an alarm is given if the infant becomes apneic.
5. Provide controlled respiration in the event of failure of natural inspiratory attempts.

Inspiratory effort can be sensed by any of several possible methods. These include negative intranasal air pressure, diaphragm movements, and electromyographic skin potentials. The simplest method appears to be nasal pressure detection since special devices need not be attached directly to the infant. Donald, and Melville and Hodder have shown this method to be practical (25) (26).

Inspiration must be sensed within a few milliseconds after its beginning in order that the augmenter deliver gas in phase with inspiration.

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[1]The Emerson Infant Respirator, a patient cycled tank type device is available in the United States. There have been no reports of its effectiveness.

Inherent delays in the mechanical linkages of the augmenter dictate detection as soon as possible. This is accomplished by detecting a negative pressure at the nose. If inspiration is to be sensed within 10 milliseconds of initiation, a differential pressure (with respect to the atmosphere) threshold of less than 2 mm H_2O must be determined using a sensitive pressure transducer. Sensitivity of this magnitude requires that the pneumatic circuitry be noncompliant to prevent attenuation of the already small negative pressure signal at the device.

Metering of air can be accomplished by means of a piston driven to deliver a predetermined volume. Volumes of 10 to 40 ml of air or a gas mixture delivered at a respiratory frequency of up to 120 breaths per minute are required. The augmenter's output pressure must be limited to a maximum of 40 cm H_2O to prevent damage to the lung. The approximate maximum pressure normally encountered is:

$$P_{max} = \frac{V_t}{C_{total}} = \frac{(2.3)(12)}{2} = 14 \text{ cm } H_2O \qquad (3\text{-}1)$$

The ability to precisely control the oxygen percentage in the inhaled gas is important. In cases where oxygenation of the patient appears adequate, current medical practice limits the oxygen concentration to 40 per cent to prevent retrolental fibroplasia (vascular growths in the eye). In the event the subject is not adequately oxygenated, as determined by blood gas measurement, higher concentrations may be used. Water vapor is usually added to the inspired gas to prevent excessive fluid loss through respiration.

Since positive pressure breathing is feasible for use on infants, the problem of how to apply pressure to the upper airway becomes an important

one. Previously, face masks have been unsatisfactory for extended use because of the difficulty of constructing them with little dead space, as well as the difficulty of obtaining a tight seal to the face. Masks suitable for infant use, according to Avery, have at least 5 cc of dead space, almost one-half of the infant's normal tidal volume (1). Endotracheal tubes and tracheotomy connections can be used if considerable caution is observed. They are, however, quite inconvenient and because they bypass the subject's nasal area, where humidification normally occurs, the augmenter output must be saturated with water vapor.

Constant attention by highly trained medical personnel may be impractical in cases where a device such as this would be used in a small community hospital. Therefore, the device should be failsafe, giving notice to attending personnel of failure of either machine or infant. It should initiate controlled respiration if the infant becomes apneic. A period of forced ventilation will often be sufficient to stimulate the infant to resume breathing. (Forced ventilation substitutes for tactile stimulation, such as turning the infant or slapping its feet to promote the resumption of regular respiration.) A common respiratory pattern in premature infants is one of periodic breathing, appearing as brief periods of apnea of 5 to 10 seconds duration in a sequence of breaths. It is common enough to be considered normal in these infants. Thus an alarm and forced cycling system must have an inherent delay of approximately 15 seconds to prevent false indication of failure.

In summary the augmenter should have the following properties:

1. Sense inspiration within 10 milliseconds by detecting negative pressure at the nose.

2. Have a face mask and pneumatic system with essentially no dead space.
3. Capable of delivering by intermittent positive pressure 10 to 40 ml of gas mixture at a constant flow rate of 75 ml per second and a repetitive rate of 120 per minute.
4. Capable of detecting the cessation of patient inspiratory attempts for a period of 15 seconds or greater, then providing a preset forced rate of respiration, while indicating cessation by a suitable alarm able to detect return of inspiratory attempts.
5. Be failsafe in operation as well as simple to operate by personnel not highly skilled in its operation.

System Description

For descriptive purposes, the augmenter can be organized into two major systems; one, the electrical system, and the other, the mechanical-pneumatic system. The electrical system provides the control function while the mechanical system performs the actual respiratory assistance. Figure 12 shows the complete respiratory augmenter.

The mechanical system provides the sensing, metering, and delivery functions of the respirator. Included are the differential pressure transducer, the metering compressor, the valve, and the face mask with its associated connecting tubing. This system is shown in block diagram form in Figure 13. Note the two independent air paths, one for inspiration and the other for expiration. Separate paths prevent mixing and eliminate dead space. The valve controls the on-off cycle of each path. Normally, when not actuated, the valve is in the position shown.

An operating cycle starts when a negative pressure (with respect to

the atmosphere) is developed in the face mask by the infant's inspiratory attempt. A rubber one-way valve (Serria Valve) prevents outside air from entering through the exhaust port during this phase. The transducer is actuated by the pressure differential, which in turn triggers the electronic system. Immediately the electronic system actuates the metering compressor and valve.

The valve rotates in such a way as to close the exhaust path and the gas inlet to the compressor as well as exposing the delivery path to the compressor. Air is then forced into the lungs under pressure generated by the travel of the compressor piston. At the completion of the gas delivery, the valve closes the delivery path and opens the exhaust path. Elastic contraction of the subject's thorax and lungs forces the respired air out. Positive pressure relative to the atmosphere opens the one-way valve, allowing the respired air to be exhausted to the atmosphere. A path is also opened by the valve action from the air or air-oxygen supply to the compressor, allowing the compressor to be recharged. The breathing cycle is ended and the device is again ready to detect the infant's next inspiratory effort.

The electrical, or electronic, system provides the sensing and timing functions for the compressor. It also provides supervisory and control functions as well as supplying power for the mechanical components. Figure 14 illustrates the organization of the component blocks. Design for the most part is based on switching type circuitry. All timing functions in the electronic system occur as a result of a pulse being received.

An output from the nasal pressure transducer, in the form of a pulse (whose wave shape approximates the pressure at the nose), is amplified and

coupled to a Schmitt Trigger stage. The trigger circuit detects the point at which the nasal pressure has exceeded a certain threshold. An output from the Schmitt Trigger actuates the forward bistable switch, which in turn actuates the forward clutch in the mechanical system. Completion of the metering action reverses the forward bistable switch state, deactivating its associated clutch and actuating the reverse bistable switch. This in turn actuates the reverse clutch, returning the valve and metering compressor piston to their initial positions. The reverse bistable switch is then reset to its initial state.

Supervisory equipment includes a respiration rate meter and a rate detector-alarm, which alerts attending personnel should natural respiration cease. An automatic timing sequence determines if the infant's failure to inspire is temporary. If the infant's respiratory rate drops below 50 per cent of the value preset by a front panel control, the timer circuit is actuated. Rates from 30 to 120 breaths per second are selectable. If at the completion of a 15 second interval, the rate has not returned to 60 per cent of its initial value, the augmenter begins ventilating the infant at a preset rate, the same rate that the detector circuit is set for. After 10 seconds, the augmenter again pauses 15 seconds to ascertain if the infant has begun respiration of its own accord. If at any time during the 10 second forced rate interval the infant regains 60 per cent of his former rate, the augmenter immediately switches back to the normal assisted respiration mode. An audible tone alarm sounds whenever the time circuit is active.

The augmenter is capable of the following operational modes:

1. Normal; assisted respiration, patient controlled.
2. Test; one cycle for each operation of the test switch.

3. Automatic; normal mode with detection of breathing failure and subsequent forced respiration.

4. Manual; adjustable rate forced breathing.

These modes are selected by means of front panel switches. Provision is made for connecting the rate meter to either the forward bistable switch, to read augmenter rate, or the Schmitt Trigger circuit, to read patient rate, if the two should differ. (This occurs during automatic mode operation when the infant has become apneic.) The alarm is failsafe so that if for any reason the augmenter is prevented from cycling, the alarm will sound. The tone generator providing the alarm is energized by a small rechargeable battery.

Test, or single cycle, operation is achieved by simulating a transducer output pulse at the input to the transducer amplifier. Single cycle operation is desirable when initially determining respiratory volume and as a method for priming the breathing circuit when an oxygen enriched mixture is used.

Details of Operation

Figure 15 shows the construction of the pneumatic system and identifies its various parts. Output volume is determined by the length of the piston stroke in the metering compressor. Rotational motion from a small induction motor is coupled to a rack and pinion gear through two clutches[1]. Activation of the forward clutch, by the forward bistable switch, causes the rack gear to push the piston inward, forcing out the desired volume at a constant rate. In a similar manner, the reverse clutch returns the piston

[1]Vibrac Corporation, Model MPC 11, Magnetic Particle Clutch.

to its original position. A tight piston seal is maintained by a diaphragm between piston and cylinder[1]. Piston stroke is limited on forward travel by a forward limit switch and on reverse travel by a reverse limit switch. The latter's position is adjustable by means of a front panel control, providing a method of varying the piston displacement from 0 to 40 ml. The forward and reverse limit switches reset the forward and reverse bistable switches respectively, disconnecting current to the appropriate magnetic clutch.

Initial rotation of the forward clutch output shaft rotates only the valve core. After a fraction of a revolution of the clutch shaft, the valve core has been rotated the necessary 90° and a friction clutch interposed between the two allows the forward clutch to rotate further without advancing the valve core. An angular lost motion coupling from the forward clutch to the rack prevents the piston from moving until sufficient time has elapsed (25 milliseconds) for the valve to be properly positioned. A solenoid latch prevents inadvertent movement of the valve core while adjusting the piston displacement. Decreasing the volume setting when the piston is idle would move the piston inward, advancing the valve core, if the latch was nonexistent. The latch solenoid is energized during the initial part of the forward cycle to permit free motion of the valve core. The valve core is repositioned to its original position upon completion of the piston's forward motion. Again the lost motion coupling prevents piston return until the valve core has returned to its initial position.

Nasal pressure is converted into an electrical signal by a Statham PM

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[1] Bellofram rolling rubber diaphragm.

97 strain gauge low pressure transducer (working range 0 to .05 psi). The strain gauge elements are connected in a bridge configuration. To eliminate stability problems inherent in a DC amplifier, the bridge output is amplified by a low frequency AC amplifier with a bandpass of 5 to 500 cps. Three stages of amplification are needed to produce a signal increase in excess of 1000. The amplified output is coupled to a Schmitt Trigger circuit which determines when a certain pressure threshold has been exceeded. A sensitivity control on the front panel adjusts the trigger threshold.

An output from the Schmitt Trigger is connected to the forward bistable switch through two AND gates. The first gate is controlled by the automatic mode timer. When an output from it and the trigger are coincident, an output is generated which is coupled to the second gate. If the reverse bistable is not energized, the output pulse from the first gate is allowed to pass through the second gate and trigger the forward bistable. An inhibiting function is necessary during the piston reset cycle to prevent pneumatic transients, arising from valve action, from prematurely actuating the forward bistable switch. An additional gate circuit connects the manual rate oscillator to the forward bistable switch in the absence of an output from the automatic mode timer. This connection allows the bistable switch to be driven by an oscillator at a rate controlled from a front panel control. Another gating circuit prevents both forward and reverse bistable switches from being operative coincidentally, which might result when the augmenter is initially turned on.

A second output from the Schmitt Trigger goes to a rate meter and rate detector. A monostable multivibrator, acting as a current source, charges a parallel RC circuit. The voltage across the capacitor is proportional to

the "on" time of the multivibrator, which in turn is proportional to the number of pulses received from the trigger. The capacitor voltage operates a front panel rate meter and also a relay connected through a DC amplifier. Contacts on the relay activate the automatic mode timer when insufficient voltage appears across the capacitor, providing the necessary detection of insufficient respiratory rate. Temperature compensation is provided in this circuit to insure stability under adverse ambient temperatures.

Power is provided by a regulated voltage supply to operate the clutches and electronics. Three voltages are used, -12 volts for the pressure transducer, -27 volts for the electronics, and -40 volts for the clutches. The clutches are rated at 28 volts, but are purposely overvoltaged to reduce engagement time to 3 to 4 milliseconds.

Transistor circuitry is used throughout and is mounted on three plug-in phenolic cards to simplify maintenance and modification. The entire unit weighs less than 25 lbs, has dimensions of approximately 6 x 13 x 16 inches, and is easily portable. The complete unit is shown in Figure 12.

Clinical Operation

As stated above, some sort of connection must be provided between machine and patient. A close fitting nasal mask of an acrylic shell, with a dead space of less than one half ml, has been developed for use with this augmenter (27). The shell is filled with a soft plastic material which remains permanently compliant, and is then fitted by pressing it to the infant's nose for a few seconds and allowed to set[1]. It is then sealed to the infant's nose with surgical (colostomy bag) cement. Newborn infants

[1]Any soft dental lining material may be used. Bosworth "Tru-Soft" dental lining is excellent for this purpose.

are mandatory nasal breathers. This fact eliminates the need for a connection to the mouth, leaving it accessible in case of vomiting, etc. The entire operation of preparing a mask takes less than 10 minutes.

Gases to be inspired are mixed and humidified in a vented plastic container external to the augmenter. Precise control of the oxygen concentration is obtained by using a calibrated venturi valve between the high pressure oxygen supply and the mixing chamber. A shallow water level is maintained in the chamber to assist in humidification since oxygen from the hospital central source is dry. It is not necessary to humidify the gas mixture to saturation since the inhaled gases pass through the nares and nasopharynx where additional humidification is accomplished.

An occasional deep breath, or sigh, is helpful in preventing additional atelactasis (alveoli closure), which tends to occur with fixed tidal volumes. Although no special device is incorporated in the augmenter to permit sighing, breaths of twice normal respirator output can be obtained by a simple manual maneuver. The exhaust one-way valve is covered with the palm of the hand, preventing expiration. An additional inspiratory gasp usually occurs, known as Head's paradoxical reflex (24). Since the pressure transducer is AC coupled, it will respond, triggering the augmenter. The augmenter delivers a second volume of air adding to the first remaining in the patient. The hand is then removed from the exhaust port, and the infant exhales. If the infant fails to respond for a second breath, the augmenter is manually triggered using the test pushbutton.

Operationally, the augmenter performance is within the specifications outlined for its design. It has been tested on several rabbits, whose respiratory system closely approximates that of a newborn infant, and used

clinically in the treatment of more than a dozen sick premature infants. Some problems of reliability, particularly with respect to clutch life, have been encountered but have been apparently overcome by the use of a better clutch[1].

[1]Vibrac Corporation, Magnetic Particle Clutch, MPC 11-C-1.

CLINICAL APPLICATION STUDY

The use of augmented respiration for the treatment of distressed infants requires knowledge of the expected performance of the infant's respiratory system. For example, it is desirable to know the alveolar ventilation required to achieve a certain reduction in the carbon dioxide concentration in the blood. It is also useful to know at what rate the reduction process occurs. Clinically useful information such as this is not easily obtained experimentally. Experimental isolation of a single variable of the respiratory process of a healthy laboratory animal is in itself difficult. Adding the complication of a fragile, sick infant whose respiration is being mechanically augmented makes the task exceedingly difficult.

A theoretical analysis of the respiratory process can yield clinically useful information. A mathematical model can be formulated incorporating the variables which have clinical significance. Solutions to the model equations provide reasonably accurate predictions of the respiratory system's response to augmentation. Since many of the biological processes relating to respiration are incompletely understood, any theoretical analysis must necessarily be at best an approximation. Even so, an approximation can be most valuable when experimentally derived information is unavailable.

A mathematical model for the carbon dioxide elimination and oxygen uptake processes of a hypothetical 2.5 kg newborn infant is devised and analyzed in this study of the clinically important aspects of respiratory augmentation. It is used to predict the effect of pulmonary blood shunts found in distressed infants. In healthy infants, essentially all of the

venous blood perfuses active alveoli on its way to the arterial circulation. All of the blood therefore participates in gas exchange with air in the lung alveoli. In distressed infants, much of the venous blood either bypasses the lungs entirely in its flow to the arterial circulation, or it perfuses nonfunctional alveoli. Shunted blood sidesteps the carbon dioxide removal and oxygen absorption processes in the lungs, leading to elevated carbon dioxide and depressed oxygen tensions. The effect of increased alveolar ventilation produced by respiratory augmentation in reducing arterial pCO_2 in the presence of pulmonary shunting is examined by use of the model.

The model is also used to examine the function of the respiratory control system in the presence of shunting. Carbon dioxide homeostasis is normally maintained by this control system. Results of the analysis help to answer the question of the ability of the newborn infant's respiratory control system to adequately maintain arterial pCO_2 when connected to a patient cycled respiratory augmenter.

Using a model of the pneumatic components of the pulmonary system, an analysis is made of the pulmonary pressure waveforms to be encountered in augmented respiration. Various tidal volumes and the air flow rates at which they are delivered are studied. The results provide a catalog of significant pressure waveforms, providing information for clinically optimizing the above variables.

Carbon Dioxide Elimination Model

Innumerable investigators have confirmed that blood pCO_2 is the dominant factor controlling pulmonary ventilation. Oxygen tension and pH of the arterial blood, together with voluntary effort, exert a strong

influence on the rate and depth of respiration only when the blood pCO_2 is at or below its normal value. (In newborn infants the normal arterial pCO_2 ranges from 30 to 35 mm H_g.) At higher levels of pCO_2 carbon dioxide is the predominant factor in respiratory control. An increase in arterial pCO_2 causes a proportional increase in lung ventilation, which in turn causes the arterial pCO_2 to fall. This mechanism maintains homeostasis of the blood pCO_2 to within a few per cent of its nominal value in spite of widely varying metabolic activity. From an engineering point of view the mechanism functions as a closed loop proportional control system.

Several studies of the cardiopulmonary system considered as a feedback controlled system appear in the literature. Grodins et al. produced the first theoretical model of the carbon dioxide "respiratory chemostat" (28). Their model included three compartments; the lungs, the tissues, and the error sensing controller linked to venous pCO_2. The model predicted surprisingly well the transients in alveolar ventilation created by the inhalation of carbon dioxide. Horgan and Lange expanded the basic model to include circulation transit time between the lungs and chemoceptors located in the midbrain (29). Their model was intended to show that periodic, or Cheyne-Stokes, respiration could be caused by abnormal transit times[1]. This would create a phase lag in the control system, causing the system to become unstable. Others have added refinements such as an additional compartment representing brain tissue and associating the chemoceptor with carbon dioxide tension in that compartment.

Chilton and Stacy developed a mathematical model of the lung compart-

[1]"Periodic" refers to variations in the amount of air breathed per minute, not respiratory rate.

ment which more accurately describes the carbon dioxide evolution as a function of time (30). Two years later they published a parallel model describing the oxygen absorption process occurring in the lung (31). These two models present a more precise description of the lung processes than used in the control model studies.

Carbon dioxide tension in the arterial blood is perhaps the best index of the adequacy of the pulmonary system function in the clinical situation. Thus the model to be described is conceived so that arterial pCO_2 or its equivalent, the arterial carbon dioxide concentration, becomes the unknown variable. The assumption is then required that metabolic output, cardiac output, and the like are known parameters.

Four principal functional units comprise the respiratory system and its controller. They are the following:

1. Lungs and associated blood vessels (CO_2 elimination).
2. Body tissues (CO_2 storage).
3. Circulatory system (CO_2 transport).
4. Chemoceptor and associated neural components (CO_2 control).

The interconnection of these components is shown in schematic form in Figure 16.

Functional mathematical descriptions are obtained by writing continuity equations for each of the first three compartments. A continuity equation equates the amount of carbon dioxide initially present in the compartment with the amount which is added and the amount which is removed. It can be written more precisely with time as a variable as shown in equation 4-1. (4-1)

$$\text{Vol} \frac{d \text{ Concentration}}{d\ t} = \text{rate of } CO_2 \text{ delivered - rate of } CO_2 \text{ removed}$$

A fourth equation is written to describe the chemoceptor-brain-respiratory muscle link. It is an experimentally derived description of the sensitivity of the controller in terms of its input, arterial pCO_2, and its output, lung ventilation per minute (commonly called $\dot{V}_E$, or minute volume).

Several assumptions must be made to allow simplification of the model to a reasonable degree of complexity. Second and third order effects are generally ignored. Where the biological process is not completely understood, an intelligent guess must be made as to what actually occurs. Assumption validity is tested by comparing the model's predicted behavior with that observed clinically. Simplifying assumptions for the purposes of this study are as follows:

1. Cardiac and metabolic outputs are constant.
2. Details of the cardiac and respiratory cycles are ignored for the examination of slowly varying transient phenomena.
3. Tissue and venous blood CO_2 tensions are equal.
4. Dissociation curves (relating tension to concentration) are linear and equal for arterial and venous blood.
5. Dissociation curve slope of blood and tissue are equal.

Beginning with the lung, the continuity equations are written as follows:

$$V_L \frac{d\left(\frac{P_{alv}}{760-47}\right)}{dt} = - \dot{V}_A \left(\frac{P_{alv}}{760-47}\right) + Q(X_v - X_l)\ (1 - k) \qquad (4\text{-}2)$$

where

V_L = lung volume (functional residual capacity) in liters

$\dot{V}_A$ = effective alveolar ventilation in liters per minute

Q = cardiac output in liters per minute

k = fraction of shunted blood

P_{alv} = CO_2 tension in alveolar gas in mm Hg

$\frac{P_{alv}}{760-47}$ = concentration in alveolar gas

X_v = concentration of CO_2 in mixed venous blood

X_L = concentration of CO_2 in arterial blood leaving the lung

The denominator of the term describing alveolar gas concentration, 760-47, represents the barometric pressure minus the partial pressure of water vapor at body temperature, 37°C. The effective fraction of cardiac output participating in gaseous exchange is represented by Q(1 - k). Arterial blood pCO_2 is assumed equal to alveolar gas pCO_2. Even with a pathologic membrane separating the capillaries from alveolar spaces, most authorities consider carbon dioxide to be so diffusible that any barrier severe enough to impede carbon dioxide diffusion would be such an overwhelming barrier to oxygen diffusion as to be incompatible with life (32).

In order to eliminate the details of diffusion, lung volume varying with inspiration and expiration, non-ventilation of alveoli, and the like, the parameter of effective alveolar ventilation is used. Effective alveolar ventilation, $\dot{V}_A$, is that volume of air needed to produce the same gas exchange in a real lung as in the constant volume idealized lung compartment. Since it is impossible to quantitate all the known physiologic mechanisms involved in respiration, the use of effective alveolar ventilation is the only logical way of assuring model accuracy. $\dot{V}_A$ can be determined clinically by use of the following relationship:

$$\dot{V}_A = \frac{V\ CO_2 \text{ evolved per minute}}{\text{av. } CO_2 \text{ concentration}} \qquad (4\text{-}3)$$

To equate alveolar gas pCO_2 with arterial blood pCO_2 the relationship between the tension of carbon dioxide physically dissolved in the blood and the total concentration of carbon dioxide in the blood must be known. Approximately 95 per cent of the total carbon dioxide in the blood is held in chemical combination. Figure 17 shows the relationship between pCO_2 and the concentration fraction in neonatal blood (33). Note the difference in carbon dioxide carrying capacity between oxygenated blood ($pO_2 = 90$) and reduced blood ($pO_2 = 40$). Oxygen and carbon dioxide concentrations simultaneously change in the lungs and tissues, giving rise to a "physiological" dissociation curve, shown in Figure 17 as the dotted line. It is this dissociation curve which provides the relationship between pCO_2 and concentration used in the model. As stated above, it is assumed that the relationship is linear. The dissociation curve zero intercept decreases as pCO_2 increases, (.075 for p_aCO_2 = 60 mm Hg vs. .10 for p_aCO_2 = 40 mm Hg) while the slope remains constant ($dX/dpCO_2 = .0067$). When high p_aCO_2 levels are anticipated in computations, Xo, the zero intercept, is assigned a value of .075, whereas when low values of p_aCO_2 are anticipated, Xo = .10 is used. For differences of $p_vCO_2 - p_aCO_2$ greater than 6 mm hg, dX/d_pCO_2 decreases while Xo increases. The error arising from the assumption of a constant slope is discussed below.

Combining the following equations

$$p_aCO_2 = p_ACO_2 \tag{4-4}$$

$$X = .0067pCO_2 + Xo \tag{4-5}$$

with 4-2 gives

$$\frac{dX_L}{dt} = -\frac{\dot{V}_A}{V_L}(X_L - Xo) + \frac{Q(1 - k)}{.21\ V_L}(X_V - X_L) \tag{4-6}$$

where

Xo = dissociation curve zero-intercept

$p_A CO_2$ = alveolar gas tensions

Similarly the carbon dioxide continuity equation for the tissue compartment is given as 4-7.

$$V_T \frac{d\ (P_T/760-47)}{dt} = M + Q(X_a - X_v) \qquad (4\text{-}7)$$

where

V_T = equivalent tissue volume in liters

p_T = tissue gas tension

M = CO_2 evolved from tissue metabolism in liters per minute

All soft tissue, excluding the blood, is included into one equivalent volume V_T, for the storage of CO_2. Carbon dioxide derived from metabolism is held in physical solution in the tissues and released to the venous blood by diffusion. Thus venous blood and tissue carbon dioxide tensions are equal. The dissociation relationship for tissue is assumed equal to that of blood. Blood plasma has essentially the same linearized dissociation curve as whole blood, and extracellular fluids are similar to plasma. No direct experimental data pertaining to tissue carbon dioxide dissociation is available for man.

Equating $p_T CO_2$ and $p_v CO_2$ together with the dissociation relationship gives

$$\frac{d\ X_v}{dt} = \frac{M}{.21\ V_T} - \frac{Q}{.21\ V_T}(X_v - X_a) \qquad (4\text{-}8)$$

Continuity in the circulatory system is represented by the following equation:

$$Q X_a = Q k K_v + Q(1 - k)X_L$$

or

$$X_a = kX_v + (1 - k)X_L \qquad (4\text{-}9)$$

where

k = effective fraction of cardiac output bypassing the lungs

Normal newborn infants may shunt as much as 25 per cent of their cardiac output from the venous to the arterial side of the circulation in the first few days following birth. Severely distressed infants may shunt as much as 70 per cent (32).

The final equation, representing the controller, is determined experimentally. It relates arterial carbon dioxide tension to respiratory minute volume. The respiratory chemoceptor is thought to be located in the midbrain. Thus it responds to brain tissue pCO_2 rather than arterial or venous tensions directly. Because tissue pCO_2 is sensed, a time delay is produced between the appearance of a change in arterial pCO_2 and a resulting change in ventilation. Information about phase delay between changes in pCO_2 and $\dot{V}_E$ is very incomplete, limiting the usefulness of any respiratory system model to accurately predict fast transient behavior.

The relationship between ventilation, expressed in terms of $\dot{V}_E$, and alveolar carbon dioxide tension, as measured by Avery et al., is used in this model (34). As stated above, alveolar and arterial carbon dioxide tensions are considered to be equal. Because of this equality, the data of Avery et al. for the 2.5 kg newborn infant can be represented by the following equation:

$$2.5\ \dot{V}_E = 0.12\ p_aCO_2 - 3.3 \qquad (4\text{-}10)$$

Equation 4-10 can be written in terms of concentration.

$$\dot{V}_E = 18\ X_a - 5.1 \qquad (4\text{-}11)$$

Only a fraction of inspired gas participates in gaseous exchange in the alveoli, due to respiratory dead space and excessive ventilation of certain alveoli. Converting equation 4-11 into an expression in terms of alveolar ventilation by adding a fractional multiplier to account for the dead space gives the following:

$$\dot{V}_A = d\ (18X_a - 5.1) \qquad (4\text{-}12)$$

where

d = dimensionless parameter, the fraction of effective minute volume

The parameter d varies from 0.0 to 0.8 depending upon conditions in the lung.

Summarizing, the carbon dioxide elimination function of the respiratory system can be represented by the following equations:

$$\frac{dX_L}{dt} = -\frac{\dot{V}_A}{V_L}(X_L - Xo) + \frac{Q(1 - k)}{.21\ V_L}(X_V - X_L) \qquad (4\text{-}6)$$

$$\frac{dX_v}{dt} = \frac{M}{.21\ V_T} - \frac{Q}{.21\ V_T}(X_v - X_a) \qquad (4\text{-}8)$$

$$X_a = kX_v + (1 - k)X_L \qquad (4\text{-}9)$$

$$\dot{V}_A = d\ (18X_a - 5.1) \qquad (4\text{-}12)$$

Oxygen Uptake Model

The arterial blood oxygen tension depends on the amount of alveolar ventilation, diffusing capacity of the lung, blood perfusion and distribution of inspired gas within the lung, and venous to arterial circulatory shunts. A study by Nelson *et al.* showed that circulatory shunts and dis-

tribution of inspired air into inactive alveoli are the principal causes of low oxygen tension in the blood of distressed newborn infants (35). Diffusion of oxygen into the alveolar capillary blood is not significantly impaired in distressed infants, according to their study.

Because of severe circulatory shunting in the distressed infant, high concentrations of oxygen in the inspired air are required to insure adequate oxygen saturation of the arterial blood. All capillary blood perfusing active alveoli will be saturated (all red cell hemoglobin chemically combined with oxygen) by the normal concentration of oxygen in room air. When this blood mixes with blood that bypassed the oxygenation process, the resulting admixture has a lower degree of oxygen saturation. If, however, additional oxygen is added to the blood perfusing the active alveoli by forcing it into physical solution, then the overall arterial oxygen concentration is increased.

A simple mathematical model describing oxygen transfer across the lungs is developed and analyzed here to predict the inspired oxygen concentration required to produce a given oxygen concentration in the arterial blood. The nomenclature for this model is the same as that used for the carbon dioxide model, with the understanding that the symbols denoting concentrations refer to oxygen unless otherwise noted.

The model is developed by writing an expression for the oxygen continuity in the lungs. Since the quantity of oxygen entering the lungs must equal that leaving under steady state conditions, the following expression applies:

$$\dot{V}_A X_{atmos} = Q (1 - k) (X_a - X_v) \qquad (4\text{-}13)$$

The arterial-venous oxygen concentration difference, $X_a - X_v$, has been

experimentally observed to be 0.04 volume-fraction in distressed infants by Strang and MacLeish (36). Using the same equation form as for tissue carbon dioxide, equation 4-8, the steady state continuity equation for oxygen dissolved in the tissues is written as follows:

$$Q(X_a - X_v) = \frac{M}{RQ} \tag{4-14}$$

where

RQ = respiratory quotient, i.e., $\frac{CO_2 \text{ vol. evolved}}{O_2 \text{ vol. uptake}}$

Assuming that Q = 0.30 liters per minute, M = 0.012 liters per minute, and RQ = 0.8, the calculated a-v difference is

$$X_a - X_v = \frac{.012}{(.3)(.8)} = .05 \tag{4-15}$$

The value computed is that commonly accepted for healthy adults. The value experimentally observed by Strang and MacLeish will be used, however, in the computations to follow in an effort to obtain greater accuracy.

Substituting $X_a - X_v = 0.04$ into equation 4-13 gives

$$\dot{V}_A = \frac{Q(1 - k)(.04)}{X_{atmos}} = \frac{(.3)(.04)(1 - k)}{.21} = .057\ (1 - k) \text{ liters per minute} \tag{4-16}$$

the minimal alveolar ventilation required to produce saturation of the blood perfusing active alveoli. $\dot{V}_A$ is observed to be greater than 0.1 to 0.2 liters per minute in distressed infants according to Nelson et al. (35). Thus spontaneous respiration is assumed to produce sufficient alveolar ventilation to permit full saturation of the available blood. The oxygen concentration of the blood leaving the active lung compartment, X_L, is given by equation 4-17.

$$X_L = .20 + (X_{atmos} - .21)(673)(.00003) \qquad (4\text{-}17)$$

The oxygen concentration of the normal atmosphere produces a concentration X_L of 0.20. If the inspired gas concentration is higher than the normal 21 per cent, additional oxygen enters the blood in physical solution. The second term of equation 4-17 describes the contribution of the physically dissolved oxygen to X_a. The partial pressure in mm Hg of oxygen in excess of that produced by the 21 per cent normal oxygen concentration is $(X_{atmos} - .21)(673)$ (atmospheric pressure minus water vapor tension minus carbon dioxide tension equals 673 mm Hg). Physically dissolved oxygen concentrations increase at the rate of 0.000031 volume-fraction per mm Hg increase in partial pressure. Combining equation 4-9, which describes circulatory shunting, with equation 4-17 produces equation 4-18.

$$X_a = \frac{.20 + .02\ (1 - k)(X_{atmos} - .21) - .24\ k}{1 - k} \qquad (4\text{-}18)$$

This equation describes the value of arterial oxygen concentration to be expected from a given value of inspired oxygen concentration.

Analysis

Infants suffering from respiratory distress show a marked increase in blood carbon dioxide tension. The basic cause for this increase is uncertain. It may result from central nervous system depression, loss of pulmonary gas interchange effectiveness, or both. Use of augmented respiration is based on the assumption of central nervous system adequacy. Thus it is desirable to determine what effect pulmonary system inefficiency has on p_aCO_2.

Respiratory regulation of p_aCO_2 is effected through proportional control (37). Deviations from the desired value of p_aCO_2 produce proportionate

increases in the output of the system's mechanism for correction. If the lung, as the correcting apparatus, is insufficiently sensitive to the error signal produced by the brain, the steady state error of the controlled system will become large. A primary characteristic of a proportional control system is its inherent error. The steady state error is inversely proportional to the system's overall sensitivity. Loss of sensitivity can result from pulmonary shunting and increased pulmonary dead space. Thus the central nervous system, acting as the system controller, may be functioning perfectly, yet the controlled variable, the p_aCO_2, may appear to be abnormally high.

Figure 18 shows the steady state p_aCO_2 of the hypothetical newborn infant whose respiratory parameters are given in Table No. 1. The data for Figure 18 was obtained by solving equation 4-19 for various values of k and d.

$$X_a = \left(k + \frac{Q(1 - k)^2}{.21d\ (18X_a - 5.1) + Q(1 - k)}\right)\left(X_a + \frac{M}{Q}\right) + \frac{.021d\ (18X_a - 5.1)}{.21d\ (18X_a - 5.1) + Q(1 - k)} \qquad (4\text{-}19)$$

Equation 4-19 is the result of combining equations 4-6, 4-8, 4-9, and 4-12. The derivatives with respect to time found in these equations are set equal to zero to obtain the steady state value of X_a. An increase in cardiac output, Q, shifts the curve representing a specific value of k downward, while an increase in metabolic output, M, shifts the curve upward. Although values for M and Q applicable to a specific infant must be introduced into the calculation of X_a, the data of Figure 18 should be reasonably representative of most newborns weighing about 2.5 kg. An infant with a high metabolic output will usually compensate by increasing cardiac output.

Variations in the arterial-venous carbon dioxide concentration difference, M/Q, between infants are minor, the value always being close to 0.04 during spontaneous respiration.

Typical values of d, the effective ventilation fraction, vary from 0.6 to 0.8 in healthy newborn infants, while k is approximately 0.2. Values of d range from 0.2 to 0.5 and k may be as high as 0.7 in distressed infants, according to the data of Nelson et al. (32). The typical path of the disease process, from a study by Strang and MacLeish, is shown in Figure 18 (36). Note that it is possible for the p_aCO_2 to increase as much as 20 to 30 mm Hg due solely to increased shunting and dead space. It is shown, then, that the increase in carbon dioxide tension can result from the normal error produced by the respiratory control system. Thus it can be concluded that during moderate distress the infant's respiratory control system is probably functioning and will prevent hyperventilation if the efficiency of the effector mechanism, the lung, is increased by respiratory augmentation.

In the case of severe respiratory distress no such conclusion can be drawn, since clinical experience shows that minute ventilation, $\dot{V}_E$, is significantly less than equation 4-12 would predict. No evidence has been presented to indicate whether the malfunction in severe distress is neural depression, respiratory muscle failure, or both. If respiratory muscle work is reduced by augmentation, $\dot{V}_E$ should increase if the malfunction is caused wholly or in part by muscle fatigue.

Both pulmonary shunting and alveolar ventilation determine how much excess carbon dioxide can be removed from storage in the body fluids. Figure 19 shows the efficiency of the pulmonary system in exhausting car-

bon dioxide as a function of shunting and alveolar ventilation. A greater efficiency implies a greater overall respiratory system sensitivity. Since the use of a respiratory augmenter increases alveolar ventilation in the distressed infant, Figure 19 shows its potential effectiveness. Efficiency for the sake of this discussion is defined in the following way:

$$\text{Efficiency (per cent)} = \frac{p_vCO_2 - p_aCO_2}{p_vCO_2} \times 100 \qquad (4\text{-}20)$$

Normally, spontaneous ventilation produces a venous-arterial difference of approximately 6 mm Hg tension. An increase in alveolar ventilation increases the efficiency of gas exchange. This in turn tends to increase the venous-arterial difference, allowing more carbon dioxide stored in the tissues to be picked up by the blood and eventually exhausted.

For computation of the data shown in Figure 19 a steady state is assumed. That is, p_vCO_2 and M remain constant. Although actually invalid, the assumption allows one to study the effect of changes in k and $\dot{V}_A$ on the potential ability of the infant to exhaust excess carbon dioxide. Analytically, the carbon dioxide content of arterial blood under these circumstances is given by

$$X_a = \left(k + \frac{Q(1 - k)^2}{.21\,\dot{V}_A + (1 - k)Q} \right) X_v + \frac{.016\,\dot{V}_A}{.21\,\dot{V}_A + Q(1 - k)} \qquad (4\text{-}21)$$

Equation 4-21 is the result of combining equations 4-6 and 4-9. X_a is converted to p_aCO_2 using the dissociation curve shown in Figure 20. X_v is assumed to remain at 0.475, corresponding to a p_aCO_2 of 60 mm Hg, and cardiac output, Q, is assumed to be 0.30. The linear physiologic dissociation curve is used in the calculations for Figure 19. Errors in p_aCO_2 resulting from the use of the physiologic dissociation curve should be less than 5

per cent, with the maximum error occurring at the conditions of $\dot{V}_A = 1.0$ and $k = 0.0$.

Inspection of Figure 19 indicates that with sufficient alveolar ventilation all values of shunting up to about $k = 0.7$ permit an ultimate decrease in p_aCO_2. Shunting in excess of $k = 0.7$ does not permit the maintenance of the necessary venous-arterial difference of M/Q. The corresponding minimal efficiency required is shown by the horizontal dotted line in Figure 19. When shunting exceeds a value of $k = 0.7$, no amount of ventilation will suffice. The data of Nelson et al. and Strang and MacLeish showed no infants surviving when venous admixture, or shunting, exceeded $k = 0.7$ (32) (36). Only a moderate increase in alveolar ventilation in excess of that occurring in spontaneous respiration is necessary in maintaining pCO_2 equilibrium for values of shunting up to $k = 0.6$. However, alveolar ventilation must be increased considerably to effect significant reductions of p_aCO_2. It is important to note that Figure 19 represents potential respiratory system ability and not the ultimate value of p_aCO_2 to be expected.

Increasing the infant's alveolar ventilation will decrease his p_aCO_2. The reduction occurs rather slowly, the p_aCO_2 changing exponentially with time. The ultimate values reached for various values of alveolar ventilation are shown in Figure 21, while the time required to reach 63 per cent of the ultimate value is shown in Figure 22. Sixty three per cent of the ultimate change occurs after a time equal to that of the infant's cardiopulmonary time constant. At a time equal to two time constants 87 per cent of the ultimate change has occurred. The time constant arises from the solution of the first order differential equation describing

carbon dioxide storage.

From a consideration of the equation of continuity for the lungs, equation 4-6, it is apparent that the lung has its own time constant. This time constant is negligible compared to that of the complete cardiopulmonary system. The time constant τ of a first order differential equation is equal to $\frac{1}{\alpha}$ when it is written in standard form.

$$\frac{d X_L}{dt} + \frac{1}{\tau} X_L = K \tag{4-22}$$

Therefore, obtaining τ_L from equation 4-6,

$$\tau_L = \frac{1}{\frac{Q(1 - k)}{.21 V_L} - \frac{\dot{V}_A}{V_L}} \tag{4-23}$$

For the typical values of $Q = 0.3$ and $V_L = 0.045$, together with the maximum expected value of $k = 0.6$ and the minimum expected $\dot{V}_A = 0.2$, the time constant $\tau_L = 2.5$ seconds approximately. Since the time constant of the entire cardiopulmonary system, τ_P, is expected to be greater than 3 minutes, the gas exchange process in the lung compartment can be assumed to be a steady state process, thus eliminating a first order differential equation from consideration. That the above assumption is valid has been verified by solving the carbon dioxide elimination model equations simultaneously using an analog computer. Solutions including the lung compartment as a dynamic process do not noticeably differ from the analytical solution below.

Combining the steady state version of the lung equation 4-6, together with 4-8 and 4-9, one obtains

$$\frac{d X_v}{dt} + \frac{Q}{.21 V_T} \left(1 - \left[k + \frac{Q(1 - k)^2}{.21 \dot{V}_A + Q(1 - k)}\right]\right) X_v = \tag{4-24}$$

$$\frac{M}{.21\ V_T} + \frac{Q}{.21\ V_T}\left(\frac{.016\ \dot{V}_A}{.21\ \dot{V}_A + Q(1-k)}\right) \qquad (4\text{-}24)$$

Solving 4-24 yields

$$X_v = X_{vss} + (X_{vo} - X_{vss})\ e^{-t/\left(\frac{.21\ V_T}{Q(1-k)} + \frac{V_T}{\dot{V}_A}\right)} \qquad (4\text{-}25)$$

where

$$X_{vss} = \frac{M}{Q(1-k)} + \frac{M}{.21\ \dot{V}_A} + \frac{.10}{(1-k)}\text{ , the steady state solution} \qquad (4\text{-}25a)$$

X_{vo} = initial venous concentration, i.e., the steady state value of X_v at the arbitrary time t = 0

If all other respiratory parameters remain constant, a change in $\dot{V}_A$, induced by an increased tidal volume from the augmenter will lower the venous carbon dioxide concentration 63 per cent of the difference between the initial and ultimate concentrations in the time

$$\tau_P = \frac{.21\ V_T}{Q(1-k)} + \frac{V_T}{\dot{V}_A}$$

The value of X_v to which the process will ultimately proceed in an infinite amount of time is given by X_{vss}, the steady state solution to the equation 4-24. After an infinite period of time

$$X_a = \frac{K\ M/Q + .10}{1-k} + \frac{4.76\ M}{\dot{V}_A} \qquad (4\text{-}26)$$

Equation 4-26 is obtained from 4-25a by combining it with the identity

$$X_a + \frac{M}{Q} = X_v \qquad (4\text{-}27)$$

Figure 21 is based on a value of M/Q = .04.

Large values of V_A, which cause $X_v - X_a$ to be greater than 0.04, change the physiological CO_2 dissociation curve slope. This change in slope can cause a maximum error of approximately 0.6 minutes in the time

constants shown in Figure 22. The error is not present in the computation of ultimate values, since during steady state conditions the $X_v - X_a$ difference will approach 0.04, or a corresponding tension difference of 6 mm Hg.

By referring to Figure 21 it can be seen that safe levels of carbon dioxide tension can be reached with moderate values of alveolar ventilation except when pulmonary shunting reaches a value of K = 0.6 or greater. A ratio of $\dot{V}_A/M = 50$ corresponds to an alveolar ventilation of 0.6 liters per minute. The theoretical minimums of p_aCO_2 for the case of $\dot{V}_A$ approaching infinity are shown along the right side of Figure 21. Note from Figure 22 that abnormally high values of shunting do not appreciably increase the time required to rid the tissues of excess carbon dioxide. It can be concluded that relatively little is gained by increasing alveolar ventilation beyond a value corresponding to $\dot{V}_A/M = 50$.

Pulmonary shunting also affects the degree of arterial blood oxygen saturation. Increased alveolar ventilation induced by respiratory augmentation will help to increase the p_aO_2 only if the additional inspired gas participates in gaseous exchange with otherwise unsaturated blood. Inspired gas oxygen concentration is the predominant factor in determining the p_aO_2 level. Figure 23 shows the p_aO_2 expected for various values of shunting and inspired oxygen concentrations. The data presented is obtained from numerical evaluation of equation 4-18. When venous admixture exceeds a value of approximately 30 per cent, complete oxygen saturation of the arterial blood cannot be attained with 100 per cent oxygen at normal barometric pressure. With shunting of 60 per cent of the blood around the active lung alveoli (k = 0.6) the arterial blood will be 75 per cent satu-

rated if pure oxygen is inhaled. When shunting becomes severe, such as $k = 0.6$, increased oxygen concentrations are ineffective in raising p_aO_2. This explains the clinical observation that very severely distressed infants ($k = 0.6$ approximately) fail to respond to increased oxygen concentrations and their cyanotic condition remains unimproved. Less severely distressed infants ($k = 0.4$ approximately) respond noticeably to increased oxygen concentrations.

Increasing the physically dissolved oxygen in the blood by means of hyperbaric oxygenation produces, with 60 per cent shunting, a p_aO_2 of 55 mm Hg at two atmospheres pressure. At three atmospheres of pure oxygen the p_aO_2 is raised to 166 mm Hg. In the case of hyperbaric oxygenation, equation 4-18 becomes

$$X_a = \frac{.216 + .0235\,(N - 1)(1 - k) - .256\,K}{1 - k} \qquad (4\text{-}28)$$

where

N = number of atmospheres pressure, absolute

Concentrations are converted to partial pressures using the neonatal blood oxygen dissociation curves of Edwards and Ross (33) for an assumed arterial CO_2 tension of 50 mm Hg. The only significant error in Figure 23, if present, is the assumption of no resistance to diffusion of oxygen across the alveolar-capillary membrane. With this assumption in mind, Figure 23 can be used for the quantitative evaluation of effective circulatory shunting.

Pressure Waveform Interpretation

Assessment of the mechanical condition of the lungs is also important in the clinical application of a respirator or augmenter. Pressures

developed in the thorax and at the nose by devices used to assist respiration are a function of the resistance, inertial component, and compliance of the thorax and total pulmonary system respectively. The monitoring of nasal and pleural pressure waveforms is a relatively simple method of qualitatively evaluating changes in the pathologic condition of the infant and also the relative effectiveness of the respiratory augmentation. Diminished lung compliance, for example, signifies increased severity of respiratory distress. Improper matching of the augmenter to the infant as indicated by abnormal pressures is another example of the usefulness of pressure monitoring.

A theoretical study of the significance of the various waveshapes encountered clinically was undertaken. An infinite variety of nasal and intrathoracic pressure waveforms are possible. Variations of the basic waveforms can be caused by changes in augmenter output volume or flow rate or change in the infant's lung compliance, etc. Hence, a number of waveforms seen previously in clinical and laboratory applications of the augmenter were chosen as representative and an effort made to simulate them. An electrical analog of the pulmonary system as described in Chapter 2 was used as the simulator.

An electrical circuit, essentially the same as Figure 2, served as an analog of the pulmonary mechanics and was used to generate voltage waveforms similar to the pressure waveforms produced by respiratory augmentation. A pulsed constant current power source connected to the terminals representing the nose simulated a constant flow respirator, while a low impedance exponential waveform voltage generator simulated the pressures produced by the respiratory muscles. A complete schematic diagram of the

simulator is shown in Figure 3. The generators were operated synchronously by a timing circuit to simulate augmented respiration.

The lungs were simulated by three parallel combinations of a resistor and capacitor in series. This circuit simulated a congested lung, producing air trapping. R_x in Figure 3 represents the expiratory resistance caused by minor flow resistances in the augmenter, particularly the resistance of the one-way valve through which expired air flows. C_c represents the combined compliance of the nasopharyngeal region of the infant and the tubing connecting the augmenter to the infant. Other components of the analog are as described previously in Chapter 2. In the analog, 1.0 microfarad represents a compliance of 1.0 ml per cm H_2O, and 1.0 megohm of resistance equals a flow resistance of 1.0 cm H_2O per ml per second.

Figures 25 through 31 show the simulated pressure waveforms produced by the analog. These figures were recorded using a curvilinear type recorder. Thus some distortion is present occurring as a slight bowing to the left. The simulator timing circuit produced an inspiratory phase of 0.3 seconds and an expiratory phase of 0.7 seconds. The expiratory phase was purposely exaggerated to enhance the separation between phases. The pleural pressure produced by the respiratory muscles was simulated with the same wave shape as used in the optimization analysis, i.e.,

$$P_{pl} = - P_o (1 - e^{-at}) \qquad (4\text{-}29)$$

The inspiratory duration lasted approximately two time constants. While it is the pleural pressure that is observed to be exponential, the muscle source is assumed exponential for simplification. It would more accurately be a sum of exponentials. However, the resulting error is small.

A large number of waveforms representing the various types of dys-

function have been simulated. The more interesting and pertinent waveforms are shown in Figures 25 through 31. Many of these will be recognized as the same wave shapes as shown in other figures in this dissertation. Pleural, intrapulmonary, and nasal pressures are shown, as well as the muscle source. The intrapulmonary and muscle pressures are shown for reference and are not observable experimentally.

Figure 25 shows the waveforms produced by constant air flow into a passive pulmonary system. It is presented to indicate the augmenter's contribution to the pressure waveform. Figures 26, 27, and 28 show the pressures observed when the augmenter characteristics are improperly matched to the infant. An indication of mismatch is most apparent in the pleural pressure waveform. The optimal tidal volume and flow rate from the augmenter produce an intrathoracic waveform as shown in Figure 29.

Figure 30 shows the results of a compliance increase of 25 per cent in the simulated lung section having least congestion. Notice the difference in the negative peaks of the pleural pressure between this figure and the preceding one. Figure 31 illustrates the opposite situation, that of stiff, congested lungs. This condition is simulated in the analog by two parallel branches of a series combination of 1.0 microfarad and 100K ohms, equivalent to a compliance of 1 ml per cm H_2O and a congestive flow resistance of 0.1 cm H_2O per ml per second.

Summary

The prognosis for the severely distressed infant is poor if pulmonary shunting exceeds 60 per cent, as shown by the data of Figures 18, 19, 21, and 22. The prognosis is good, however, if pulmonary shunting remains less than 40 per cent, assuming that adequate alveolar ventilation can be

maintained.

Abnormally high blood carbon dioxide tensions are shown to be caused, at least in part, by normal functioning of the respiratory control system. Large values of pulmonary shunting and dead space reduce the system's sensitivity and thus produce a large operating error in the system. An arbitrary measure of the effector portion of the system's sensitivity is shown in Figure 19. Data is presented in Figures 21 and 22 to show the potential effect of increased alveolar ventilation on the excessive carbon dioxide tension for the hypothetical infant. Figure 23 shows the concentration of inspired oxygen necessary to achieve oxygenation of the arterial blood when shunting is present. Severe shunting is shown to prevent normal p_aO_2 levels even when pure oxygen is inhaled. Finally, the effect of pulmonary dysfunction on pulmonary pressure waveforms seen clinically is discussed. Pleural and nasal pressure waveforms generated by the action of a constant flow respiratory augmenter provide a good qualitative index of the sufficiency of augmented respiration.

SUMMARY OF CLINICAL RESULTS

An indisputable conclusion regarding the efficacy of respiratory augmentation for specific therapy in the treatment of respiratory distress is impossible at this time. Controlled experiments matching treated infants and similarly distressed untreated infants are not feasible. Only a long term statistical study can reveal the adequacy of respiratory augmentation therapy for distressed infants. With these limitations in mind, the clinical "success" of the respiratory augmentation process described in this study will be reviewed.

The respiratory augmenter was first tested on urethane anesthetized rabbits, the attachment to the augmenter being by means of tracheotomy (38). Rabbits were used to simulate newborn infants during the development of the equipment and associated theory. A few rabbits were subjected to respiratory augmentation for 48 hours. None showed any evidence of lung damage at necropsy.

The first clinical trial of the augmenter involved a week old three pound premature infant who had developed recurring periods of apnea 48 hours previous to the start of respiratory augmentation. During the four hour period prior to the application of the augmenter, periods of apnea in excess of 8 minutes occurred at about half hour intervals. The infant appeared cyanotic and his muscle tone was nearly absent. It was evident to the attending pediatricians that death was imminent. The infant's color improved markedly shortly after being connected to the augmenter, and his muscle tone soon returned. No further apnea occurred; therefore, respiratory augmentation was stopped after 12 hours. Subsequently, the apnea returned. Augmentation was resumed, but death occurred 48 hours later.

From clinical evaluation, it was felt that death was due to a central nervous system malfunction incurred during the anoxic intervals existing before the augmenter was applied[1]. No blood gas measurements were obtained during this trial.

Another application of the augmenter was in conjunction with the treatment of a four pound premature infant. Within 12 hours after birth, this infant's respiratory rate had risen to 72 breaths per minute. An X-ray examination made shortly thereafter showed severe bilateral hyaline membrane disease. Respiratory augmentation was instituted when the infant was 20 hours of age. Blood gas data obtained concurrently indicated a p_aCO_2 of 40 mm Hg and a p_aO_2 of 19 mm Hg. (The infant was inhaling a 40 per cent oxygen concentration at the time.) The severe shunting indicated by the very low p_aO_2 is shown in Figure 23 to be in excess of 60 per cent. Acetylcholine (administered iv.) was employed to lessen the apparent vasospasm, and thus to reduce shunting. With the augmenter delivering a minute volume, $\dot{V}_E$, of approximately 2200 ml per minute, the infant's pCO_2 level was maintained continuously at a level of 30 to 35 mm Hg. Respiratory augmentation was continued for approximately 80 hours, after which the infant recovered uneventfully.

Although many of the infants treated are now alive and healthy, it cannot be said with certainty that survival was directly attributable to respiratory augmentation. Further research should help to clarify this point. It is certain, however, that the augmenter helps to reduce the infant's respiratory effort and also promotes the elimination of excess

[1]McCormack, W. C., McFarland Clinic, Ames, Iowa, Clinical records. Private communications. 1963.

carbon dioxide.

When the distressed infants were placed on the augmenter, a marked improvement in color and a decrease in apparent respiratory effort were almost always observed. The infants soon went to sleep. To rule out coincidental improvement, in most cases the respiratory augmenter has been removed briefly and the infant placed in an incubator. With an identical oxygen concentration maintained in the incubator as that delivered by the augmenter, the infant reverted to labored respiration, as evidenced by increased thoracic wall retraction. The infant's skin color soon became darker, indicating a decrease in blood oxygen saturation.

A method for measuring the relative contributions of the augmenter and the infant to the total respiratory effort has not yet been devised (39). If the patient's pleural pressure is positive (relative to that at the end of expiratory pause) during the inspiratory phase when respiration is augmented, the augmenter must be contributing to the total respiratory effort. After the brief interval following connection to the augmenter, during which adaptation occurs, positive going pleural pressures have been observed in practically all infants and laboratory animals. Figure 32 shows the nasal and intraesophageal (intraesophageal and pleural pressures being equivalent) pressures measured in a distressed infant connected to the augmenter. Note the negative going pressure produced by an attempt to sigh.

The respiratory augmenter has been used in the treatment of 16 infants to date and appears to be successful in fulfilling its intended purpose.

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and Mr. J. T. McConnell, who spent many patient hours in helping to construct the augmenters.

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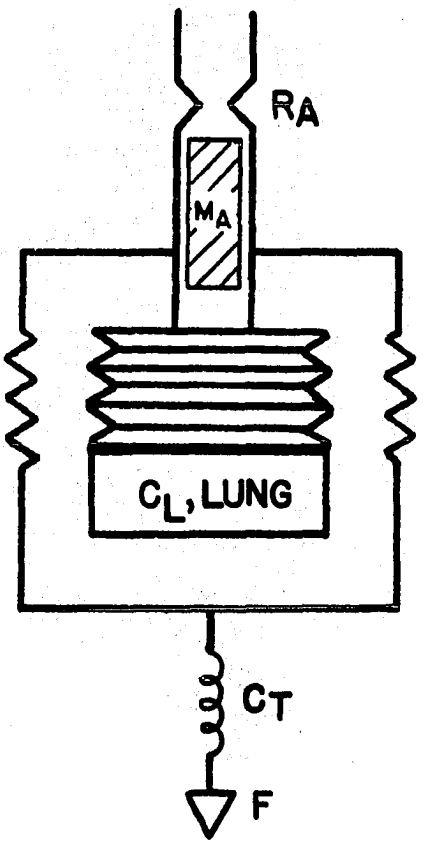
FIGURES



R_A = AIRWAY RESISTANCE

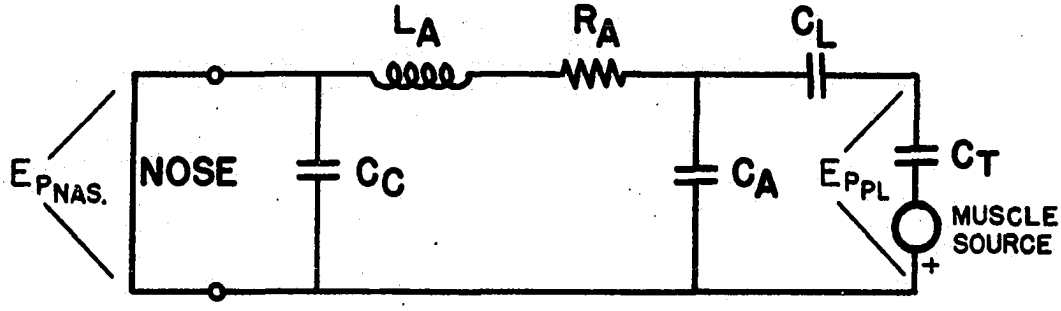
M_A = AIRWAY GAS MASS

C_L = LUNG COMPLIANCE

C_T = THORAX COMPLIANCE

F = RESPIRATORY MUSCLE FORCE

FIGURE 1 SIMPLE MECHANICAL ANALOG OF THE PULMONARY SYSTEM



TYPICAL PARAMETERS FOR NEWBORN INFANT

R_A = 30 CM H_2O / L / SEC

L_A = .013 CM H_2O / L / SEC^2

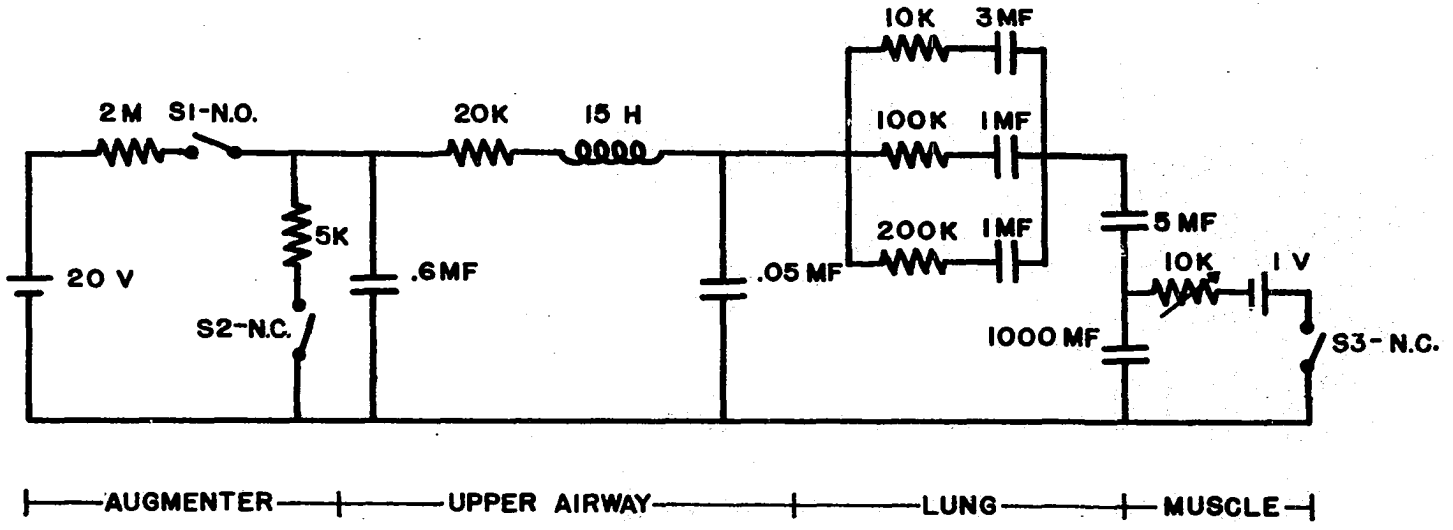
C_A = 1 ML / CM H_2O / L FRC

C_C = .2 ML / CM H_2O

C_L = 5 ML / CM H_2O

C_T = 5 ML / CM H_2O

FIGURE 2 PULMONARY SYSTEM ELECTRICAL ANALOG



S1, S2, & S3 ARE OPERATED SIMULTANEOUSLY BY TIMER TO SIMULATE INSPIRATION.

CIRCUIT REPRESENTS DISTRESSED INFANT WITH RESPIRATION AUGMENTED BY A CONSTANT FLOW (100.ML/SEC) TYPE AUGMENTER.

1 CM H_2O = .1 VOLT 1 L/SEC = .1 MA

FIGURE 3 PULMONARY SYSTEM SIMULATOR

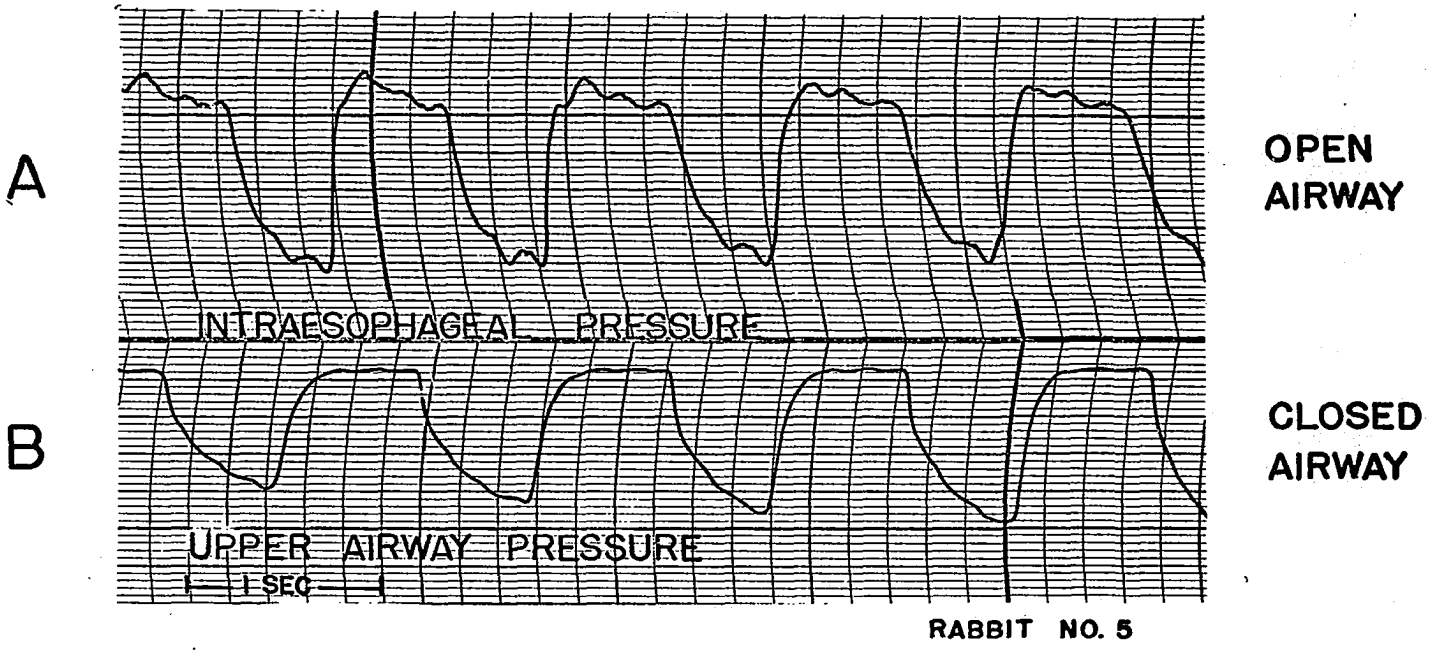


FIGURE 4 INSPIRATORY PRESSURES

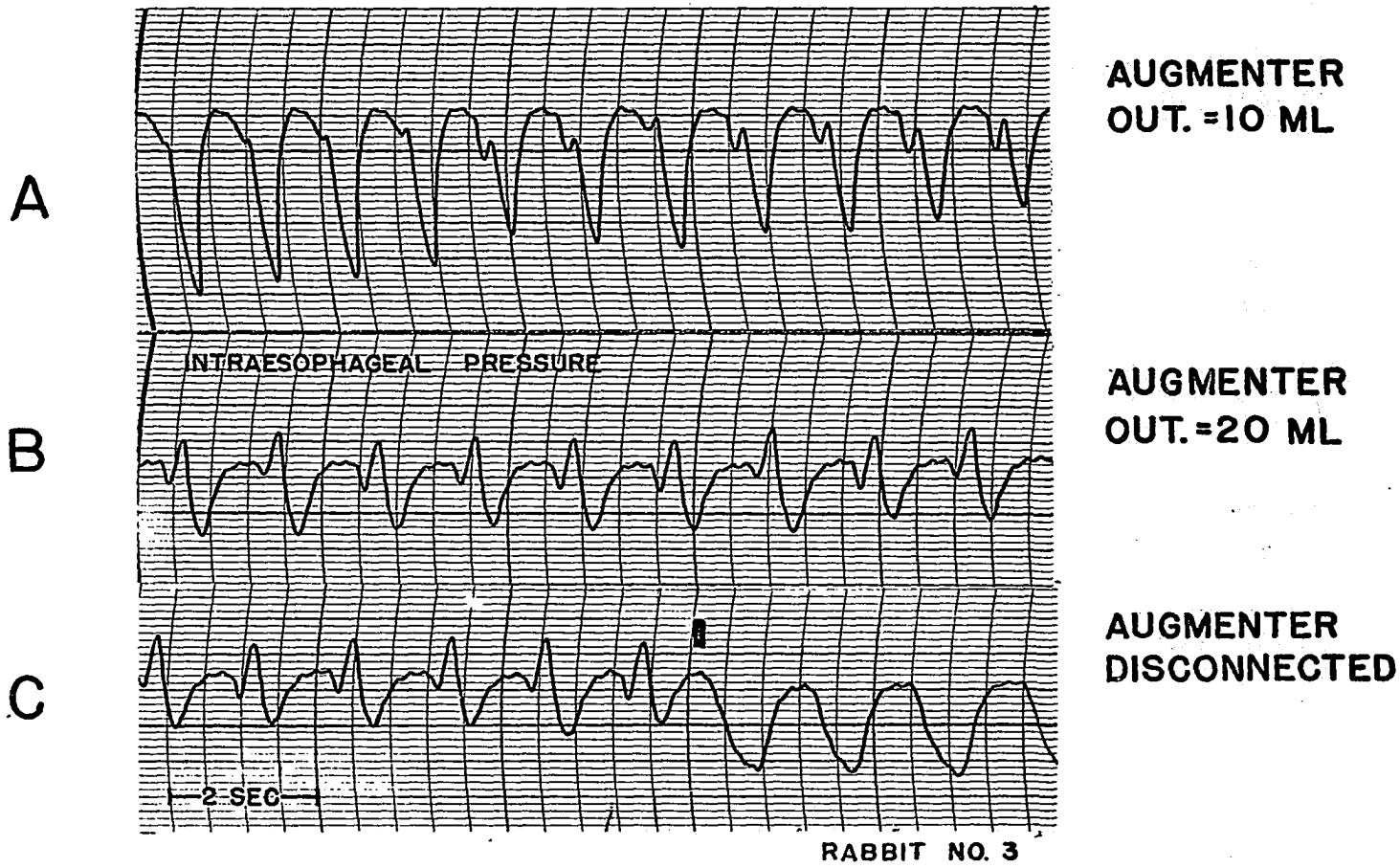


FIGURE 5 ADAPTATION TO RESPIRATORY AUGMENTATION

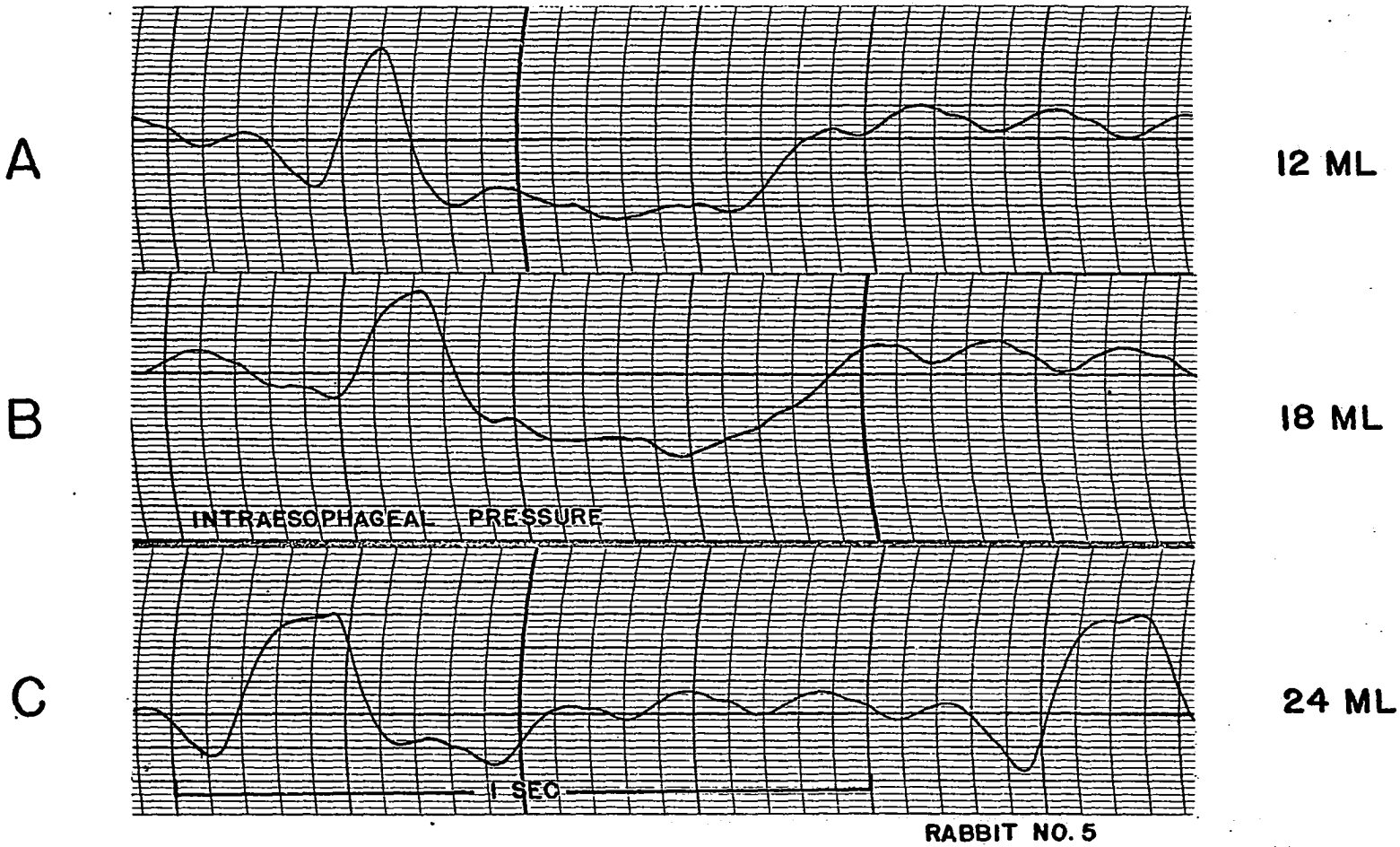


FIGURE 6 INSPIRATORY DURATION AS A FUNCTION OF TIDAL VOLUME IN AUGMENTED RESPIRATION

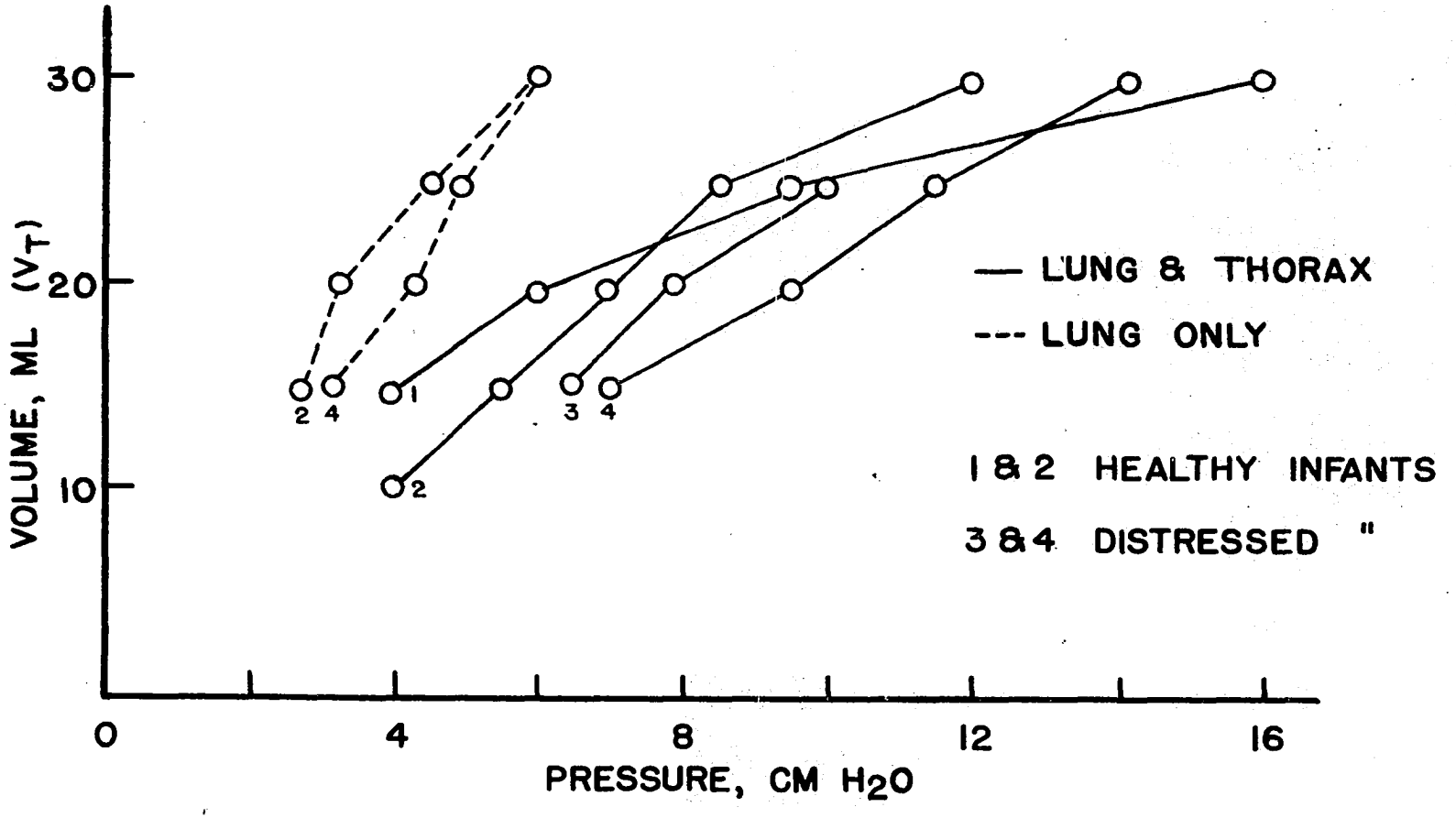


FIGURE 7 PRESSURE-VOLUME CURVES

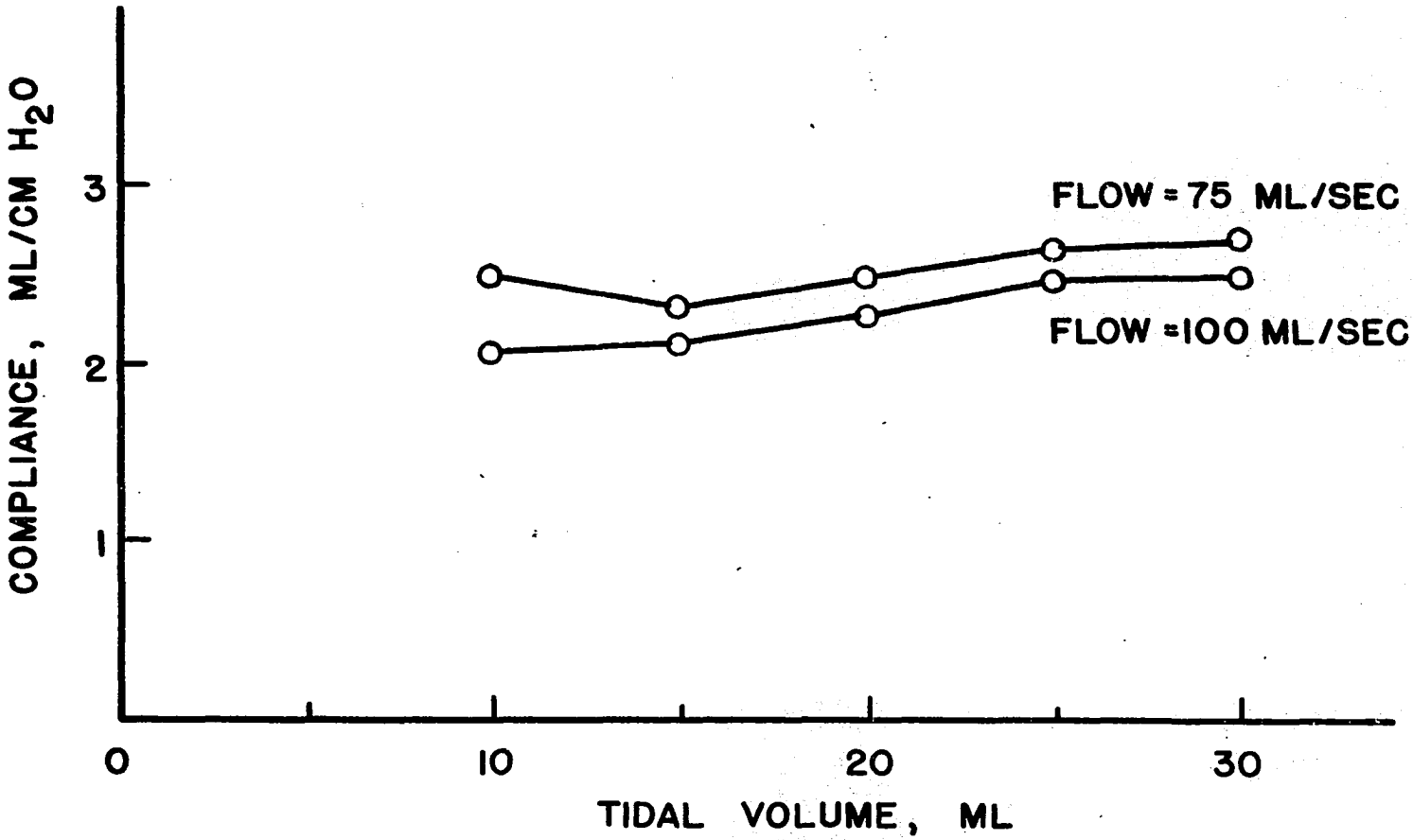


FIGURE 8 TOTAL COMPLIANCE AS OBSERVED DURING AUGMENTED RESPIRATION

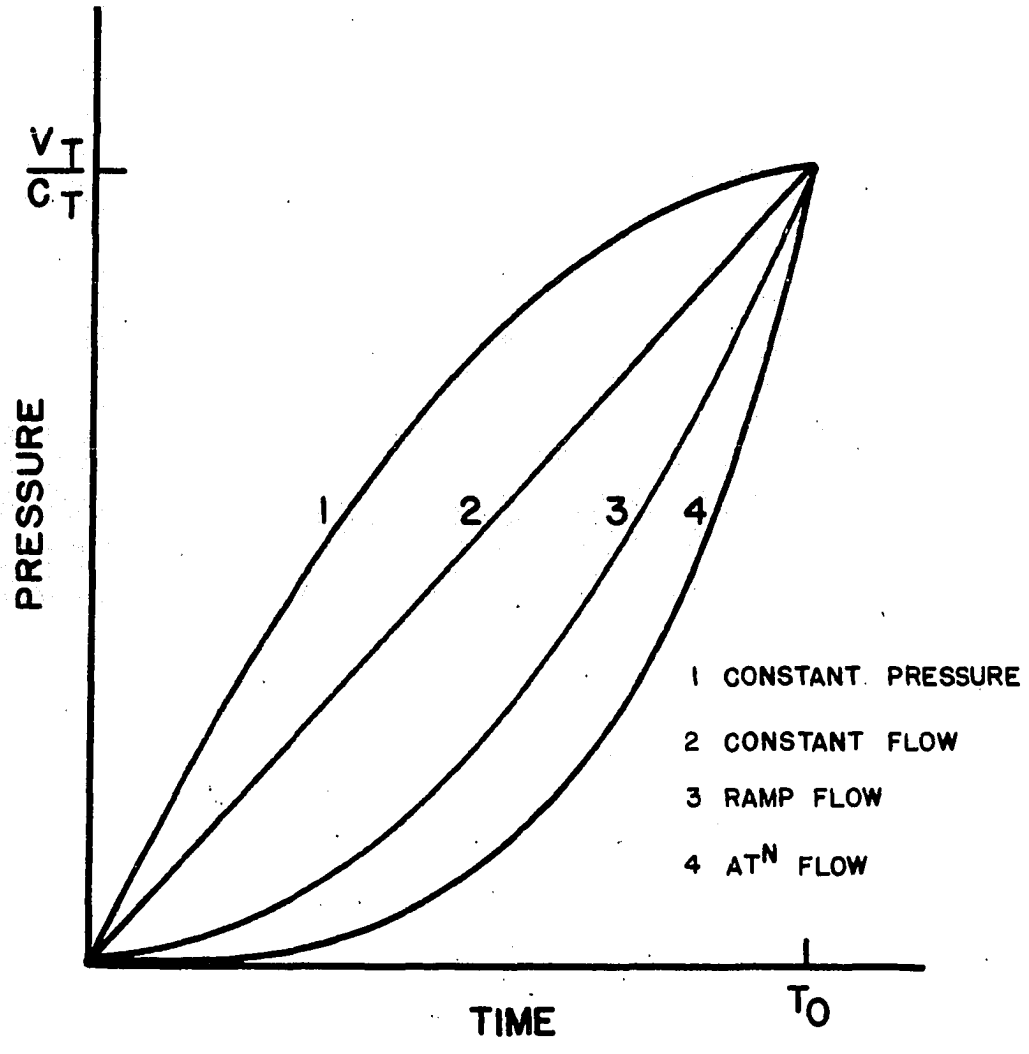


FIGURE 9 PLEURAL PRESSURE PRODUCED BY ARTIFICIALLY INDUCED RESPIRATION

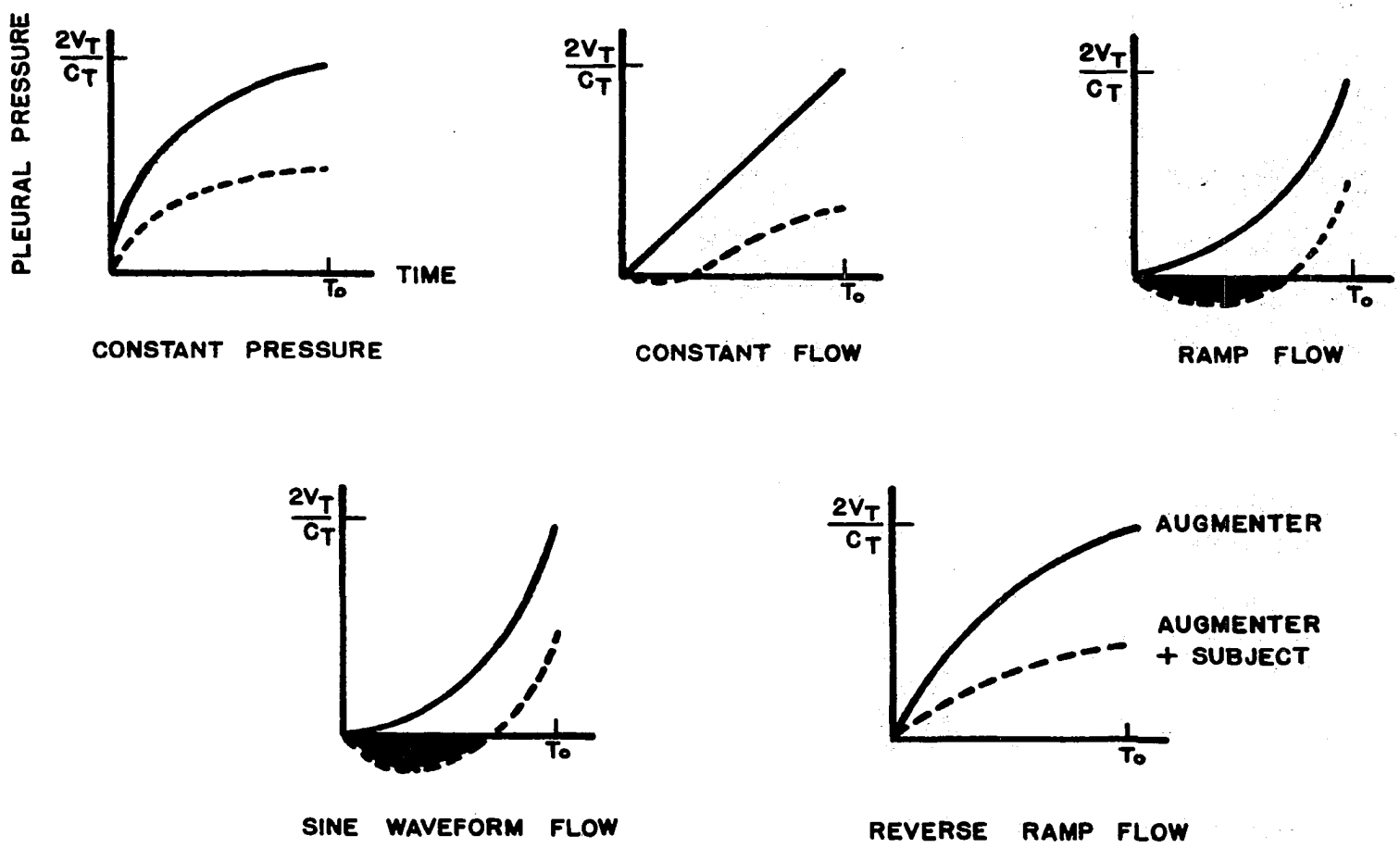


FIGURE 10 PLEURAL PRESSURES PRODUCED BY VARIOUS AUGMENTATION FLOW WAVEFORMS

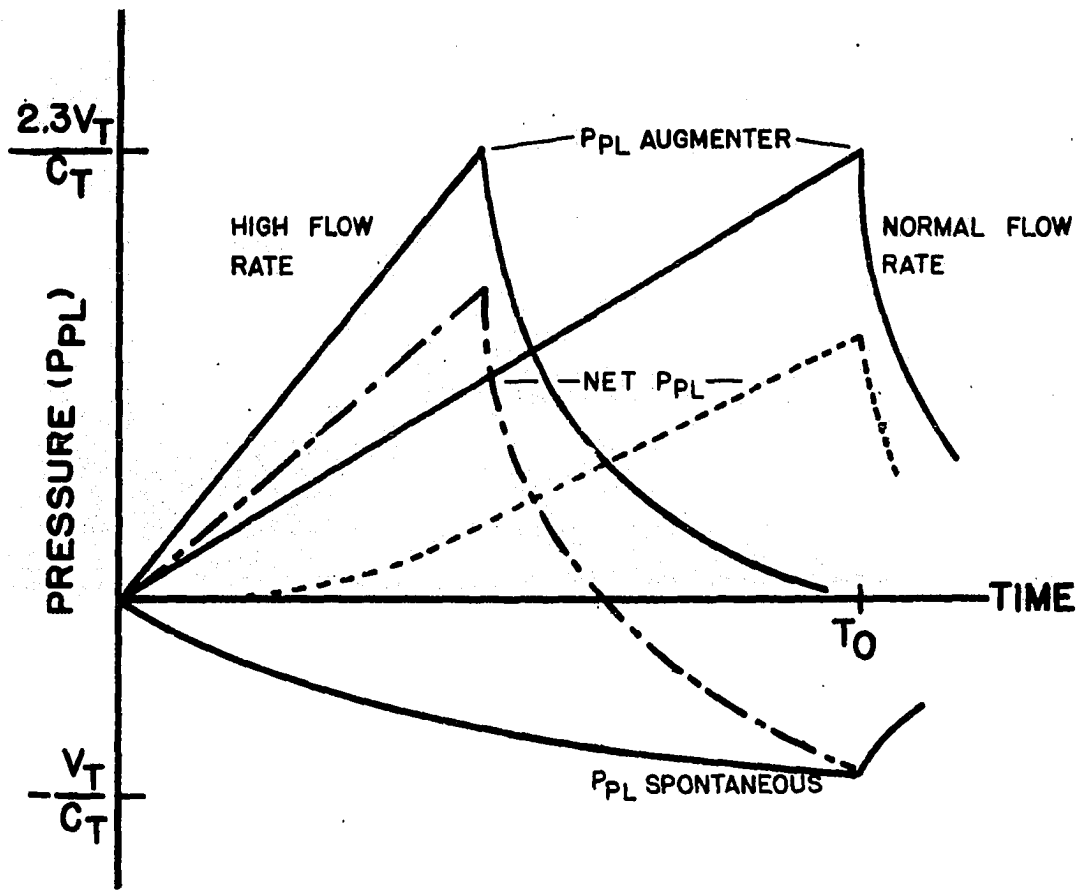
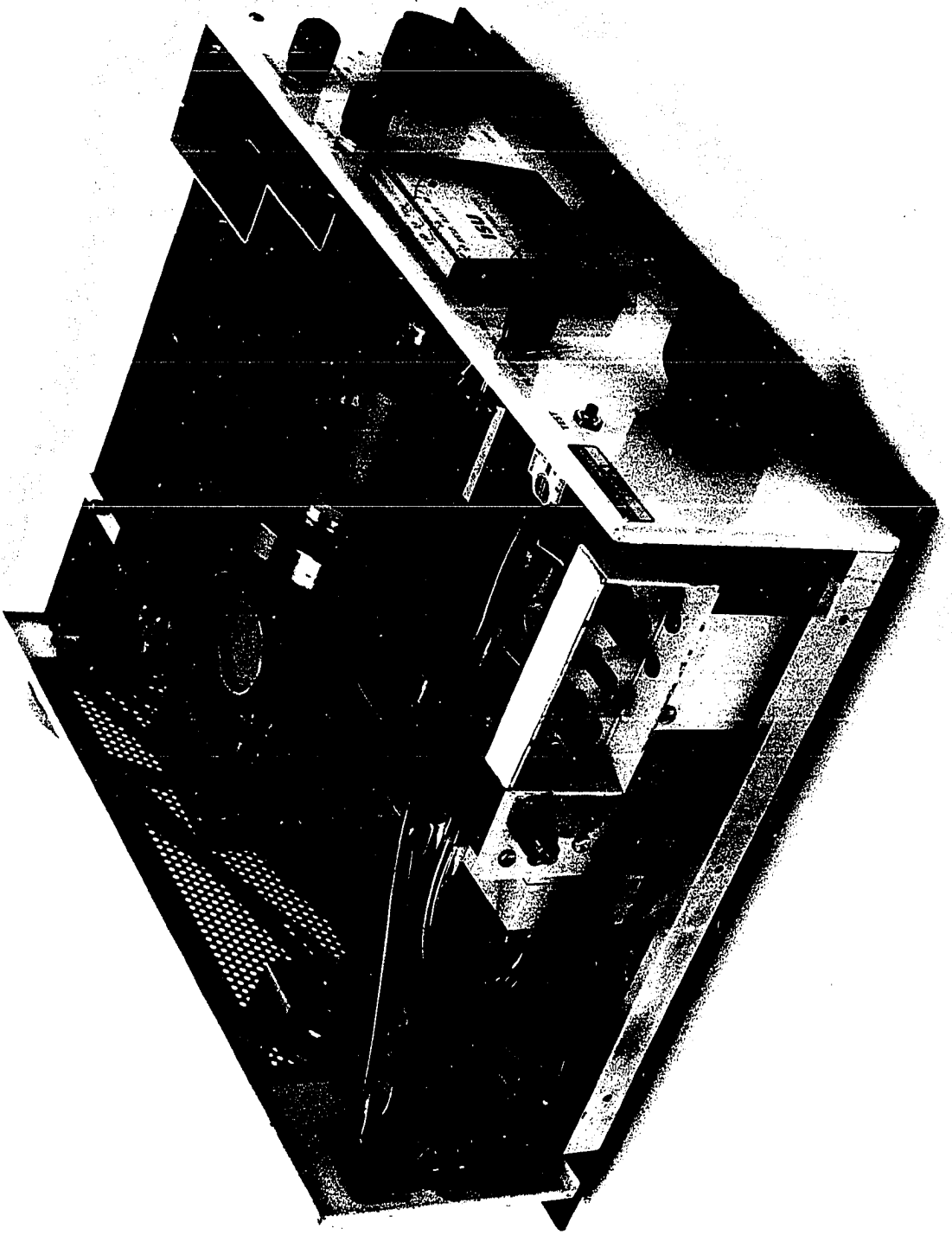


FIGURE 11 COMPONENTS OF PLEURAL PRESSURE OBSERVED DURING INSPIRATION

Figure 12 Respiratory augmenter with top cover removed



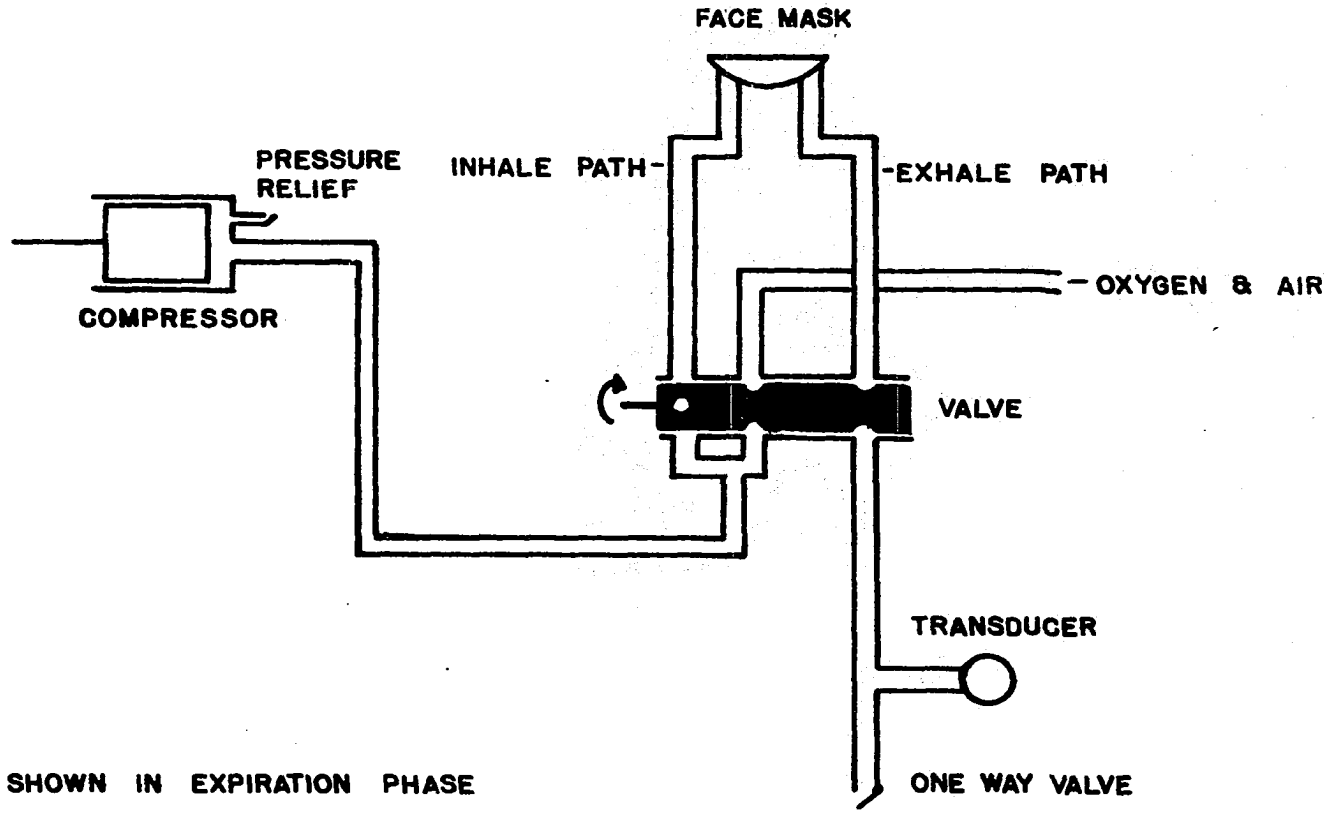


FIGURE 13 AUGMENTER PNEUMATIC CIRCUIT

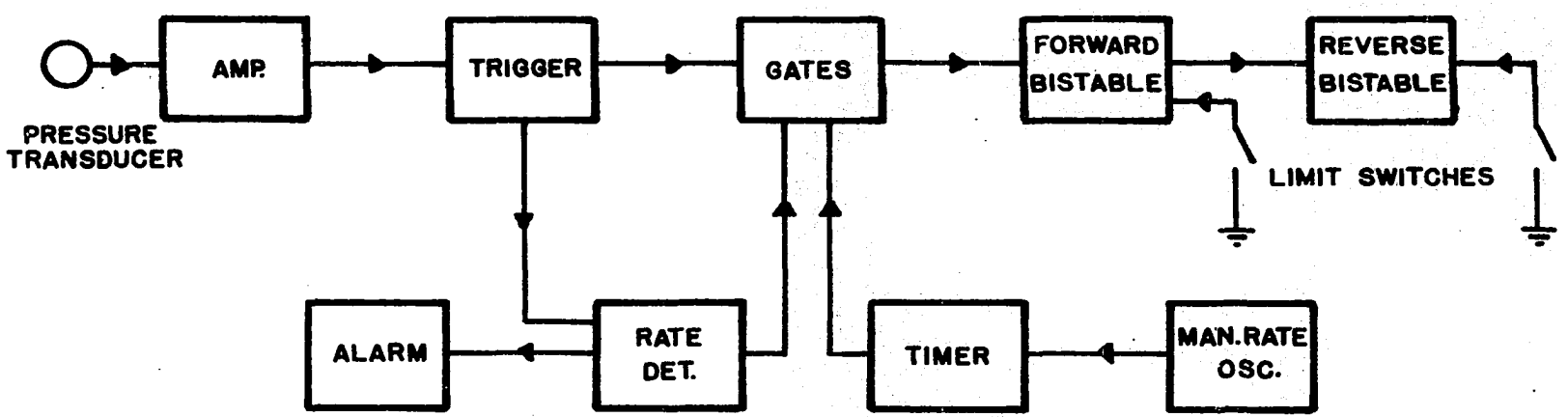


FIGURE 14 AUGMENTER ELECTRICAL BLOCK DIAGRAM

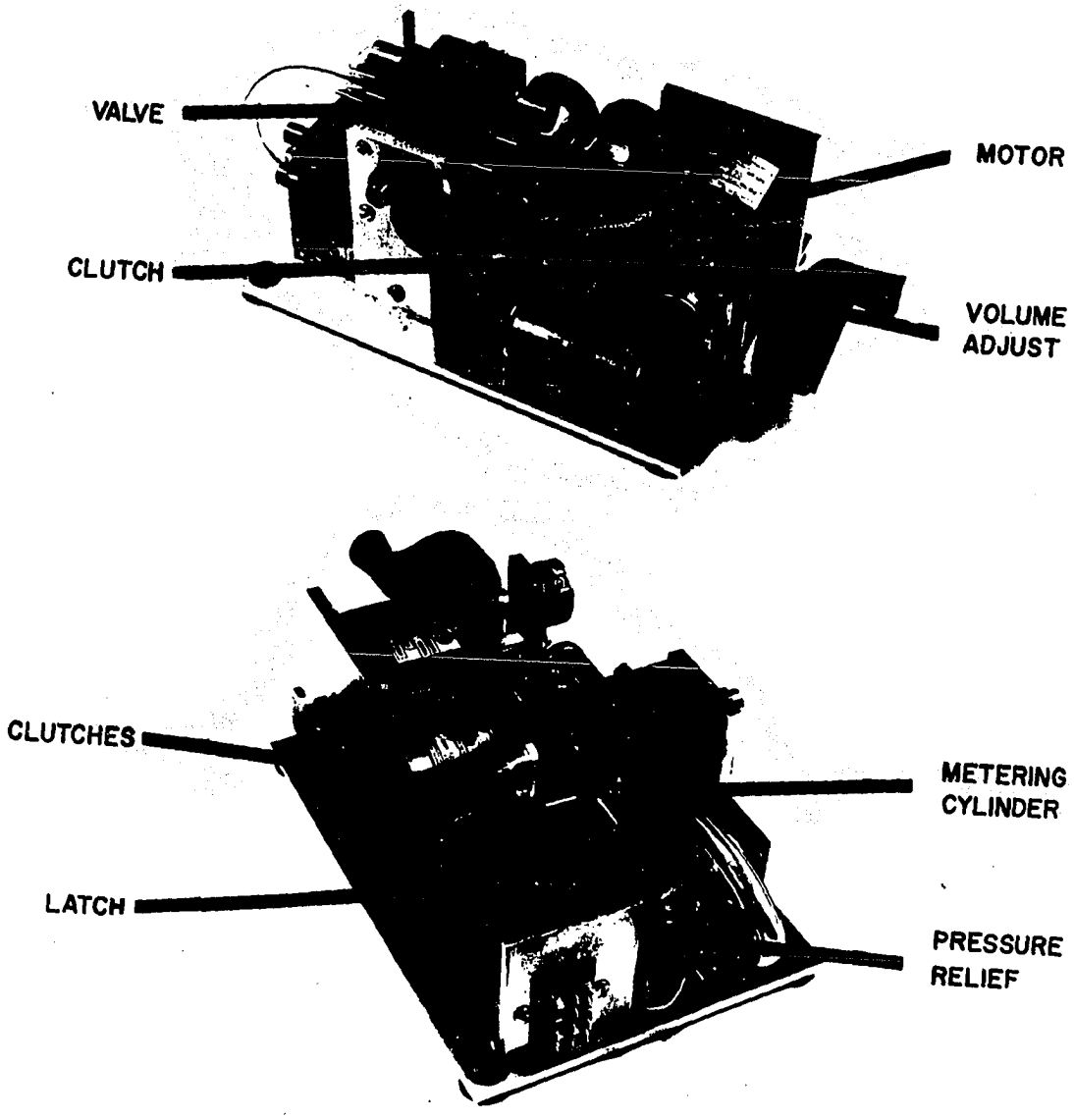


FIGURE 15 AUGMENTER MECHANICAL SYSTEM

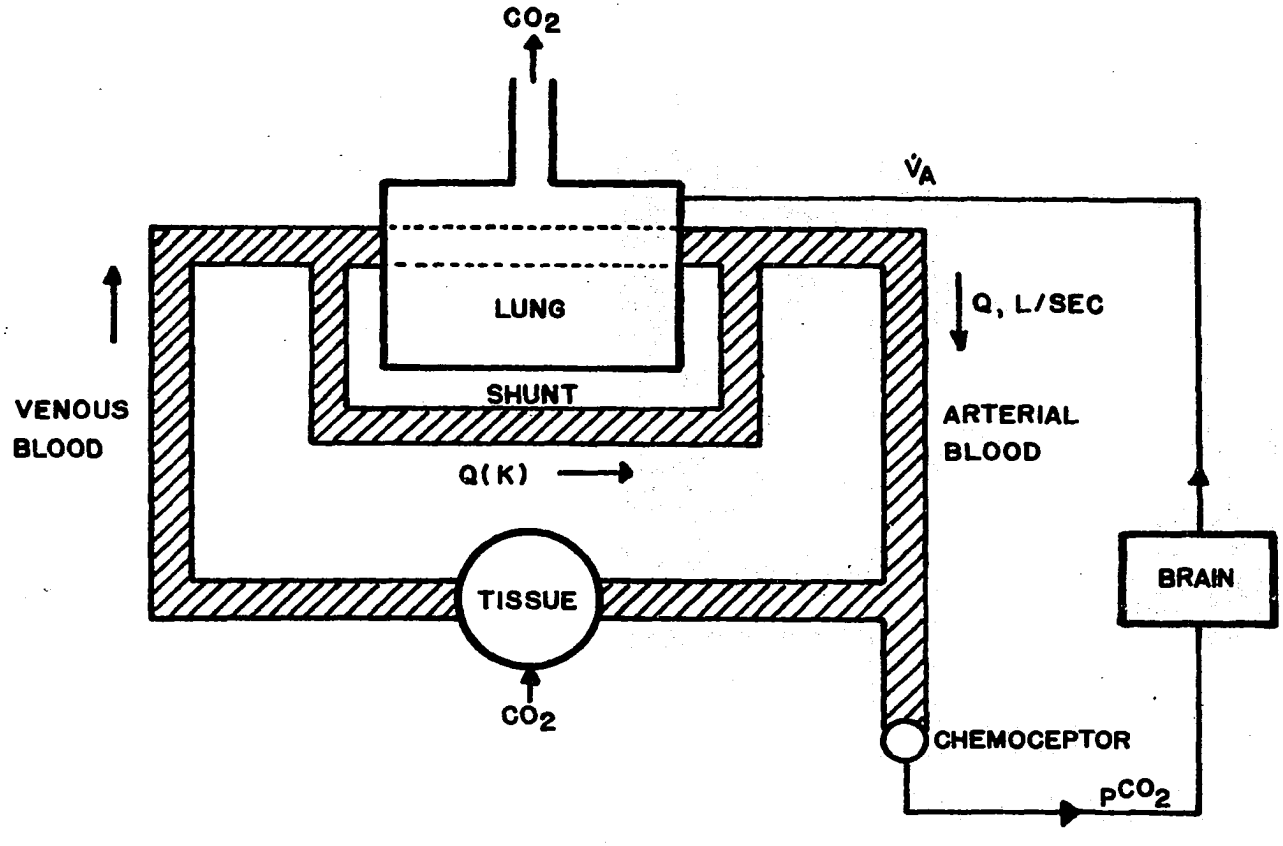


FIGURE 16 CO_2 ELIMINATION MODEL DIAGRAM

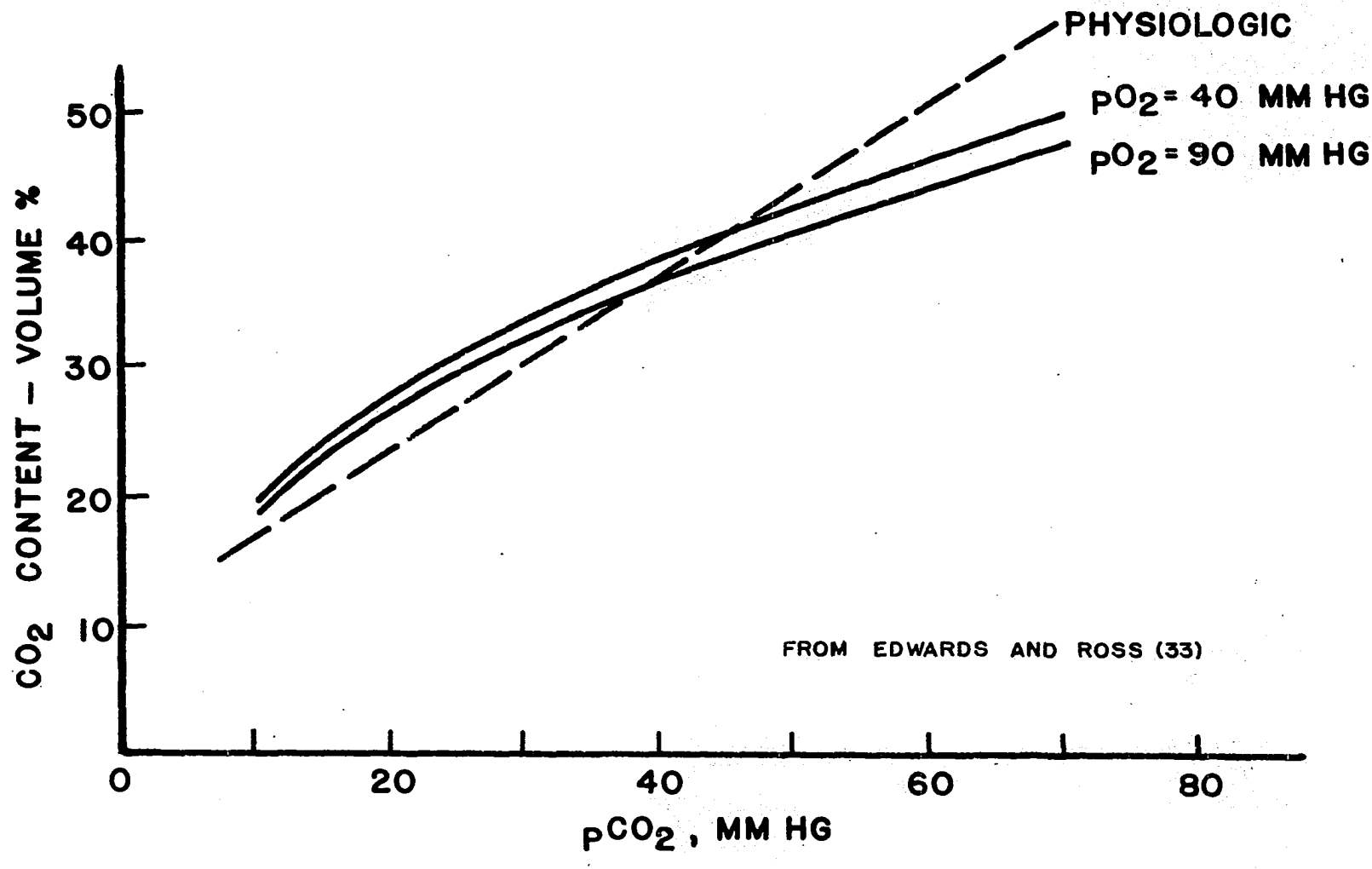


FIGURE 17 NEONATAL BLOOD CO_2 DISSOCIATION CURVES

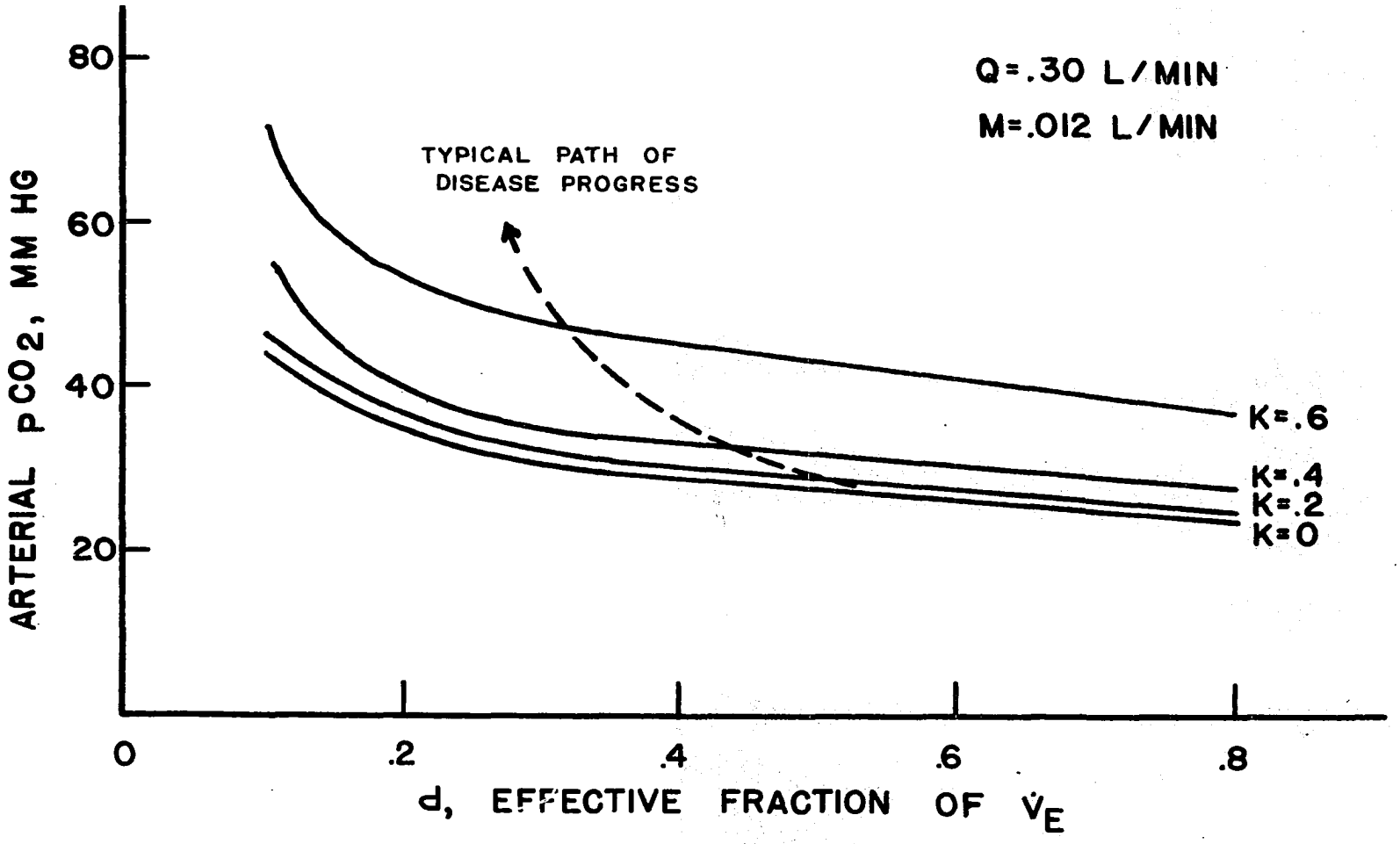


FIGURE 18 STEADY STATE ARTERIAL P_{CO_2}

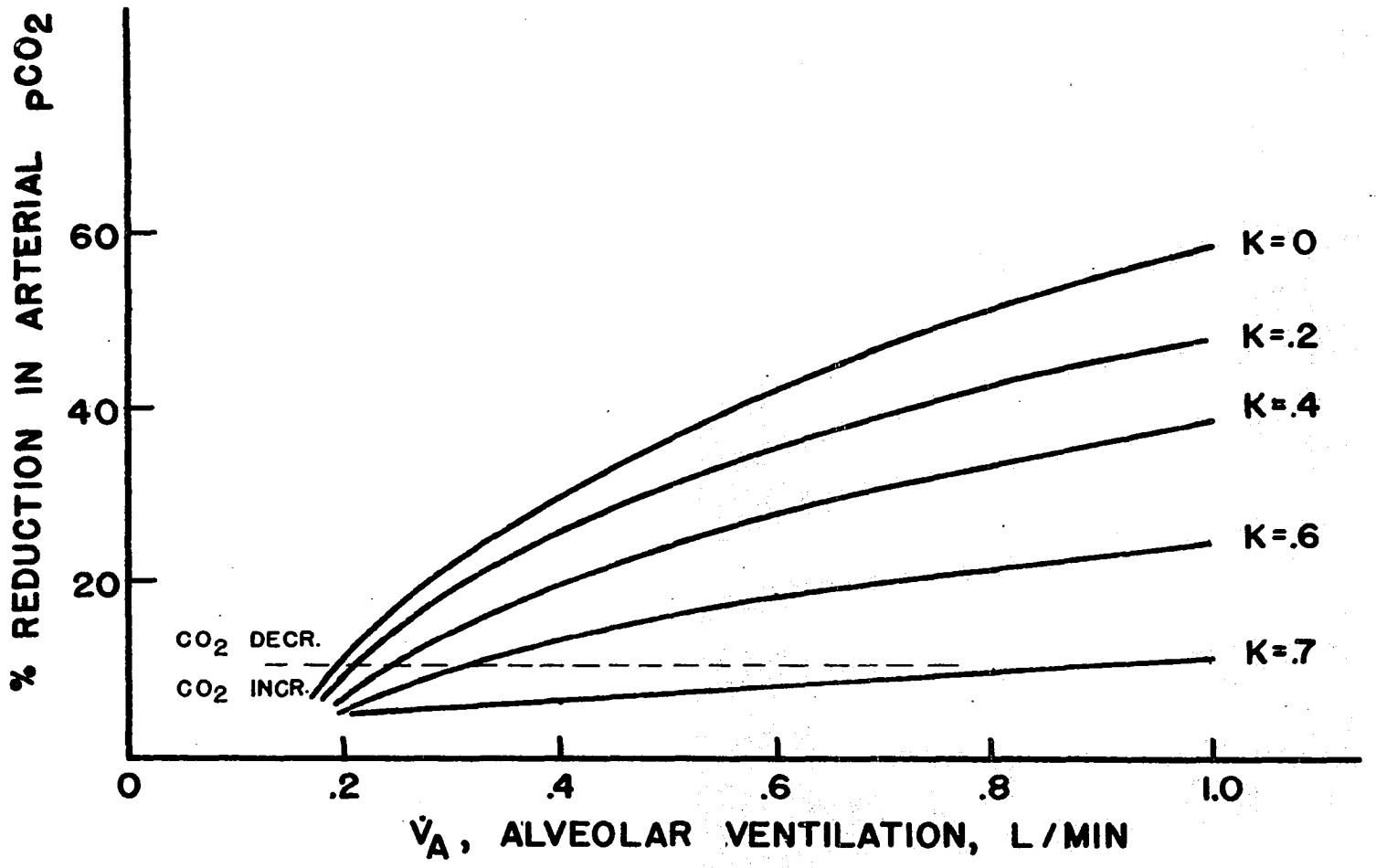


FIGURE 19 POTENTIAL RESPIRATORY SYSTEM EFFICIENCY

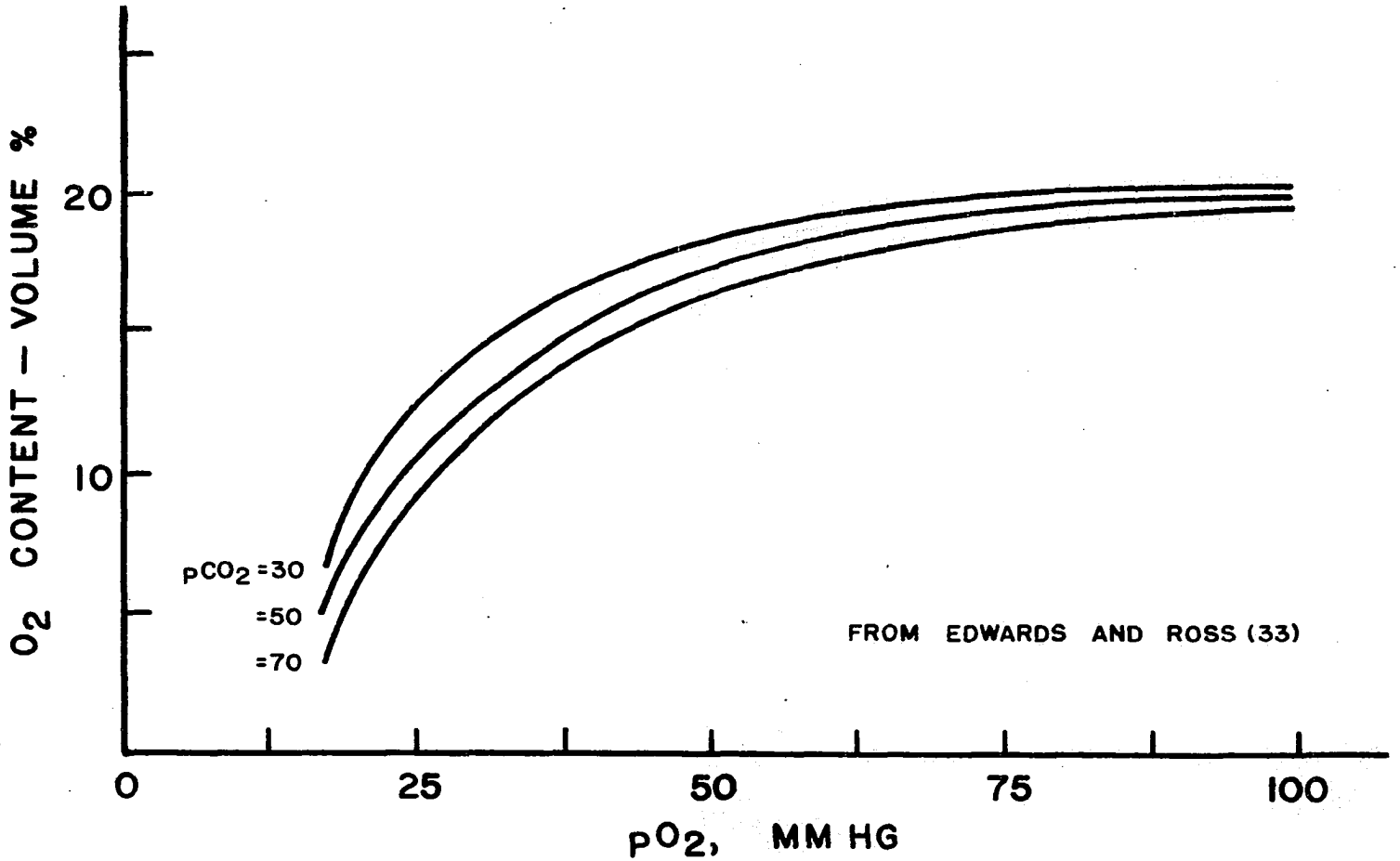


FIGURE 20 NEONATAL BLOOD O_2 DISSOCIATION CURVES

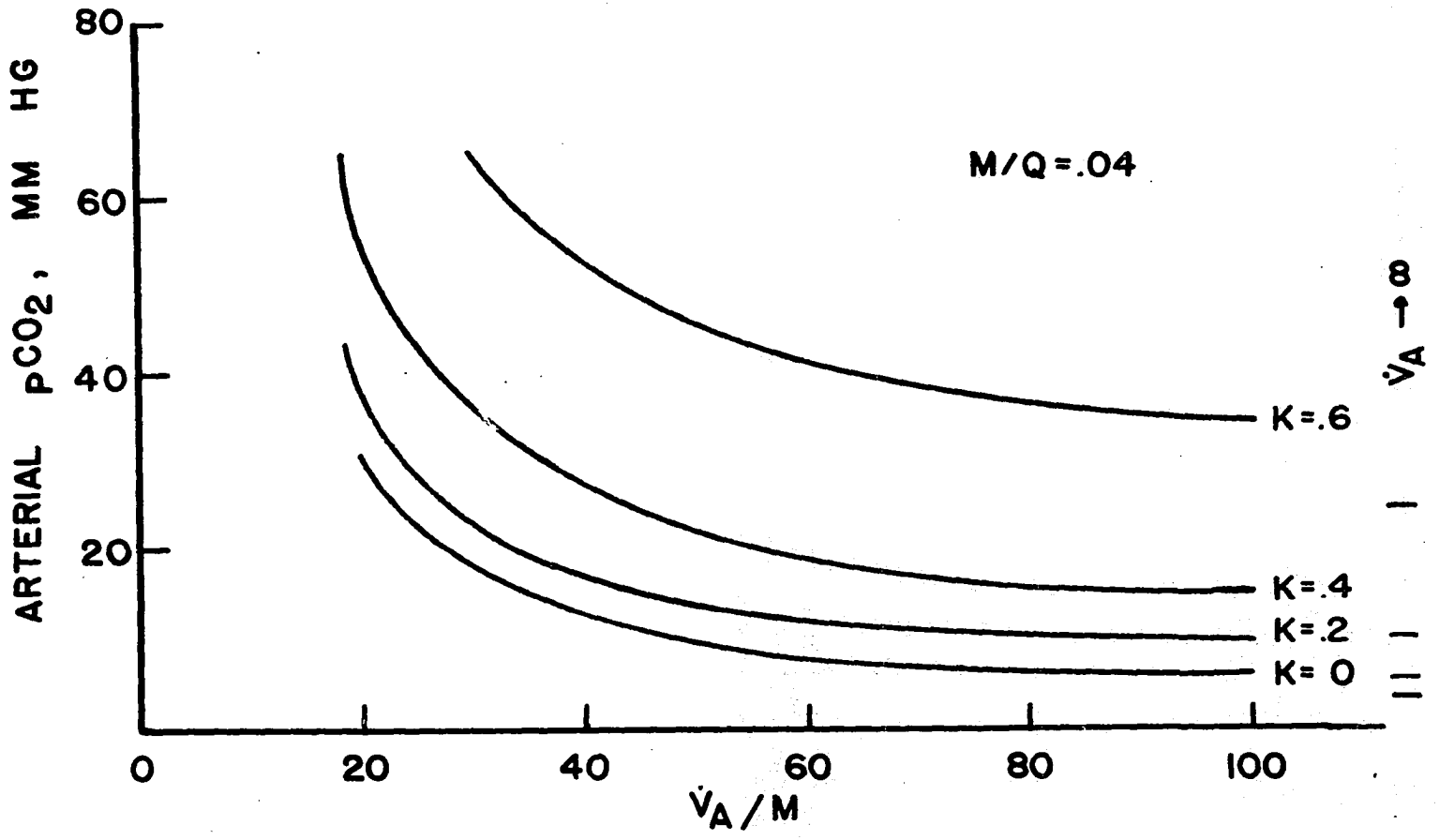


FIGURE 21 ULTIMATE ARTERIAL pCO_2 (AUGMENTED RESPIRATION)

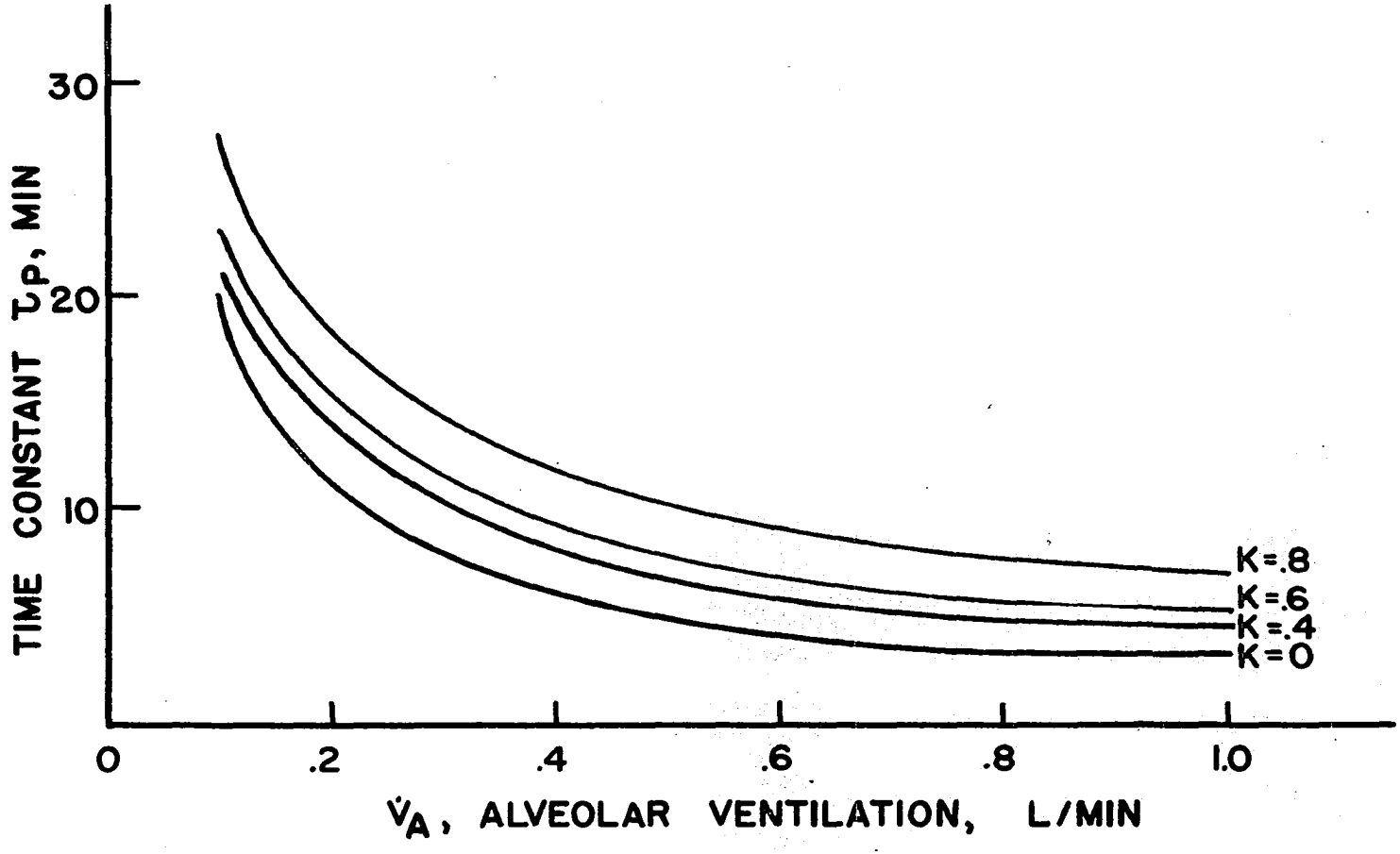


FIGURE 22 TISSUE CO_2 ELIMINATION TIME CONSTANT

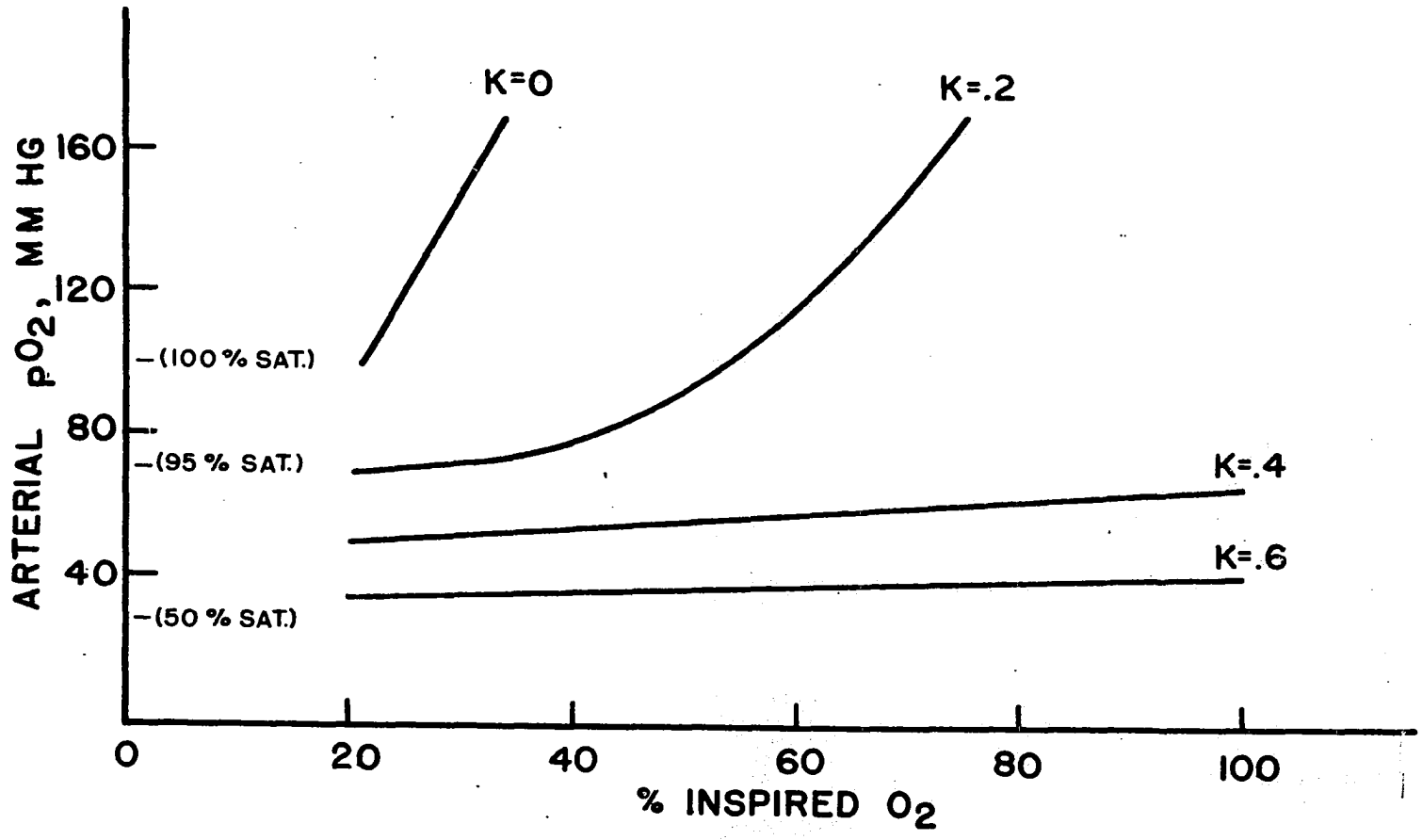


FIGURE 23 ARTERIAL pO_2 AS A FUNCTION OF INSPIRED O_2 CONCENTRATION

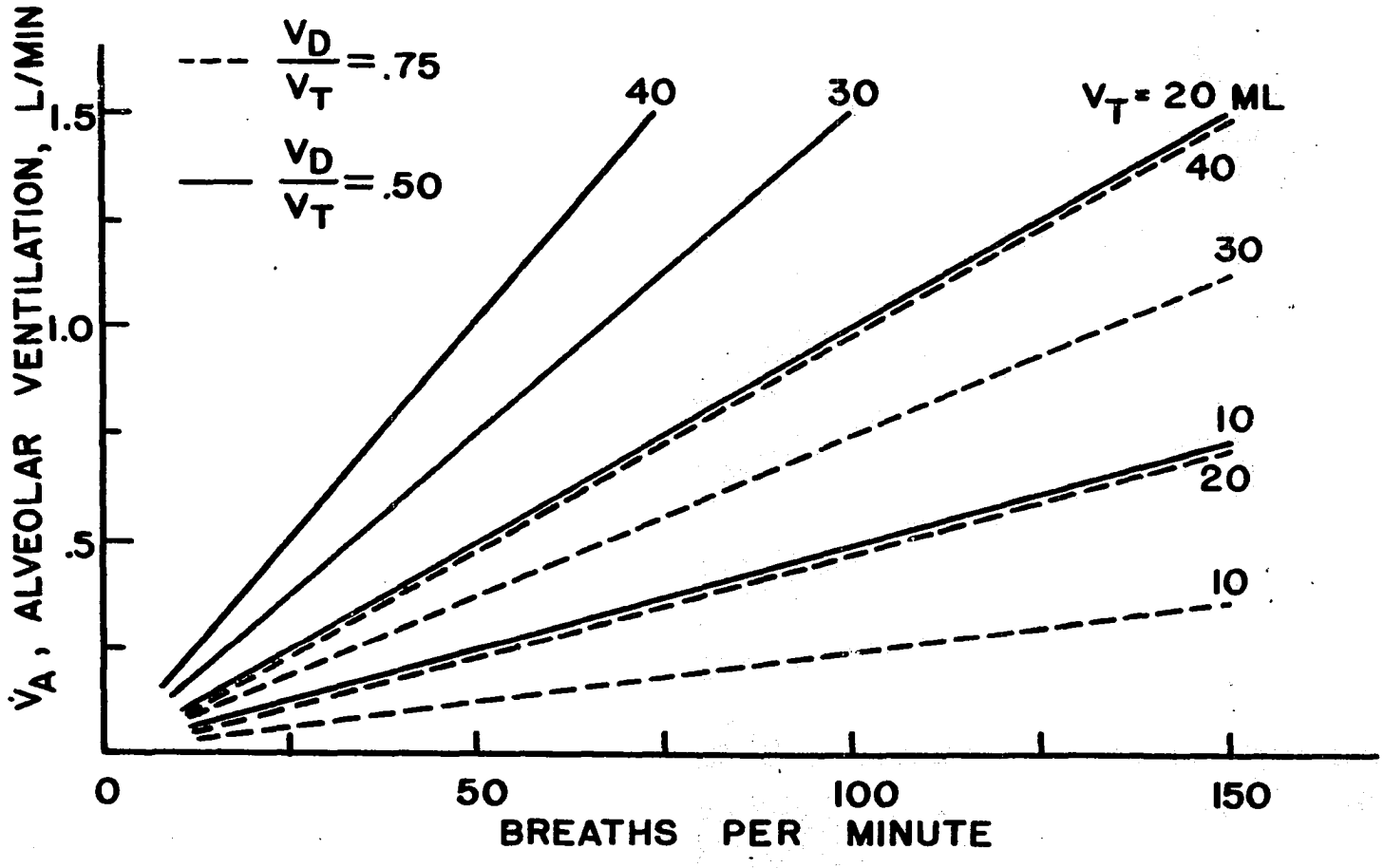


FIGURE 24 ALVEOLAR VENTILATION AS A FUNCTION OF AUGMENTER OUTPUT

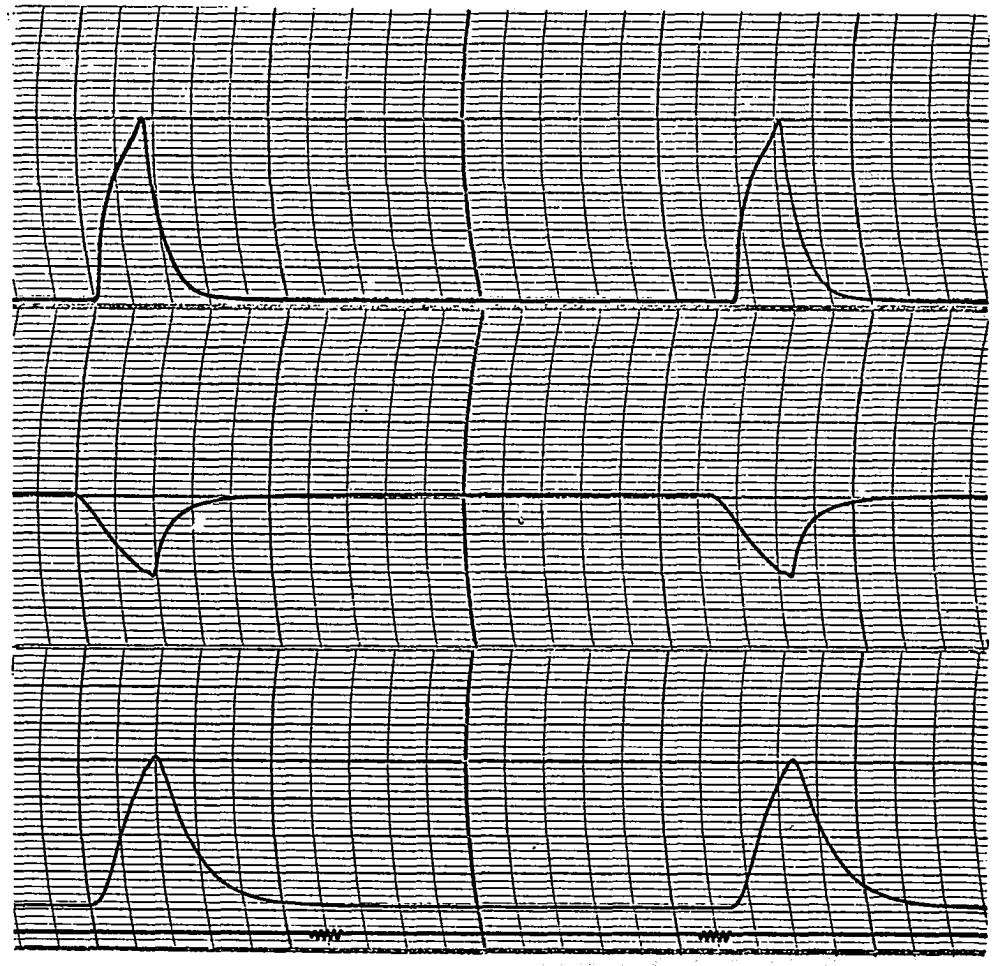


FIGURE 25 SIMULATED PULMONARY PRESSURES PRODUCED BY RESPIRATORY AUGMENTATION

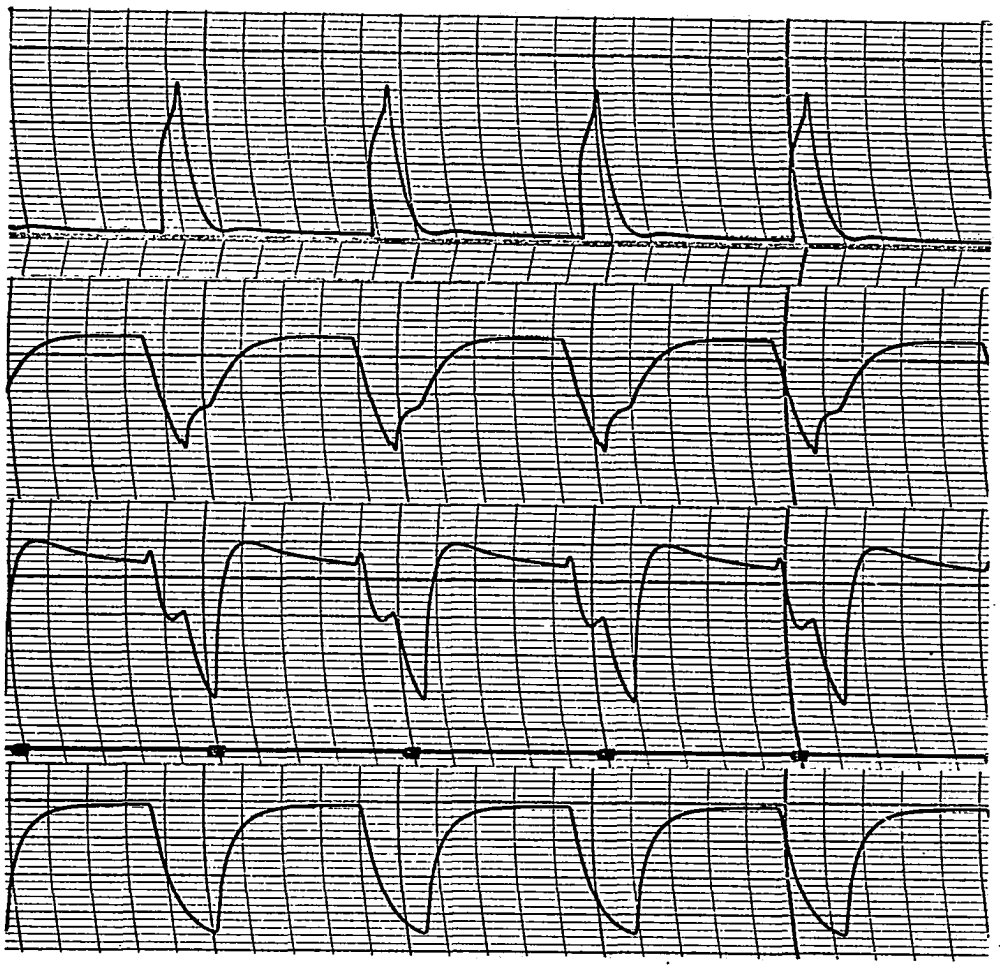


FIGURE 26 SIMULATED PULMONARY PRESSURES PRODUCED BY RESPIRATORY AUGMENTATION

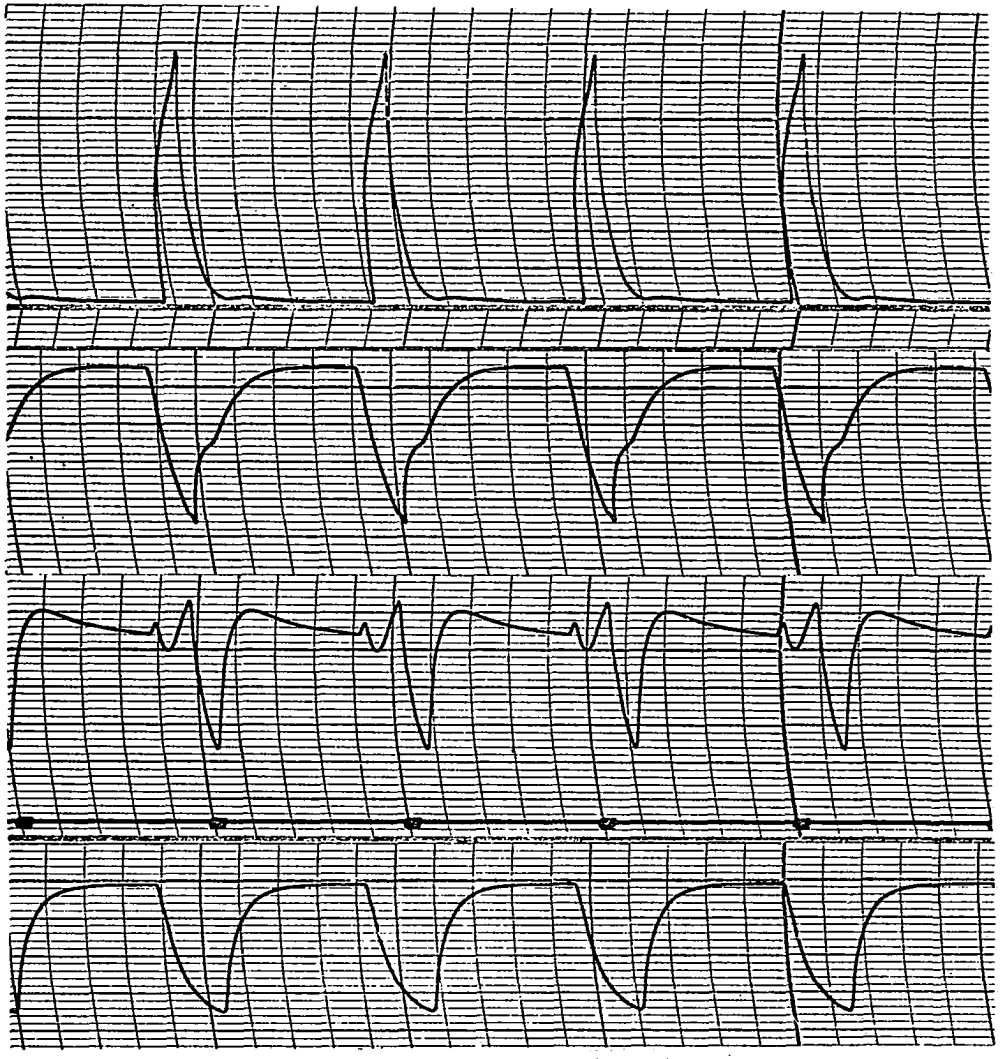


FIGURE 27 SIMULATED PULMONARY PRESSURES PRODUCED BY RESPIRATORY AUGMENTATION

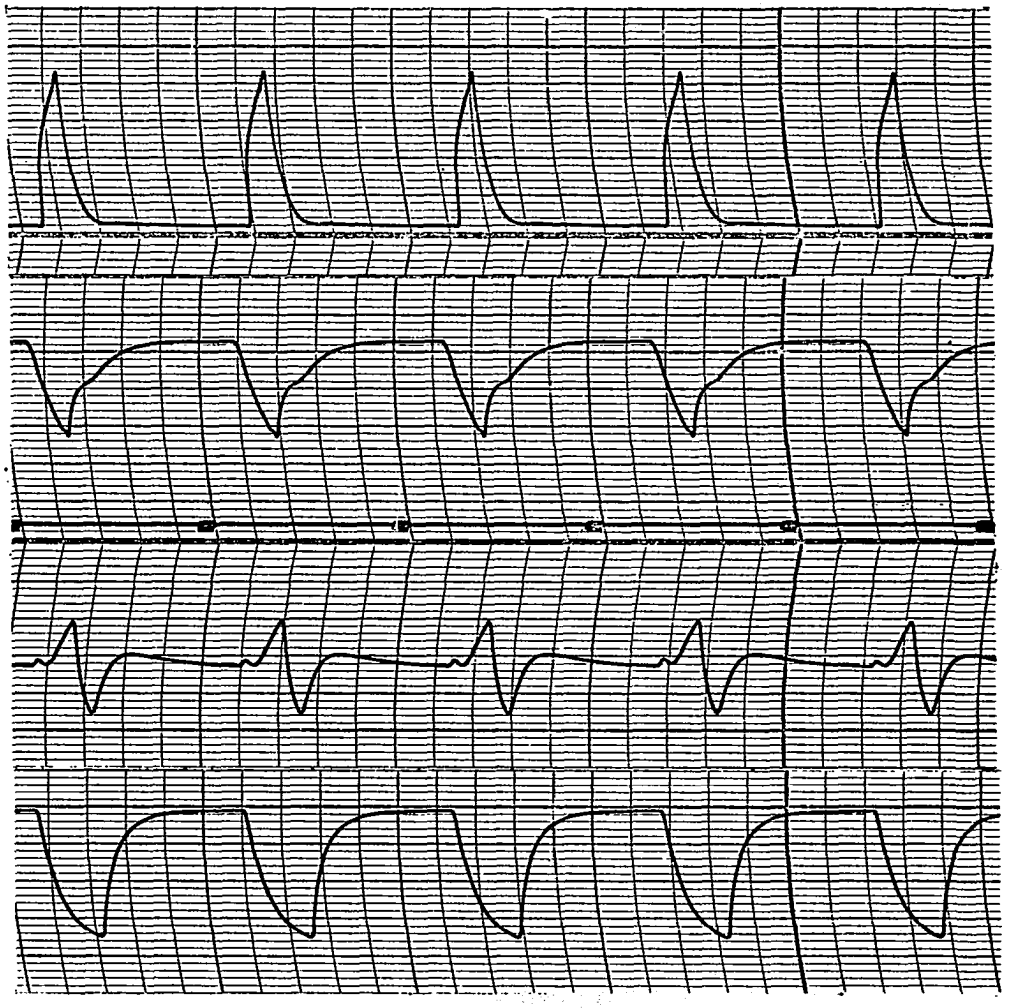


FIGURE 28 SIMULATED PULMONARY PRESSURES PRODUCED BY RESPIRATORY AUGMENTATION

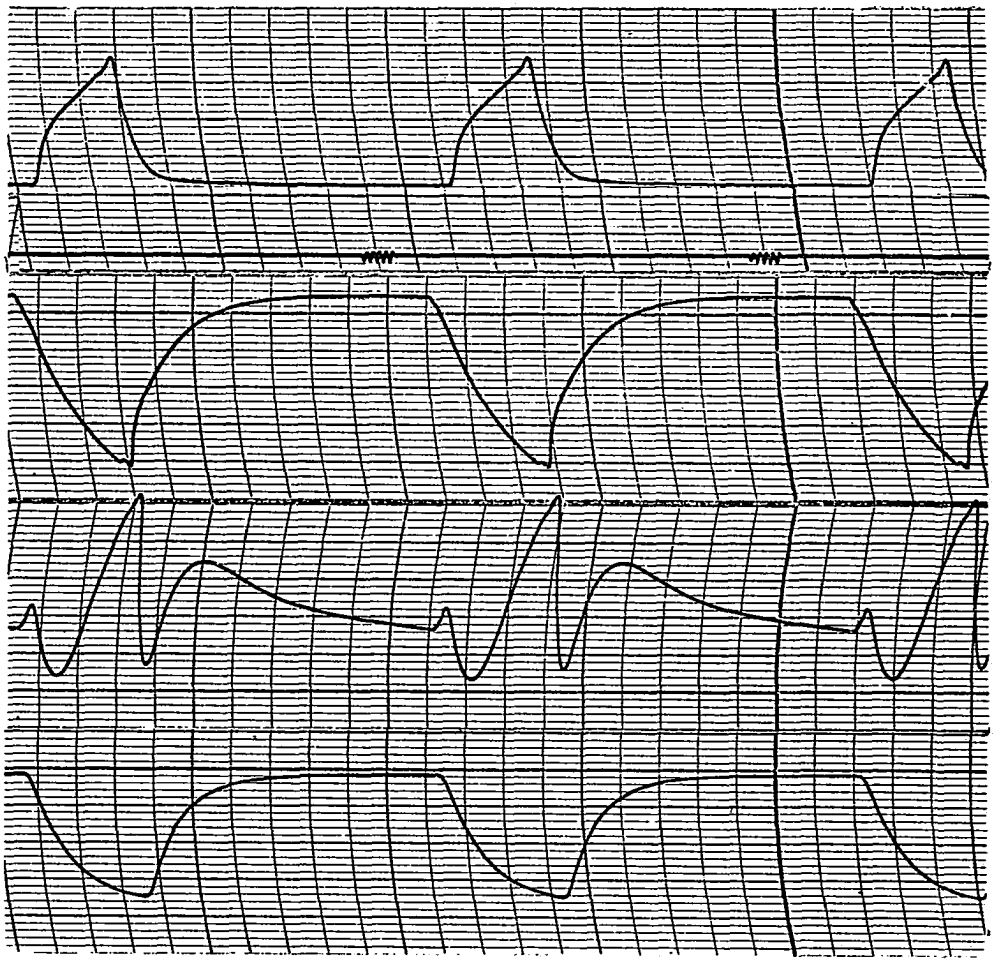


FIGURE 29 SIMULATED PULMONARY PRESSURES PRODUCED BY RESPIRATORY AUGMENTATION

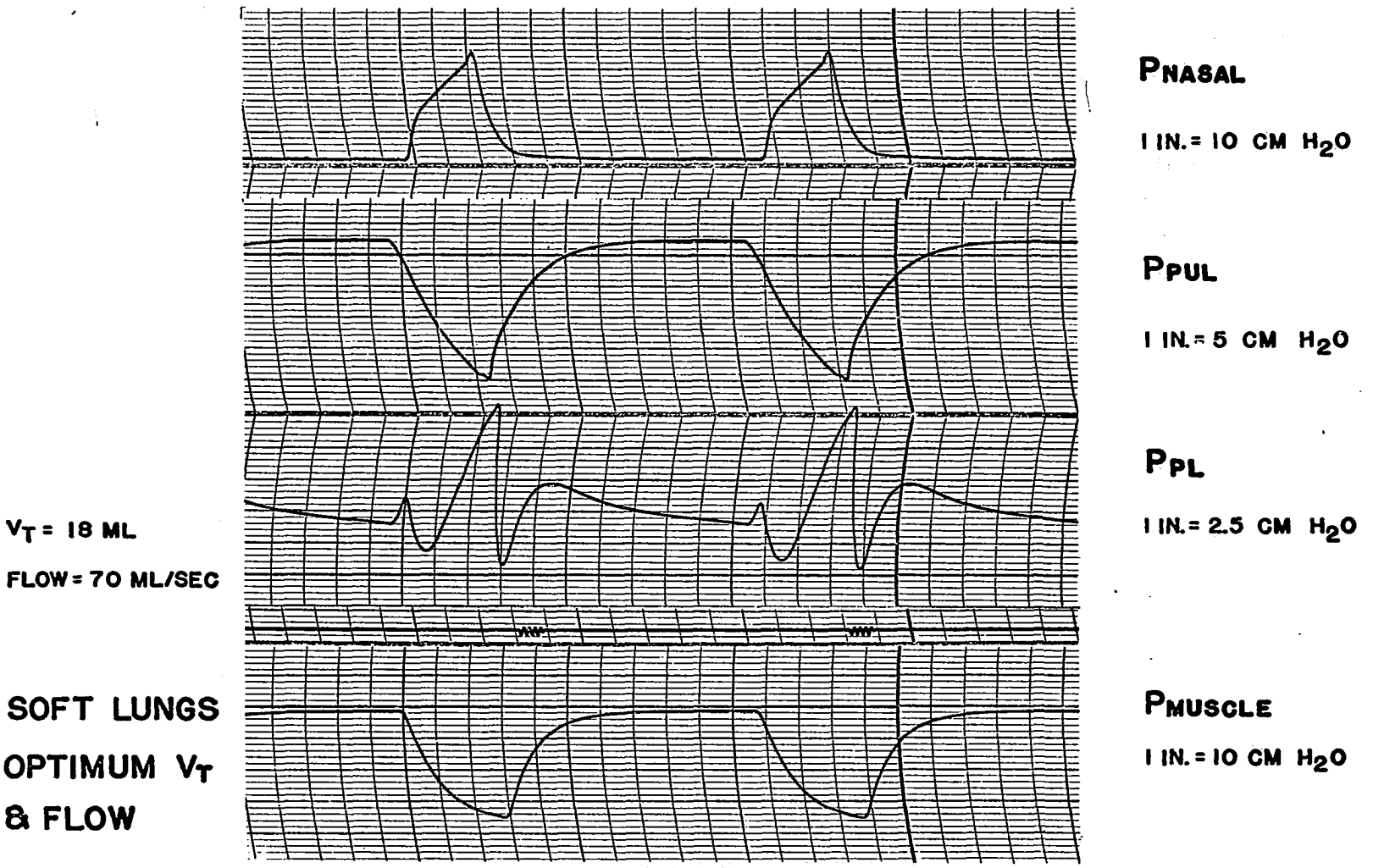


FIGURE 30 SIMULATED PULMONARY PRESSURES PRODUCED BY RESPIRATORY AUGMENTATION

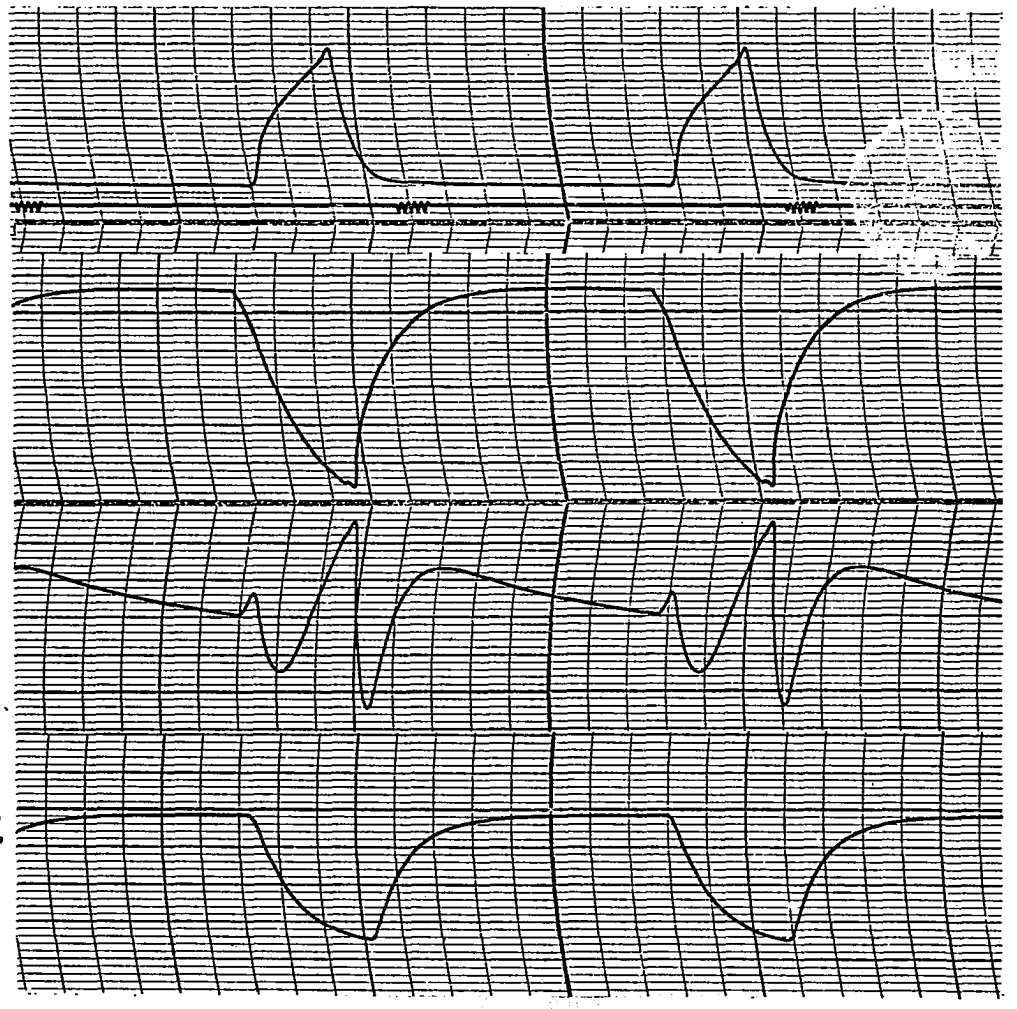


FIGURE 31 SIMULATED PULMONARY PRESSURES PRODUCED BY RESPIRATORY AUGMENTATION

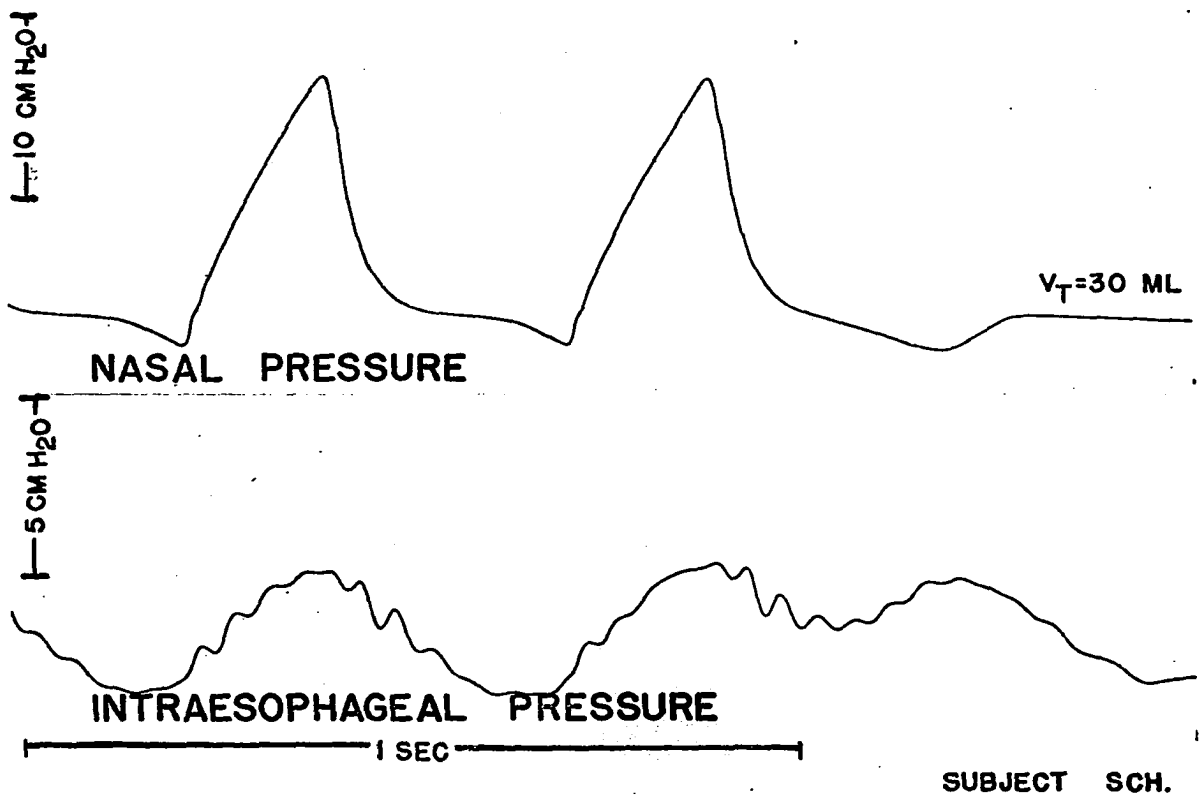


FIGURE 32 PRESSURES OBSERVED IN A DISTRESSED INFANT DURING RESPIRATORY AUGMENTATION

TABLES

Table 1. Cardiopulmonary parameters of newborn infant[a]

Parameter	Healthy infant	Distressed infant[b]
Respiratory rate	35 b/min	70 b/min
Lung compliance, C_l	5 ml/cm H_2O	2 ml/cm H_2O
Thorax compliance, C_t	5 ml/cm H_2O	
Airway resistance, R_a	30 cm H_2O/l/sec	
Mass of gas in airway, M_a	.013 cm H_2O/l/sec^2	
Tidal volume, V_t	12 ml	10 ml
Dead space, V_d	4 ml	6 ml
Cardiac output, Q	.30 l/min	
Metabolic output, M	.012 l/min	
Equivalent tissue volume, V_T	2.0 l	
Lung volume (F.R.C.), V_L	80 ml	45 ml

[a]Average for 2.5 kg premature infant.

[b]Where not given, values are either the same as for healthy infants or unknown.