

TO MY WIFE FROSSO
and
MY CHILDREN, MENELAS and SONIA

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ASPECTS OF PULMONARY MECHANICS IN HEALTH AND DISEASE

by

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ABSTRACT

The morphology of integrated phrenic electroneurogram (E_{PHR}) and of tracheal (P_T) and transdiaphragmatic pressure (P_{di}) waves as well as the interrelationship between these variables was studied in cats breathing room air and different hypercapnic or hypoxic mixtures.

The shape of E_{PHR} , P_T and P_{di} during occluded inspiratory efforts varied considerably between animals from convex to concave but in each animal it remained unchanged by hypercapnia and hypoxia. The shape of P_T and P_{di} occlusion waves reflected that of E_{PHR} . The fixed relationship of E_{PHR} with P_{di} and P_T indicated a proportional increase in activity among all inspiratory muscles with increased chemical drive. The constant relationship between E_{PHR} and transdiaphragmatic pressure, $P_{di}(mus)$, during room air breathing, hypoxia and hypercapnia suggests that the pressure losses due to the force-velocity relationship of the diaphragm are negligible in cats. A substantial volume-related decrease in $P_{di}(mus)$ indicated that at higher lung volumes the effectiveness of the diaphragm as pressure generator decreases.

Increased level of anesthesia had no effect on the morphology of occluded and unoccluded E_{PHR} , P_T

and Pdi waves and on their interrelationships suggesting that the anesthetic used (pentobarbital sodium) had no effect on diaphragmatic neuromuscular transmission) and on the effectiveness of the diaphragm to produce pressure, until the death of the animal. Increased anesthetic dose depressed in the same proportion the rate of rise of E_{PHR} , Pdi and V, while the mechanical properties of the respiratory system remained unchanged. Increasing pentobarbital dose appears to mimic specifically reductions in the input from the chemoreceptors.

A model was developed taking into consideration the shape of the time course of the respiratory driving pressure waves in order to explain discrepancies between phrenic activity or airway occlusion pressures and spirometric measurements.

In humans, the rate of change of mouth occlusion pressure at the onset of inspiration was significantly related to work loads during muscular exercise, indicating that mouth occlusion pressure is a useful index of respiratory "centres" output.

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X u.

SYMBOLS AND ABBREVIATIONS

C	Compliance
C ₅	Fifth cervical root of phrenic nerve
CIA	Central inspiratory activity
CO ₂	Carbon dioxide
CNS	Central nervous system
ΔP_{ga}	Difference between active and relaxed gastric pressure
ΔP_{ga}^o	Same as above during occlusion
dP/dt	Rate of change of pressure (used as rate of change of mouth occlusion pressure in Chapter V).
E _L	Elastance of the lung
EMG	Electromyogram
ENG	Electroneurogram
E _{PHR}	Electroneurogram of phrenic nerve
E _{PHR} ^o	Electroneurogram of phrenic nerve during occlusion
E _{rs}	Passive elastance of the respiratory system
E _{rs} '	Effective elastance of the respiratory system
E _w	Elastance of the chest wall
f	Respiratory frequency
FEV _{1.0}	Forced expiratory volume at 1 sec
FI _{O2}	Inspired oxygen concentration
FRC	Functional residual capacity
FVC	Forced vital capacity

Ht	Height
i.p	Intraperitoneal
i.v.	Intravenous
I.C.	Inspiratory capacity
kPa	Kilopascal
log	Logarithm
N ₂	Nitrogen
O ₂	Oxygen
P _{ACO₂}	Alveolar partial pressure of carbon dioxide
P _{di}	Transdiaphragmatic pressure
P _{di} ⁰	Transdiaphragmatic pressure during occlusion
P _{di(mus)}	Active transdiaphragmatic pressure (net pressure developed by the diaphragm during spontaneous breathing).
P _{es}	Esophageal pressure
P _{ga}	Gastric pressure
P _m	Mouth pressure
P _T	Tracheal pressure
P _T ⁰	Tracheal pressure during occlusion
P _x	Pressure at time x

R_{aw}	Airway resistance
R_l	Pulmonary flow resistance
r_s	Respiratory system
R_{rs}	Resistance of the respiratory system
R'_{rs}	Effective resistance of the respiratory system
RV	Residual volume
$sGaw$	Specific airway conductance
τ	Time constant
T_I	Time of inspiration
T_E	Time of expiration
T_T	Total duration of the breathing cycle
TLC	Total lung capacity
V	Volume
$\dot{V}$	Flow
$\bar{\dot{V}}$	Instantaneous mean flow
$\dot{V}_A$	Alveolar ventilation
$\dot{V}_E$	Minute ventilation
V_T	Tidal volume
V_T/T_I	Mean inspiratory flow
V_{tg}	Thoracic gas volume
V_x	Volume at time x
Wt	Weight

PROLOGUE

This thesis is divided into six Chapters. The introduction or Chapter I deals with the evolution of ideas leading to the present work, including a review of the literature and bibliography. Chapters II, III and IV describe animal experiments and Chapter V studies on humans.

In Chapter II the morphology of the phrenic electrical activity and that of the respiratory pressure waves during occlusion (static) in cats, is discussed.

In Chapter III, the relationship between phrenic activity, respiratory pressures and spirometric variables during spontaneous breathing (dynamic) in cats is described.

In Chapter IV, the effect of increased levels of anesthesia (pentobarbital sodium) on the respiratory output is discussed.

In Chapter V, the non-invasive methods used in the animal experiments were applied to humans, during muscular exercise.

Chapter VI provides the concluding remarks.

In Chapters II, III, IV and V a list of specific references is included.

CHAPTER I

INTRODUCTION

I.I. GENERAL CONCEPTS

The main function of the respiratory system is to provide an adequate supply of O_2 to the body in order to match its oxygen demands and to remove the produced CO_2 . Since there are continuous and quite often substantial alterations in the metabolic demands of the body, the respiratory system has to adjust its activities in such a way that the internal environment is kept constant. This implies a well organized control system. In a modern cybernetic analysis this system could operate through a homeostatic feedback loop or loops. Although the idea of homeostasis is a very old one, first stated by the famous Greek physician Hippocrates (460-360 BC) (1,2) it was Claude Bernard who made his theory of constant "milieu intérieur" the basic principle of modern homeostasis (3). However, it was much later in 1950 following the publication of the influential book of Norbert Wiener "Cybernetics" that the general idea of "negative feedback loop" was introduced to biological systems and applied in respiration (4-8).

In a feedback loop system analysis, the part that collects and integrates information about the function of the system, and accordingly modifies its decisions, is called the regulator or controller. In the respiratory system this is usually known as the respiratory "centre" or "centres." The next important

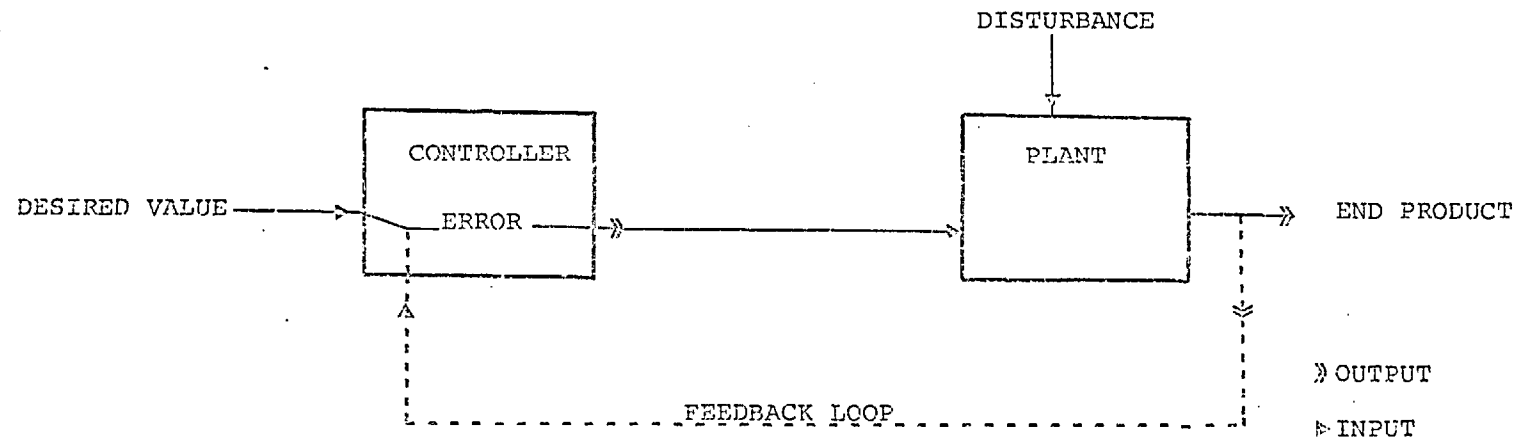


Figure 1: Feedback control system

part or unit of a feedback system is called the controlled unit or the plant. In the respiratory system this is represented by the ventilatory pump. The two major units are connected by a so-called closed loops, or in a feedback fashion. In other words, the output of the controlling system becomes the input of the plant and the output of the plant in its turn is one of the inputs to the controller (Fig.1).

The principal goal of this arrangement is to modify the output of the plant in such a way that the input in the controller be equal or close to some desired value, despite various disturbances that tend to upset this relationship. The controller accomplishes that by comparing the two signals (output of the plant and the desired value) and generating an error signal. Thereafter it translates the error signal into an appropriate controlling signal (output of the controller) in order to modify the output of the plant in the direction to minimize the error signal.

Clearly, there is great complexity in such a feedback loop analysis, especially when it is applied in biological systems (9,11). Thus, the study of all mechanisms involved in the control of breathing is extremely difficult, and for someone like the author who lacks advanced mathematical and neurophysiological background almost impossible.

Hence, the author had limited his investigations

to one part of system, namely the output of the "respiratory centres," the so-called controlling signal.

In other words, the main purpose of this thesis was to study the controlling signal as it leaves the controlling unit (respiratory "centres") and follow it through its various transformations until it is finally translated to an end product (ventilation). Obviously a number of transformations take place, since the signal has to travel down the brainstem to reach the alpha motoneurons and through the peripheral nerves to arrive at the respiratory muscles and cause their activation and contraction. As a result of the contraction of the respiratory muscles, a change in the driving pressure of the ventilatory pump is produced which in turn causes airflow.

Although the present work is focusing only on the pathways that link the controller with the respiratory pump at its end product (ventilation), a brief review of the functions of the other main parts of the system will follow.

I.2. RESPIRATORY CONTROLLER

The first evidence that the central part of the respiratory control system lies outside the actual ventilatory apparatus was provided by Galen (Galinos, AD 130-199). Galen performed spinal transection between the 3-4 cervical vertebrae in animals and observed that breathing ceased immediately.

Therefore, he suggested that some principle travels from the brain through the spinal cord, and next to the nerves to cause a muscle contraction. These were probably the first experiments suggesting that the location of the controller is in the Central Nervous System (CNS) (12,13).

The next important step in the localization of the controller came in the 19th Century when LeGallois showed that breathing would continue even if everything in the CNS above the medulla was removed (14). Shortly after this Flourens in 1858 wrote that he had localized the respiratory "centres" in a tiny area in the medulla which he named "noeud vital" (15). The same investigator showed that this "noeud" is a bilateral structure (16).

Since then a vast quantity of anatomical and physiological information about the "centres" have been accumulated. Important contributions were those of Lumsden in 1923 who defined the pontine pneumotaxic centre, the apneustic centre and the medullary centre (17).

However, from this time on, it became evident that the "centres" could not be regarded as a definite anatomical unit with a precise location and specific ability to generate the respiratory rhythm.

Experiments reported by Gessell in 1936 made quite clear that several parts, widely distributed over the lower brainstem, play a significant role in the genesis of the controlling signal (18).

More recent work produced new evidence that in anesthetized or decerebrated animals there are groups of cells located in the brainstem which are activated synchronously with respiration. Under the above experimental conditions, these neurons have been localized in the nucleus of tractus solitarius (19) and nucleus retroambiguus (20). Recording in these areas have shown that activity starting from zero increases throughout inspiration and stops quite abruptly at end of inspiration. This activity has been termed as Central Inspiratory Activity (CIA) and considered to increase as a ramp during inspiration. Some of the neurons of nucleus retroambiguus were shown to fire also during expiration (20). The functional mechanism underlying this rhythmic excitation is still far from being clearly understood. The two leading hypotheses are a pacemaker type automatic firing cells, similar to those found in invertebrate nervous systems (21,22,23) and a self-oscillating network with appropriate interconnections (19).

In addition, it has been shown that the CIA is terminated prematurely when the vagus nerve, the nucleus parabranchialis or other parts of the medulla are stimulated during inspiration. All of these are considered to function through the "off-switch" neural circuit responsible for the termination of inspiration (19,24). Furthermore, neurons in the nucleus parabranchialis were

found to exhibit activity at the end of inspiration and to represent the "off-switch" circuit, but there is still a lot of discussion about such a circuit (25).

Based on the work of Cohen (26-31), von Euler (32-35) and others (36,37) hypothetical models had been developed (38-47) in order to explain the automatic control of breathing. To what extent these models could be applied to awake animals or humans is not yet clear, but many experiments have shown difference between anesthetized and non-anesthetized animals and between the behaviour of different species (48-51).

Furthermore, after leaving the medullary inspiratory neurons the signal can follow different pathways towards the alpha-motoneurons, through which it undergoes considerable modifications as a result of influences from other brain structures which project on the same reticulo-spinal connections (52). In addition, at the level of the alpha-motoneurone pool the signal can be influenced by discharges from the cortex descending in the cortico-spinal tract and various other reflex loops, such as intercostal-intercostal, intercostal-phrenic, phrenic-phrenic or direct activation of gamma loop (53-58).

However, regardless of all the complexities and the numerous connections of the controlling system inside the CNS, it was shown that in anesthetized animals the integrated phrenic activity bears a very

close relationship with the electrical activity of the medullary inspiratory neurons (59).

Finally, since this thesis is not going to provide direct experimental evidence about the functions ~~and~~ the locations of the respiratory "centres," this term is going to be used in a purely operational fashion. In other words, it will include not only the function of neurons in the brainstem, but all the modifications that the controlling signal may undergo before its exit from the CNS.

I.3. MEASUREMENTS OF RESPIRATORY OUTPUT

Based on the fact that a number of locations of neurons widely distributed in the CNS are involved in the genesis of the controlling signal and the complexity of their interconnection, one could argue that a "quantitative" measurement of the signal would only be possible at a level lower than the alpha-motoneurons, where the first summation of various signals takes place. From the alpha-motoneurons the signal travels the peripheral nerves as neural discharge, and arrives at the neuromuscular junctions where it is translated to muscle action potentials and thereafter into muscle tension (pressure) and finally into airflow.

It follows that as the signal leaves the CNS, it can be assessed at various levels, such as the peripheral nerves, the respiratory muscles, as end-product (ventilation) or even in between these stages, e.g. muscle

tension (pressure), work of breathing, O_2 cost of breathing.

I.3.1. Electroneurogram of Peripheral Nerves

The electroneurogram (ENG) is a measure of the action potentials recorded from the proximal end of a cut peripheral nerve. With the available technology, it is possible to have recordings of the whole nerve or of a single neural fibre. The latter allows detection of responses of individual motoneurons, and therefore the existence or not of subpopulations in the pool of alpha-motor-neurons.

In the whole nerve electroneurogram, the action potentials of a number of ~~nerve~~ fibres are recorded, and therefore the signal is related to the frequency and size of those potentials.

Since, standardization of all the electrical properties of the surrounding elements and the number of ~~nerve~~ fibers responsible for the signal (depending on the preparation of the nerve) is impossible, this method does not provide a quantitative measure of neural activity. Therefore comparison of such measurements between different animals is unfeasible.

Furthermore, since this method is invasive, its use is mainly limited to animal experiments.

I.3.2. Electromyogram of Respiratory Muscles

The electromyogram is the record of the electrical activity generated by a muscle during contraction.

Similar to electroneurogram, the electromyogram can be obtained from a single motor unit or from whole muscle. The former constitutes the functional unit of the striated muscle and consists of a ~~nerve~~ ~~body~~, an axon which terminates by branching into a number of muscle fibers. The couplings of neural endings with the muscle fibers are called end-plates or in a general term neuromuscular junction. When the neural discharge travelling along the axon reaches the end-plate, acetyl-choline is released causing depolarization of the muscle fiber. This depolarization travels centrifugally and is followed by repolarization. These processes produce the action potential of the fiber and can be recorded with a very small electrode (needle or wire) inserted into the muscle.

The electromyogram of a muscle (EMG) during contraction consists of various action potentials of the motor units active during the contraction. Therefore, these electrical potentials have variable spatial and temporal origin, and the EMG signal which represents their sum, resembles electrical noise. When the signal is sampled directly on the muscle, it is affected mainly by the electrodes material, size and distance. But, when sampling is made from the body's surface, the signal is influenced by skin conductivity, distance from the muscle to the electrodes and position of the electrodes in relation to the axis of the contracting muscle, and from noise from other muscles. All of these factors make subject to subject comparison of EMG's very

difficult. In the case of the respiratory muscle EMG, the methods applied in animals or in humans consist of the direct insertion of electrodes (needles), the esophageal electrodes and the surface electrodes. There are several practical problems in each of these techniques which have been extensively discussed in the excellent book "Respiratory Muscles," edited by Campbell, Agostoni and Newsom Davis (96).

I.3.3. Airway Occlusion Pressure

This is the pressure generated by the respiratory muscles contracting against the closed airways, and is usually measured at the mouth or trachea. This pressure is similar to the dP/dt measured by the cardiologists during an iso-volumetric contraction of the heart (60,61). This method is based on the knowledge that the tension (pressure) developed by a muscle during an isometric contraction is linearly related to EMG activity of the muscle (62,63). In the case of respiratory muscles, it has been shown that the isometric tension (pressure developed is also approximately linearly related to the integrated phrenic activity (64). When an occlusion is performed at functional residual capacity (FRC), the elastic recoil of the respiratory system is zero and the pressure measured is the one developed by the muscle contraction. Since, during occlusion there is no flow of gas and lung volume does not change (except for a very small change due to decompression) the

measured airway pressure is not influenced by the mechanical properties of the respiratory system, namely resistance and compliance. The first systematic application of this method in the studies of control of breathing was performed on anesthetized cats (65). Anesthetized animals as well as humans do not react to the occluded load and the following inspiratory effort is essentially identical to the preceding unoccluded one. This has been assessed by means of phrenic ENG (66) or diaphragmatic EMG (64). The only difference during occlusion is that the inspiratory effort is quite prolonged due to no change in volume and therefore no vagal lung volume-related inhibitory effect (44,67).

However, conscious men quickly become aware of the occlusion and react in various ways. This reaction needs at least 200-250 ms from the onset of inspiratory effort to be activated and therefore this period is free of any cortical or other reflex effect. Thus, Whitelaw et al (68) proposed that the pressure measured .1sec after the occlusion represents an index of the central inspiratory drive in conscious men (68). Similarly, the rate of change (dp/dt) of the pressure during the first 200 ms of an occluded breath has been used as a similar index by others (69, 70).

However, it is clear that the occlusion pressure depends on the effectiveness of all inspiratory muscles to contract and produce pressure. This depends on the intrinsic properties of the muscles, e.g. force-length

and force-velocity relationship, and their geometry, which in turn depends on the overall configuration of the respiratory system (71).

I.3.4. Work and Oxygen Cost of Breathing

Regarding the ventilatory pump as a machine, one can view its output as the mechanical work produced, and the metabolic energy spent by the muscles as the energy consumption of the machine. In these terms the efficiency of the pump is represented by the ratio of mechanical work produced to the energy used.

Although it would be difficult to conceive that regulation of mechanical efficiency is the primary task of the controlling system, it is quite feasible that the respiratory system operates in the direction to improve useful work and minimize energy cost.

In the case of the respiratory system, work can be estimated from the equation $W = \int P \cdot dV$ using the pressure volume diagrams of the lung and chest wall (72). Work of breathing has been suggested as an estimate of activity of the respiratory "centres" and has been applied in patients with severe mechanical impairment of their lungs and therefore low $\dot{V}_E$ and $\dot{V}_A$ but with normal or even increased muscle activity (73). However, there are several limitations of this method, since work of breathing does not include energy spent in distortion or in the antagonistic action of different muscle groups, both being important during fast breathing or in disease

(74,75,76). In addition, as work is related to load by a bell-shaped curve (77), for work to be independent of load, one has to assume that the loads under investigation are all on the flat part of the curve (top of the bell). To overcome some of these limitations, oxygen cost of breathing has been proposed as an alternative measurement of respiratory "centres" output (78). This measurement although it has certain advantages over the work of breathing since it includes the energy spent on distortion or muscle group antagonism, it is difficult to perform accurately. Hence, both work or oxygen cost of breathing are seldom in use nowadays.

I.3.5. Spirometry

Since the classical work of Haldane and Priestley (79), pulmonary ventilation ($\dot{V}_E$) (the end product of the ventilatory system) became the most commonly used measure of the output of the respiratory "centres." Clearly, this fundamental measurement is still a very useful index of output used in all studies of control of breathing.

Minute ventilation in general has been partitioned into tidal volume (V_T) and respiratory frequency (f), but recently it became apparent that a more detailed analysis of the spirometric variables is needed in order to understand by which means the respiratory system produces a given minute ventilation. Obviously, slow deep or rapid shallow breathing may result in the same minute ventilation, but by completely different mechanisms. The necessity to partition the respiratory cycle into various phases was recognized long ago by Barcroft and Margaria (80).

They point out that ventilation is affected by changes in the duration of inspiration (T_I), expiration (T_E) and of pauses, if any, and in the rate of lung filling. However, it was quite recently that minute ventilation was expressed as product of mean inspiratory flow (V_T/T_I) and of the ratio (T_I/T_{TOT}) according to the equation $\dot{V}_E = (V_T/T_I) \times (T_I/T_{TOT})$ (81,82). The dimensionless ratio T_I/T_{TOT} has been termed inspiratory "duty cycle" to denote that it expresses the fraction of the total breathing cycle during which the inspiratory muscles are active. By this analysis ventilation is divided into two components: mean inspiratory flow which has been shown to be related to central inspiratory activity (83) ("inspiratory drive") and to the ratio T_I/T_{TOT} reflecting respiratory "timing" (82). Plotting the various parameters of the spirogram against each other, e.g., $\dot{V}_E$ vs. V_T ("Hey" plot), V_T vs. T_I ("Clark-von Euler" plot), $\dot{V}_E$ vs. V_T/T_I , a number of conclusions could be derived (81-86). Furthermore, as shown by Newsom Davis and Stagg (87) some of these subdivisions of $\dot{V}_E$ appear to be ^{more} ~~relatively~~ constant parameters of the spirogram (V_T/T_I) than others (T_I/T_E). The remaining are highly variable (V_T , f , T_I , T_{TOT}). The interrelationships between these variables will be discussed in more detail in Chapters III and IV of this thesis. In addition, the effect of the shape of the spirogram (volume-time profile) on ventilation will be examined in line with previous reports (81,88) and possible explanations for these

various spirographic shapes will be proposed.

I.3.6. Partitioning of lung volume

The application of linearized magnetometers (89) has made the recording of the two components of tidal volume (one due to rib-cage and the other due to diaphragmatic-abdominal motion) quite simple.

Konno and Mead (90) using a similar method showed the advantages of such a partitioning. The same group of investigators showed that ventilation can be ~~derived~~ from movements of various parts of the system (89). In this method, changes in antero-posterior diameters of the rib-cage and abdomen are recorded and a spirometer is only used for calibration. Since during the actual measurements a mouthpiece, mask or noseclip are not required, this method allows recording of volumetric changes with a minimal disturbance to the subject (91-93).

Finally, a number of interesting books, have been published describing in detail the above methods and their application in studies of control of breathing (94-103).

In the present work, the animal experiments were designed to investigate the various transformation of the controlling signal as it is translated from electrical activity of the peripheral nerves into muscle tension (driving pressure) and thereafter into airflow.

Previously, these transform functions have been studied by applying electrical stimulation on the nerves and monitoring the results (112-114) or by investigating

each transform function separately (64,66,86).

Thus, the purpose of this thesis was to investigate the controlling signal as it is generated by the respiratory "centres," to follow it through the various stages and to describe the governing relationships of these stages. These relationships were studied during increased respiratory drive induced by hypercapnia and hypoxia, and during diminished drive due to increased level of pentobarbital anesthesia.

Finally, some of these variables were studied in humans, during increased ventilation induced by muscular exercise.

I.4. HISTORICAL REVIEW

The first scientific experiments on the respiratory output have been performed as early as the 2nd century A.D. by Galen (12,13,104). His observation that breathing stops immediately after a 3-4 cervical vertebral spinal transection is the earliest evidence that there is connection between the action of breathing and CNS. Even earlier ancient Greeks had a similar belief; they considered the diaphragm as the seat of a part of the soul which they called phrenes (φρένες). What ancient Greeks meant exactly by the word "phrenes" is difficult to understand, but probably had a combined meaning of the soul and mind. In other words, phrenes was responsible for emotions, desires and sensations both pleasant and unpleasant (105,106,107). Thus, this ancient fiction has a tendency to relate breathing

and mind. Inherited from this belief is the name of the nerve supplying the diaphragm which is called phrenic. Similar experiments to those of Galen have been repeated by Lorry much later in 1760 (108). Earlier (in 1667), by dividing the phrenic nerves Lower made a dog breathe "like a broken-winded horse" (109).

The discovery of electricity in the eighteenth century opened a new field of experimentations on nerves and muscles. Following the application of electrical stimulation of nerves described by Raymond du Bois (110), Duchenne in 1867 studied diaphragmatic contraction by phrenic nerve stimulation. He showed that diaphragmatic contraction caused expansion of the transverse and antero-posterior diameters of rib-cage (111). Similar methods are still in use (112,113,114). Furthermore, based on the pioneering experiments of Duchenne, a clinical method was developed in order to ventilate the lungs by electro-phrenic stimulation (115,116).

Recording of the actual currents of the phrenic nerve had to wait for the technological advances of the 20th century which provided methods of adequate amplification of the electrical signals. As such, the galvanometer invented by Einthoven (1903) was first used. Ditter in 1910 provided the first recording of phrenic electrical activity by connecting the cut-end of the nerve to a string galvanometer (117). In another study, Ditter and Garten (118) using two large string galvanometers simultaneously recorded phrenic and diaphragmatic

activity and even with this very small amplification they were able to identify corresponding electrical waves between the nerve and the muscle. The development of the vacuum tube amplifier allowed more reliable recordings of electrical activity of nerves. Its application to the phrenic nerve was first reported by Gasser and Newcomer in 1921 (119). These early reports were followed by a great number of investigations on the phrenic nerve action potentials recorded either from the whole nerve or from single fibres. The latter was described as early as 1928 by Adrian and Bronk (120,121).

With recent technological advances, apart from amplification, various other electrical treatments have been applied to the electrical signal of the respiratory motoneurons such as, rectification, filtration and integration. However, certain problems still remain (122) and will be discussed in chapter II.

In parallel with the development of the electro-neurogram, recordings of respiratory muscle electro-myogram became a popular method in respiratory investigations (123-129).

An application of electromyography in the studies of control of breathing has been made by Bergström et al (130) in 1961, but it was Lourenço and his colleagues who put forward the idea of measuring respiratory "centres" output by diaphragmatic EMG (64, 131, 132).

Using the respiratory muscles as the level of assessment of respiratory output, the basic principles

of the intrinsic properties of the muscles have to be considered.

Relationships such as force-length and force-velocity may influence the measurements. These relationships have been first established on other skeletal muscles by Hill(133)and Wilkie (134, 135), but soon have been applied to the respiratory muscles by Agostoni (136), Marshall(112), Pengelly et al (113), Sears et al (137) and Green et al (138). The current ideas are that force-length and force-velocity characteristics of the inspiratory muscles provide an effective internal elastance and resistance of the muscle, and thus determine its internal impedance (139).

However, before the development of the above electrical methods, investigators studied breathing by simple means such as observation (140) or by recording of movements of various surfaces of the body. Paul Bert in 1870 invented devices to record movement of parts of the body surface not only in human, but also in a variety of other species, including fish (141). Similar experiments have also been reported in 1889 by Head (142). The pneumograph introduced by Marey in 1855 has been widely used to study relative motion of the thorax and abdomen during breathing (143). The latest improvement in monitoring motion at the body surfaces in relation to ventilation are the respiratory magnetometers, introduced by Mead ^{et al} (144).

However, since its invention in 1846 by Hutchison (144) the spirometer is still the simplest method for

measurement of overall respiratory output. This is not surprising since it measures the end-result of the action of the entire respiratory system. As important developments of this method one could consider the invention of pneumotachography by Fleisch (145) and the introduction of body plethysmography by Dubois et al (146) and the modifications by Mead (147). However, the major change since Hutchison's time is the interpretation of the spirometric measurements. As influential work in the field of detailed analysis of the spirogram, the following contributions can be considered as most important: Haldane and Priestley (79), Barcroft and Margaria (80), those of Proctor and co-workers (148-150), the work by Hey et al (84) and more recently those by Clark and von Euler (83) and Milic-Emili (82).

The vicar Steven Hales (1677-1761) was probably the first who measured the upper airway pressure during occlusion in a living animal (horse) and expressed it in inches of wine (151). Later (1870) Paul Bert also measured the same pressure in a variety of species (141). In 1918 Haldane also recorded the mouth pressure during lung inflation or deflation in men, in order to investigate the Hering-Breuer reflex (152,153).

Dejours and co-workers in 1962, suggested that when the respiratory muscles are contracting against an occlusion the pressure developed in the airways could represent "activity" of the respiratory centres (154). This idea was not further explored by them. Recording

of the airway occlusion pressure was used for different purposes, such as to detect underventilation in anesthetized patients (155) or to estimate the neuromuscular reserve during anesthesia (156) or as a measure of the pressure available in newborns to expand their lungs during the first breath (157). The first systematic application of the airway occlusion pressure as an index of respiratory "centres" output was made in 1973 by Grunstein and co-workers in anesthetized cats (65). This was followed by the first successful application of this method in conscious subjects made by Whitelaw and co-workers (168). A great number of reports followed these two papers, the technique being applied in a variety of conditions (69,70,158-176).

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CHAPTER II

TIME COURSE OF PHRENIC ACTIVITY AND
RESPIRATORY PRESSURES DURING AIRWAY
OCCLUSION IN CATS

II.1.INTRODUCTION

Recent studies (3-5,9,11,13,21) have shown that in anesthetized animals the control of breathing depends mainly on (a) the central inspiratory activity, CIA, (b) the inspiratory "off-switch" mechanisms, and (c) the factors controlling the duration of expiration. The work of von Euler et al (9,10) suggests that the rate of rise of phrenic activity can be used as an index of CIA. While several investigators have studied factors that affect the rate of rise of phrenic activity, such as CO₂ and body temperature (7-9,20), no systematic investigations have been done in order to define the shape of the phrenic electroneurogram (EPHR). Clearly, the morphology of E_{PHR} must affect the time course of the pressure developed by the diaphragm, as well as the shape of the spirogram.

In the present investigation we have studied the effects of hypercapnia and hypoxia on the shape of E_{PHR} ("moving average") in anesthetized, spontaneously breathing cats. In addition, we have investigated the relationship between E_{PHR} and both transdiaphragmatic and airway (tracheal) pressure during occluded inspiratory efforts. The relationship between E_{PHR} and airway occlusion pressure has been previously studied (7,8). Since the transdiaphragmatic pressure (P_{di}) is a more direct measure of diaphragmatic activity than the pressure change on only one side of it (airway occlusion pressure), a comparison between E_{PHR}

and Pdi is a useful extension of the previous investigations.

II.2. METHODS

The experiments were performed on eight spontaneously breathing adult cats (2.8-3.7kg), initially anesthetized with pentobarbital sodium (35 mg/kg i.p.). Additional doses (3 mg/kg) were given intravenously when needed.

The animals were held supine on a heated operating table. Rectal temperature was monitored continuously and kept between 37-38°C. The cats were intubated and the femoral vein cannulated. The tracheal tube was connected to a pneumotachograph (Fleish No.00) for the measurement of airflow ($\dot{V}$) and, by electrical integration, of changes in lung volume (V). The flow resistance of the equipment was .015 cm H₂O/ml/s. Tracheal pressure (P_T) was obtained by connecting a side arm of the tracheal tube to a pressure transducer (Schlumberger H-5035). Esophageal (P_{es}) and gastric pressure (P_{ga}) were measured by means of two air-filled latex balloon-polythene catheter systems inserted into esophagus and stomach, respectively. The catheters were connected to two identical pressure transducers (Schlumberger H-5020). In one animal P_{ga} was not measured. The frequency response of the pneumotachograph and pressure transducers was flat up to 10 cycles per second.

Phrenic electrical activity was recorded from the C5 root. The nerve was isolated, cut to avoid recording of

afferent activity, and laid on bipolar platinum electrodes with the distal end fixed and kept in a pool of warm (37 - 38°C) mineral oil. The signal was amplified by passing through a Grass amplifier (model RPS 107) with a band pass of 50-10,000 Hz. The amplified signal underwent full-wave rectification, and the rectified signal was integrated by an RC low-pass filter with a time constant of 100 ms. By this means the "moving average" of phrenic activity was obtained (8).

End-tidal CO_2 (PACO_2) was measured with a rapid CO_2 analyzer (BECKMAN LB-2) and inspired O_2 concentration was monitored with an O_2 analyzer (BECKMAN OM-14). All variables were recorded on a pen recorder (Gould-Alenco EN 68) at a speed of 25 or 50 mm/sec.

Airway occlusions were performed at end-expiratory lung volume at intervals of 3-5 minutes. Occlusions were made while the animal breathed room air, different CO_2 mixtures in 60% O_2 (balance N_2) and hypoxic mixtures under steady-state conditions. Oxygen (60%) was given during the CO_2 runs to eliminate the hypoxic drive. In the hypoxic runs PACO_2 was kept constant by adding CO_2 to the inspired gas (iso-capnic hypoxia).

Six animals were used in the hypercapnic study, each being exposed to at least four different inhaled CO_2 concentrations. Seven cats were used in the hypoxic study

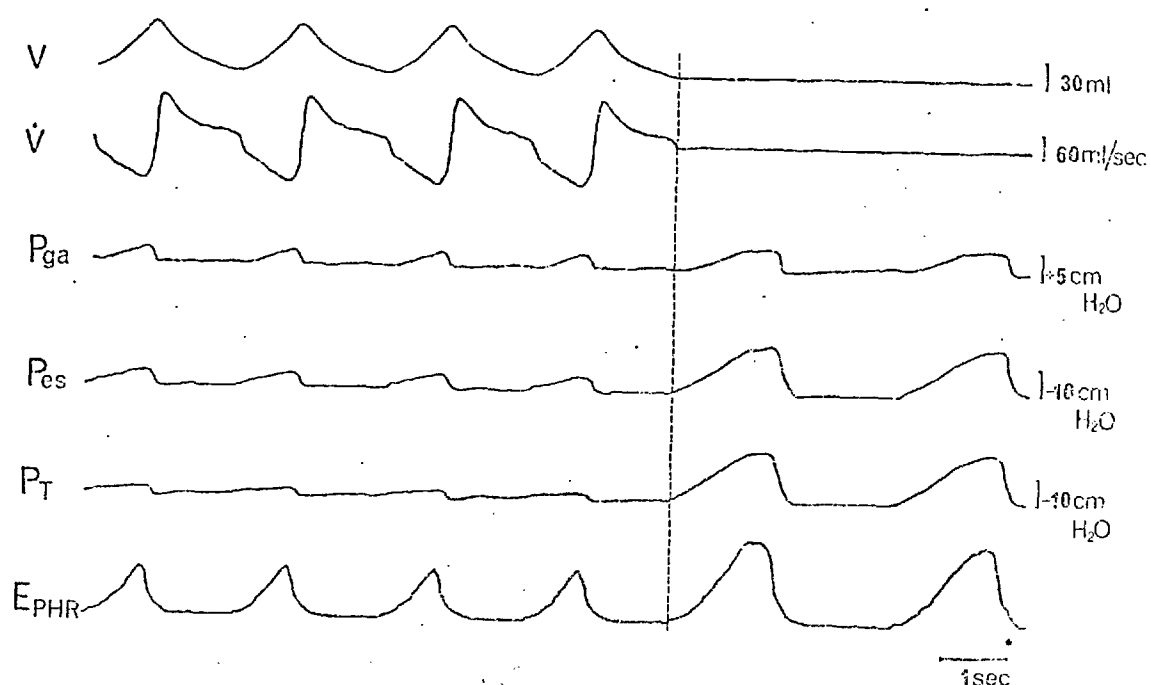


Fig. 2. Traces obtained in cat A during CO_2 inhalation ($\text{PACO}_2 = 47\text{ mmHg}$). From top to bottom: Lung volume changes (V), airflow ($\dot{V}$), gastric (P_{ga}), esophageal (P_{es}) and tracheal (P_T) pressure, and integrated phrenic activity (E_{PHR}). Four unoccluded and two occluded breaths are shown. Broken line indicates the onset of phrenic activity during the first occluded effort.

and inhaled inspired O_2 concentrations ranging from 21 to 9.6%.

11.3. RESULTS

In all cats, under steady-state conditions (inhalation of each gas mixture for more than 10 min) the pattern of breathing was regular. Figure 2 shows a representative record obtained from an animal breathing a hypercapnic mixture ($P_{ACO_2} = 47$ mmHg). Four control breaths and two efforts during airway occlusion at end-expiration are shown. During occlusion, tracheal pressure started changing either almost synchronously with the onset of E_{PHR} (broken vertical line in Fig.2), or more commonly, slightly later. This delay, which varied both within and between animals, averaged about 20 ms(18).

During both occluded and unoccluded breaths, gastric pressure in general remained constant during most of expiration (Fig.2), indicating that the abdominal muscles did not exhibit phasic respiratory activity (1). In all of these instances, the tracheal pressure during the occluded expiration returned to zero (atmospheric) pressure, providing further evidence that the expiratory muscles were not phasically active. During hypercapnia and hypoxia, however, in three cats (B,C,D) the gastric pressure increased somewhat toward the end of expiration, indicating some activity of abdominal muscles. This activity does not appear to have

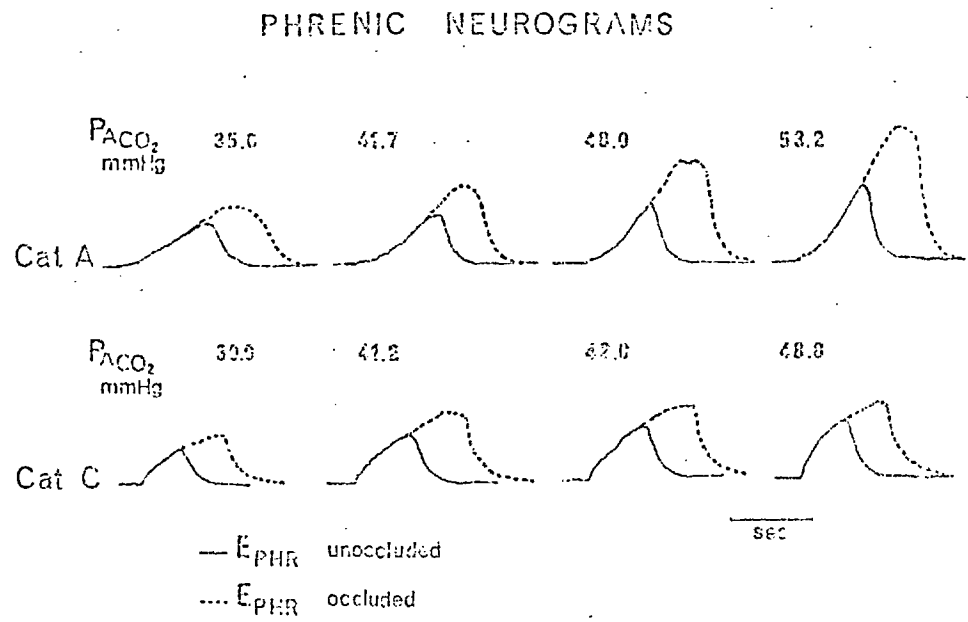


Fig. 3 Tracings of the phrenic activity (E_{PHR}) of the first occluded and of the preceding unoccluded breath in two cats at different level of P_{ACO_2}

affected the end-expiratory lung volume, since during the occluded expiration, before the late positive deflection in P_{ga} , there was a plateau in tracheal pressure which corresponded to atmospheric pressure. Furthermore, the end-expiratory values of P_{es} remained in these three cats, as well in all other animals, the same during hypoxia and hypercapnia as during room air breathing. Thus, it is reasonable to assume that even in these cases, the end-expiratory lung volume corresponded to the relaxed volume of the respiratory system. A constancy of the functional residual capacity in pentobarbital anesthetized cats during CO_2 inhalation has been previously reported (13).

II.3.1. Effect of airway occlusion on E_{PHR} .

This was investigated by superimposing the occluded E_{PHR} on that of the preceding unoccluded breath, as shown in Fig.3 for two cats studied at different levels of P_{ACO_2} . In all cats, the initial part of the unoccluded E_{PHR} was virtually identical with that of the occluded E_{PHR} . During room air breathing, the rapid decline in control (unoccluded) E_{PHR} was usually preceded by a phase of slow change during which control E_{PHR} gradually deviated from the occluded E_{PHR} (Fig.3, cat A). According to Younes et al (22), this phase represents lung volume-related graded inhibition of CIA during the unoccluded inspiration. During room air breathing, the duration of phase was found to vary in the

HYPERCAPNIA

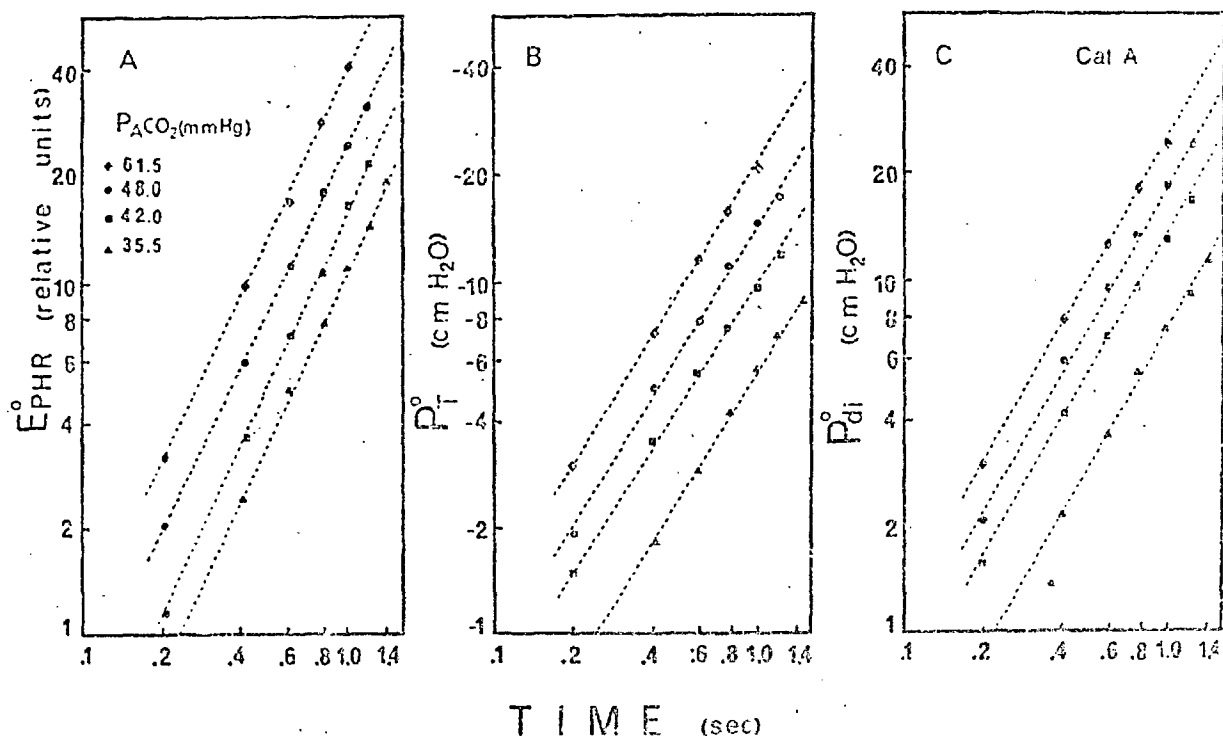


Fig. 4 A: relationship between phrenic activity during occluded inspirations (E_{PHR}^O) and time at different levels of P_{ACO_2} ; B: relationship between tracheal occlusion pressure (P_{TO}^O) and time; C: relationship between active occluded transdiaphragmatic pressure (P_{di}^O) and time. All plots are expressed in log-log fashion. Dots represent values obtained at .2 s intervals from the onset of each occluded inspiration.

different cats, averaging .1s (range:0-.3s). As can be seen in Fig.3 (cat A), the duration of this phase progressively diminished with increasing P_{ACO_2} . A similar trend was observed in all cats during both hypoxic and hypercapnic stimulation of respiration.

II.3.2. Shape of E_{PHR} .

Fig.3 shows that the shape of the rising part of the E_{PHR} -time profile varied markedly from one cat to another, cat A displaying curves with an upward concavity and cat C with an upward convexity. In both cats, an increase in P_{ACO_2} resulted in increased amplitude of the E_{PHR} signal while its waveform remained virtually unchanged.

When the log values of E_{PHR} (relative units), measured every 200 ms from the onset of phrenic activity during occluded inspirations, were plotted against the logarithm of the corresponding time, the relationships became straight (Fig.4A), permitting regression lines to be calculated by the least square method. These regression lines had highly significant correlation coefficients, ranging from .993 to .999 in all animals, under all experimental conditions (breathing room air, CO_2 and hypoxic mixtures). These regression lines are expressed by the equation:

$$\log E_{PHR}^0 = \log a + b \log T \quad (1)$$

where a is the value (r.u.) of occluded E_{PHR} (E_{PHR}^0) at one second, b is a dimensionless constant representing the

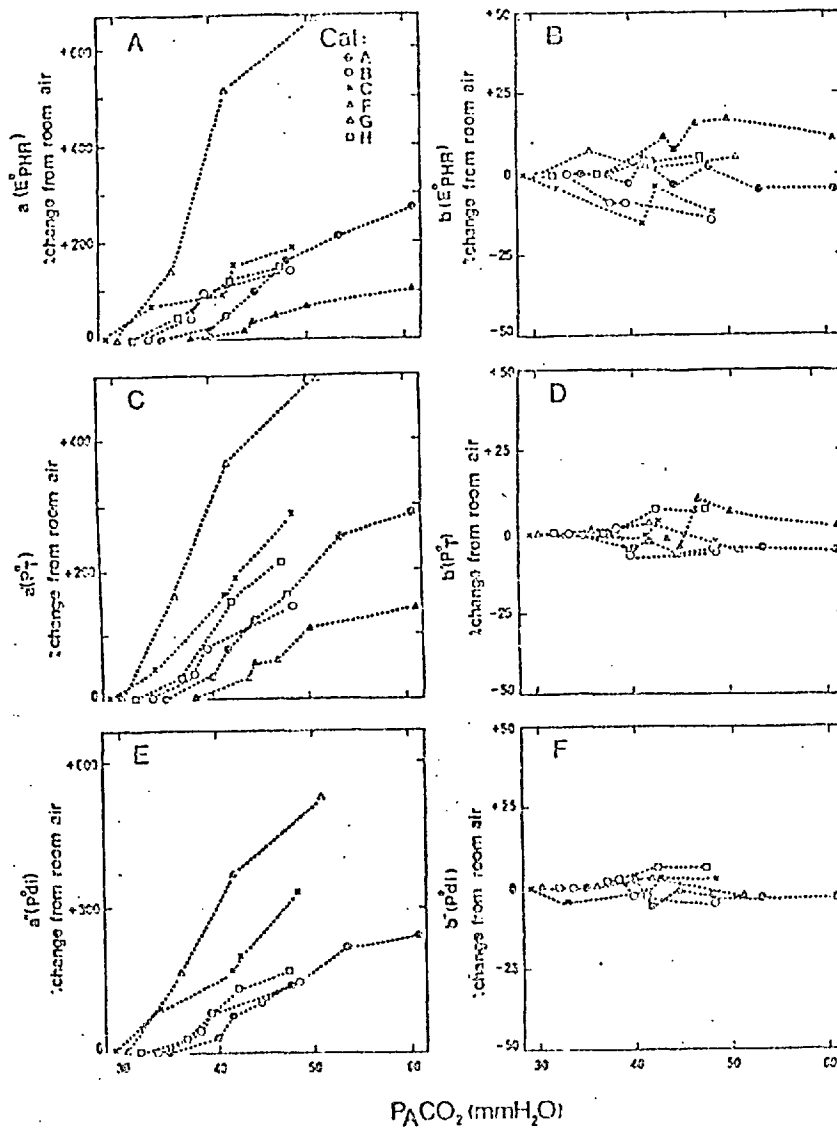


Fig. 5 Panels A,C and E show, respectively, the relationship of occluded values at 1 second of E_{PHR} (a), P_T (a') and P_{di} (a'') (expressed as percentage change from room air values) with end-tidal P_{ACO_2} . Panels B, D and F show respectively the relationship of the shape indices of the occluded E_{PHR} (b), P_T (b') and P_{di} (b'') waves (expressed as percentage change from room air values) with end-tidal P_{ACO_2} . Results on all cats are shown.

H Y P O X I A

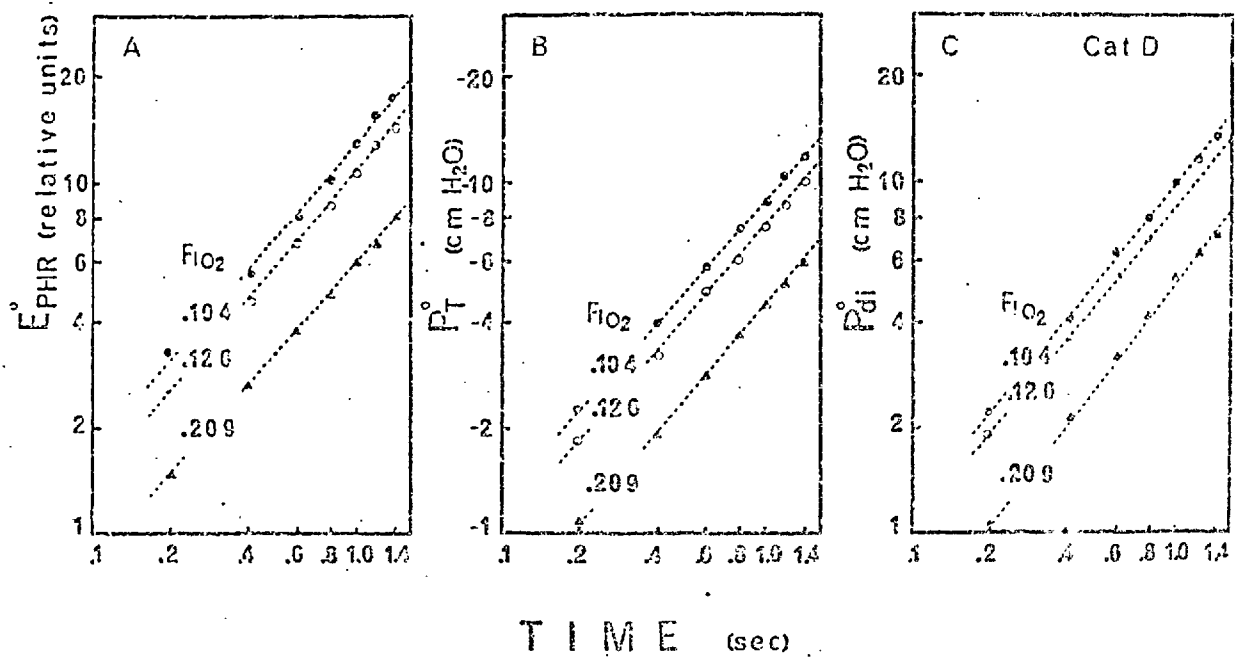


Fig. 6 Plots as in Fig. 4, but at various levels of F_{IO_2} .

HYPOXIA

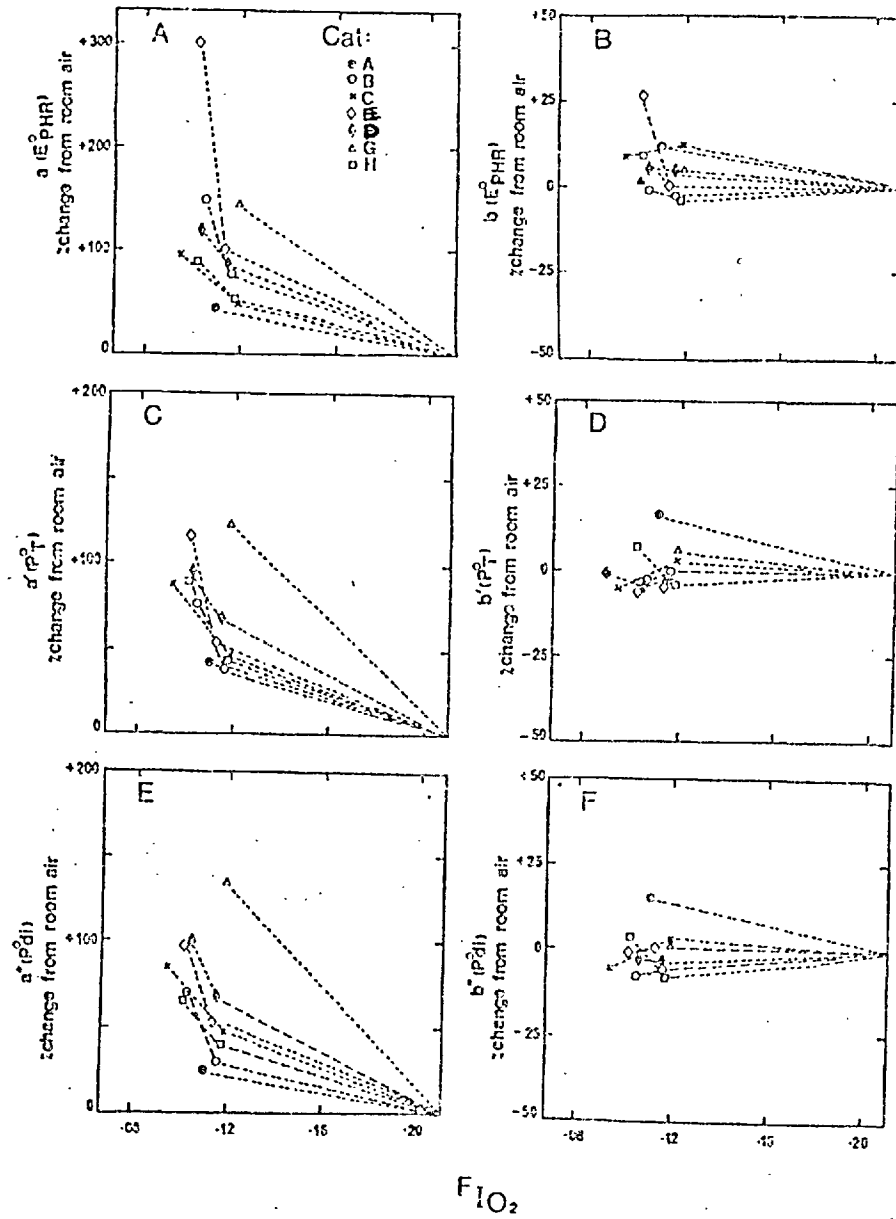


Fig. 7 Plots as in Fig. 5, but at various levels of F_{IO_2} .

TABLE 1: Values of constants in equations 2-4 of 8 cats
breathing room air.

CAT	$\overset{\circ}{E}_{PHR} = aT^b$		$\overset{\circ}{P}_T = a'T^{b'}$		$\overset{\circ}{P}_{di} = a''T^{b''}$	
	a (r.u.)	b	a' (cmH ₂ O)	b'	a'' (cmH ₂ O)	b''
A	10.6	1.58	5.5	1.29	7.4	1.35
B	15.6	1.21	16.0	0.90	17.5	0.94
C	15.6	0.91	8.5	0.89	8.6	0.90
D	6.0	0.88	4.6	0.90	5.0	0.94
E	11.7	1.50	9.5	1.02	10.2	1.10
F	9.0	0.69	6.3	0.80	-	-
G	5.6	1.55	5.3	1.41	5.6	1.46
H	5.4	0.98	8.7	0.95	10.9	1.00
Mean	9.9	1.16	8.05	1.02	9.31	1.10
± SD	4.2	0.35	3.68	0.21	4.22	0.22

slope of the lines, and T is the time (seconds) from the onset of phrenic activity. Since the relationship between $\log E_{PHR}^O$ and $\log$ time was linear, E_{PHR}^O can be described as a simple power function of time, of the form:

$$E_{PHR}^O = aT^b \quad (2)$$

When the E_{PHR} -time profile is linear, the constant b is equal to 1; when the shape of E_{PHR} has an upward concavity, b is >1 ; when the shape is convex upwards, b is <1 . Therefore, the constant b is a useful index for representing the shape of E_{PHR} . During room air breathing, the constant b was found to vary from .69 to 1.58 between the different animals studied (Table 1).

As shown in Fig. 4A, during CO_2 inhalation the $\log E_{PHR}^O$ vs. $\log T$ relationships were displaced upward (increased a) but the slopes remained virtually unchanged. Similar results were found in all cats (Fig. 5A,B). These results indicate that the rate of rise of phrenic ENG increases with P_{ACO_2} but the shape of the rising part of the E_{PHR} wave remains essentially unchanged. Hypoxia also appears to affect only the values of a, while it has little effect on the shape of the occluded E_{PHR} wave (Fig. 6A and 7A,B). Only in one cat (5) there was a substantial increase in the value of b during inhalation of a hypoxic mixture (Fig. 7B), indicating that in this cat the shape of the E_{PHR} was changed substantially when breathing 10% O_2 .

As expected from the data in Fig.3, the morphology of the rising part of E_{PHR} (up to the onset of graded inhibition of CIA) was in all cats the same during the unoccluded as in the occluded breaths.

II.3.3. Shape of tracheal occlusion pressure wave.

When the logarithm of the values of occluded tracheal pressure (P_T^O), measured every 200 ms from the onset of a negative deflection, was plotted against the logarithm of time, straight lines were obtained (Fig.4 B and 5B). The correlation coefficients (r) were highly significant in all animals under all experimental conditions, ranging from .994 to .999 in all efforts analyzed. Therefore, as for E_{PHR} , the rising part of the tracheal occlusion pressure wave can be approximated by a simple power function of time, as previously proposed by Murphy and Milic-Emili (17):

$$P_T^O = a'T^{b'} \quad (3)$$

where T is the time from the onset of the occluded effort (sec), a' is a constant representing the value of P_T^O at 1 sec (cm H_2O) and b' is a dimensionless constant describing the shape of the occlusion pressure wave.

During room air breathing, the values of constant b' varied from .80 to 1.41 between the different animals (Table 1).

Inhalation of hypercapnic (Figs.4B and 5C,D) and hypoxic (Figs.6B and 7C,D) mixtures resulted in marked increases in the values of a' , while the shape index b'

showed only small and non-systematic variability. The maximum change in b' , relative to the room air values, amounted to 8% during hypercapnia and 10% during hypoxia.

II.3.4.. Shape of the transdiaphragmatic pressure wave during occlusion.

P_T^O represented in our cats the net or active pressure developed on the thoracic side of the diaphragm during the occluded efforts. By subtracting P_T^O from the corresponding values of pressure developed on the abdominal side of the diaphragm (henceforth referred to as ΔP_{Ga}^O), the active transdiaphragmatic pressure (P_{di}^O) was obtained. ΔP_{Ga}^O was computed as the difference between active and relaxed P_{Ga} . During room air breathing, respiratory muscle activity appeared to be absent at end-expiration in all cats, and hence the end-expiratory values of P_{Ga} represented relaxation values. In 5 of the cats, P_{Ga} at the end of expiration did not change with respiratory drive. In the three cats (B,C,G) where during hypercapnia and/or hypoxia there was evidence of abdominal activity toward end-expiration (increase in P_{Ga} during late expiration), P_{Ga} at the start of inspiration was at times somewhat higher during hypoxia and hypercapnia than during room air breathing, indicating that some abdominal activity persisted during early inspiration (1). In no instance, however, did this increase in P_{Ga} exceed 1 cm H_2O .

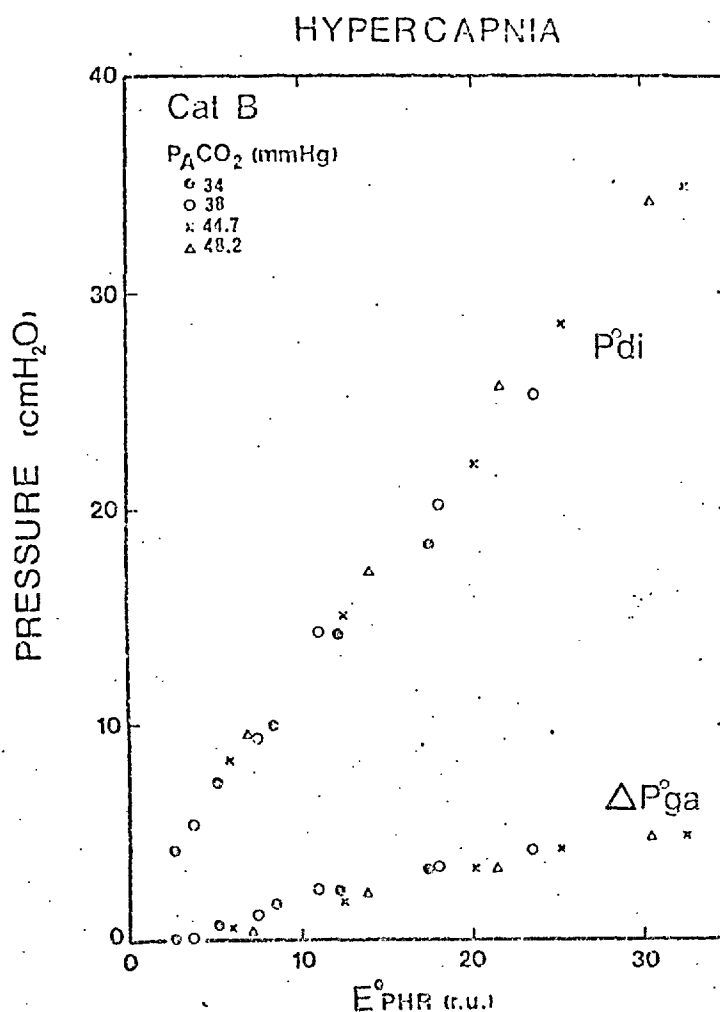


Fig. 8 Changes in gastric (P_{ga}^{O}) and active trans-diaphragmatic pressure (P_{di}^{O}) during five occluded inspiratory efforts plotted against the corresponding phrenic activity ($E_{\text{PHR}}^{\text{O}}$) at different levels of P_{ACO_2} (different symbols) in cat B. Points represent values obtained at .2 s intervals from the onset of phrenic activity

Similar to E_{PHR}^O and P_T^O , the relationship between $\log P_{di}^O$ and $\log$ time was approximately linear (Figs. 4C and 6C), with correlation coefficients varying between .994 and .999 in the seven animals, under all conditions tested. Hence, the P_{di}^O vs. time relationship during the occluded inspiratory efforts can also be described by a simple power function:

$$P_{di}^O = a'' T^{b''} \quad (4)$$

where T is time in seconds, a'' is P_{di}^O at one second (cm H₂O), and b'' (slope in Figs. 4C and 6C) is a dimensionless constant representing the shape of the P_{di}^O wave.

During room air breathing, the values of the constant b'' were found to vary in our cats from .90 to 1.46 (Table 1). As for E_{PHR}^O and P_T^O , inhalation of CO₂ and hypoxic mixtures caused marked increases in a'' , associated with small, non-systematic variations in the values of b'' (Figs. 5E, F and 7E, F).

II.3.5. Relationship between E_{PHR}^O , P_{di}^O and ΔP_{ga}^O

Figure 8 shows plots of P_{di}^O and ΔP_{ga}^O against E_{PHR}^O in cat B during 4 occluded inspiratory efforts made at different values of P_{ACO_2} . The experimental points represent values obtained at .2 second intervals after the onset of phrenic activity. It can be seen that the above relationships did not change perceptibly with increasing CO₂ drive. Since the vertical distance between the P_{di}^O and ΔP_{ga}^O values

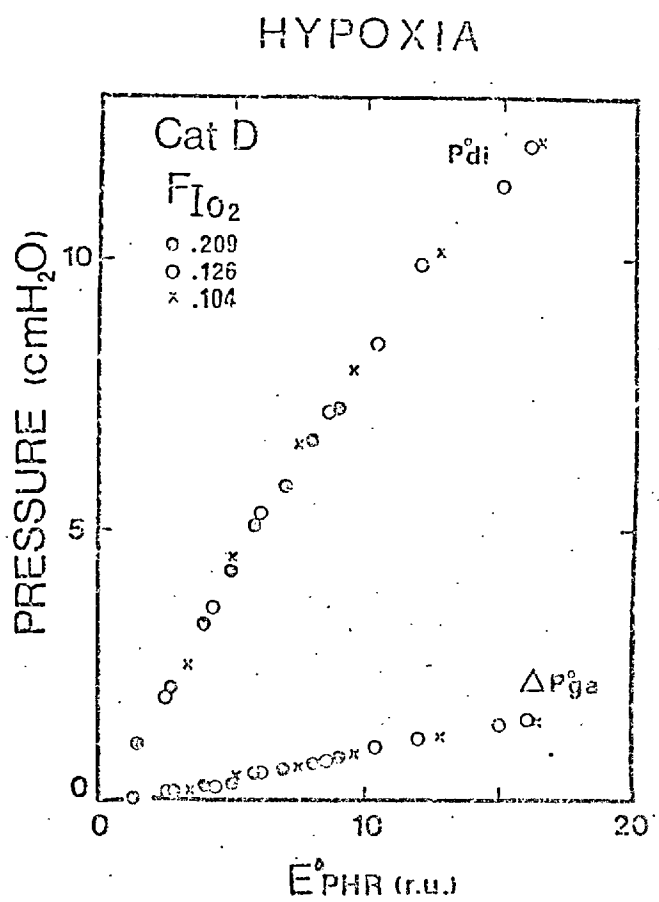


Fig. 9 Plots as in Fig. 8 for three different levels of $F_{I_{O_2}}$. Cat D.

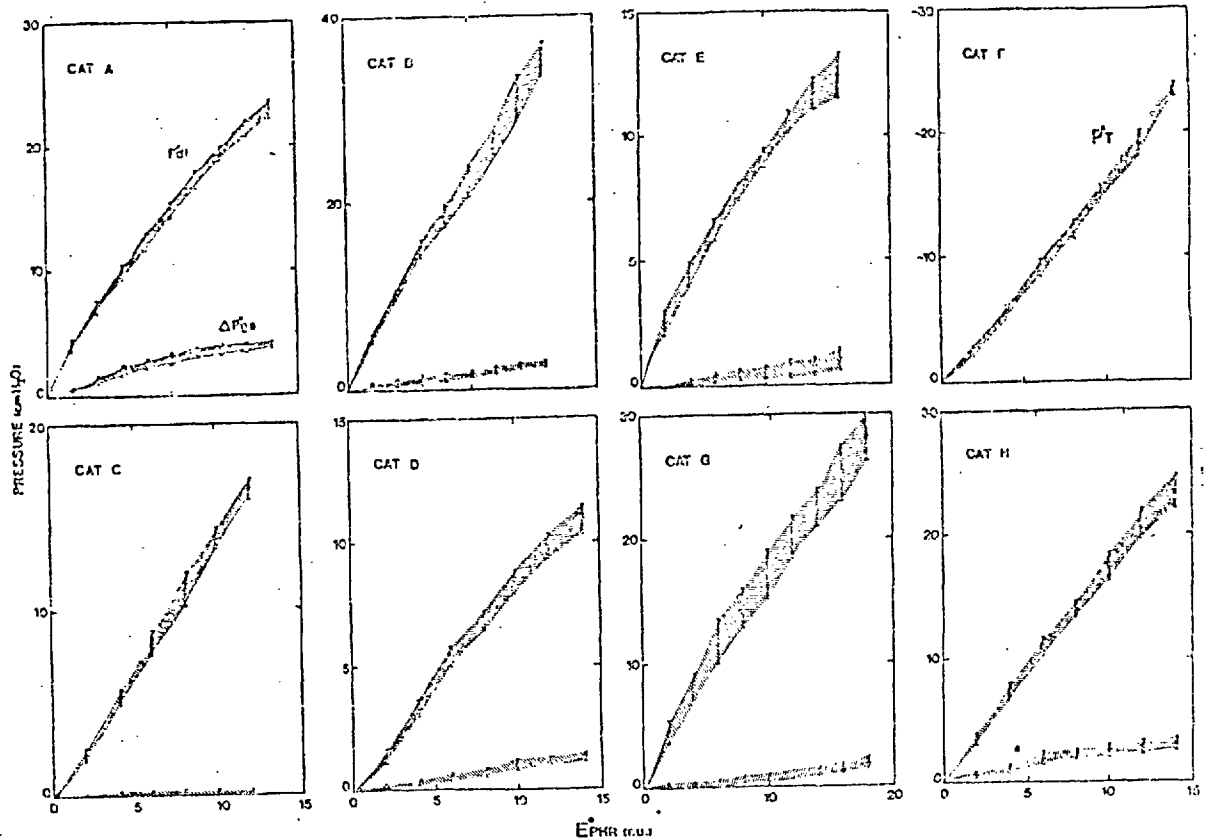


Fig. 10 Average relationships (solid lines) 1 SD (bars) of P_{d1}^O and ΔP_{ga}^O with E_{PHR}^O in 7 cats breathing room air, hypoxic and/or hypercapnic mixtures. In cat F, gastric pressure was not measured, and consequently only P_T^O values are given. In cat **E** results obtained with $FI_{O_2} = .1$ were not used in our computation.

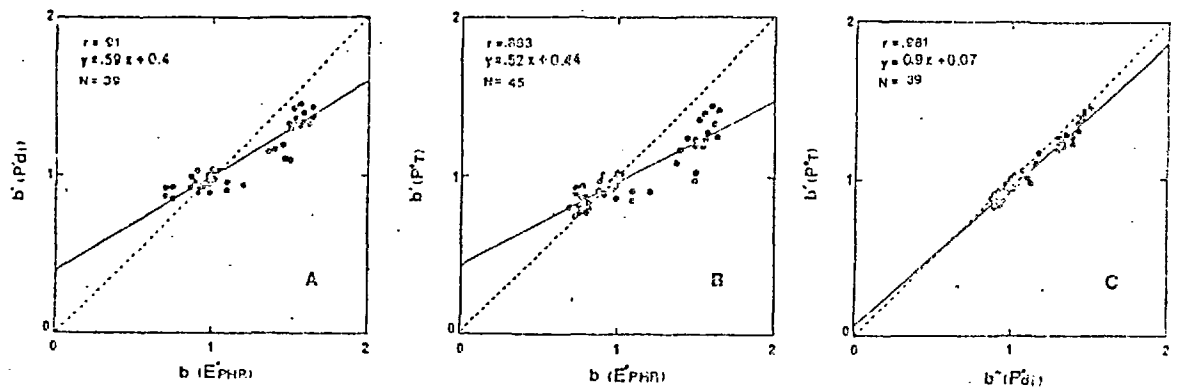


Fig. 11 Plots of the constants b'' (A) and b' (B) against the corresponding b values of E_{PHR}^O , together with relationship between b' and b'' (C). Data obtained in all animals during room air breathing, hypercapnia and hypoxia are shown. Identity is shown by broken lines.

in Fig.8 represents P_T^O , it follows that also the E_{PHR} vs. P_T^O relationship was approximately the same during room air breathing as with increased P_{ACO_2} . This was the case in all cats subjected to CO_2 stimulation.

Figure 9 illustrates the effect of hypoxia on the P_{di}^O and ΔP_{ga}^O relationships with E_{PHR}^O in cat D. As for CO_2 , these relationships were not affected by hypoxic stimulation. Similar results were found in all animals, except for cat E which shifted the relationships to the right when breathing the most hypoxic mixture ($F_{IO_2}=0.1$). This is the cat which changed the shape (b) of the E_{PHR} wave with $F_{IO_2}=0.1$ (Fig.7B).

Figure 10 shows the average relationships ($\pm$ SD) of P_{di}^O and ΔP_{ga}^O with E_{PHR}^O in seven cats, together with the corresponding plot of P_T^O vs. E_{PHR}^O in the cat (F) in which gastric pressure was not measured. In each cat, the relationships were computed lumping the room air, CO_2 and/or hypoxic values. In cat ~~F~~, the results obtained with $F_{IO_2}=0.1$ were omitted from the calculations. In general the pressure changes on the abdominal side of the diaphragm (ΔP_{ga}^O) represented only a small fraction of the total pressure developed by the diaphragm during the occluded efforts.

II.3.6. Relationship between the shape of E_{PHR}^O , P_{di}^O and P_T^O waves.

In Fig.11A and B the values of b' and b'' , obtained in all cats under all experimental conditions, are plotted against the corresponding values of b . The correlations

were statistically significant ($P < .001$), indicating the shape of the $\overset{O}{P_{di}}$ and $\overset{O}{P_T}$ waves is modulated by the time course of $\overset{O}{E_{PHR}}$. A significant correlation ($P < .001$) was also found between the values of b' and b'' (Fig. 11C).

II.4. DISCUSSION

In agreement with previous reports (8,13,21,20), we have found that airway occlusion at end-expiration results in a prolongation of inspiration as a consequence of removal of lung volume-related vagal inhibition of inspiration. As previously shown in cats (4,7,8,21), the initial part of the phrenic neurogram during the occluded inspiration was found to be identical to that of the preceding unoccluded breaths. This initial phase was followed by a variable period during which the unoccluded $\overset{O}{E_{PHR}}$ gradually deviated from the occluded one. The duration of this phase of graded volume-related inhibition of CIA (22) varied between cats (range: 0 to .3 sec during room air breathing) and diminished with increased respiratory drive.

Our results show that the morphology of $\overset{O}{E_{PHR}}$ varied considerably between the different animals, but within each animal it was not substantially changed by either hypercapnia or hypoxia. This is in agreement with previous reports (4,7-9,14) which showed that during CO_2 inhalation the general pattern of integrated phrenic discharge remained similar to that obtained during room air breathing.

Only in cat E we found a substantial change in the shape of the phrenic electroneurogram during inhalation of 10% O₂. Whether this reflected a change in CIA due to hypoxia or deterioration of the C₅ root is not clear. The latter is more likely as the shape of both occlusion P_T and P_{di} waves did not change when this cat was subjected to 10% O₂.

We found that the rising part of the "moving average" E_{PHR}-time profile can be described as a useful approximation by a simple power function (Equation 2) with two constants: one (a) providing a measure of the amplitude of the neural signal, and the other (b) representing its shape. The value of the shape index b was found to vary between animals, ranging from .69 (upward convexity of the E_{PHR}-time profile) to 1.58 (upward concavity). Similar differences in shape of E_{PHR} can be recognized in experimental records reported by other authors (2,4,7-10,20). In discussing these inter-animal differences in shape of the phrenic neurogram, technological aspects must be considered first. As indicated by previous work (2,7) and in the Appendix, the "moving average" technique does distort the phrenic signal. However, the near constancy of the shape of the measured E_{PHR}'s in each cat under all conditions tested implies that the shape of the "true" (undistorted) phrenic signal was also constant, or nearly so, during hypoxia,

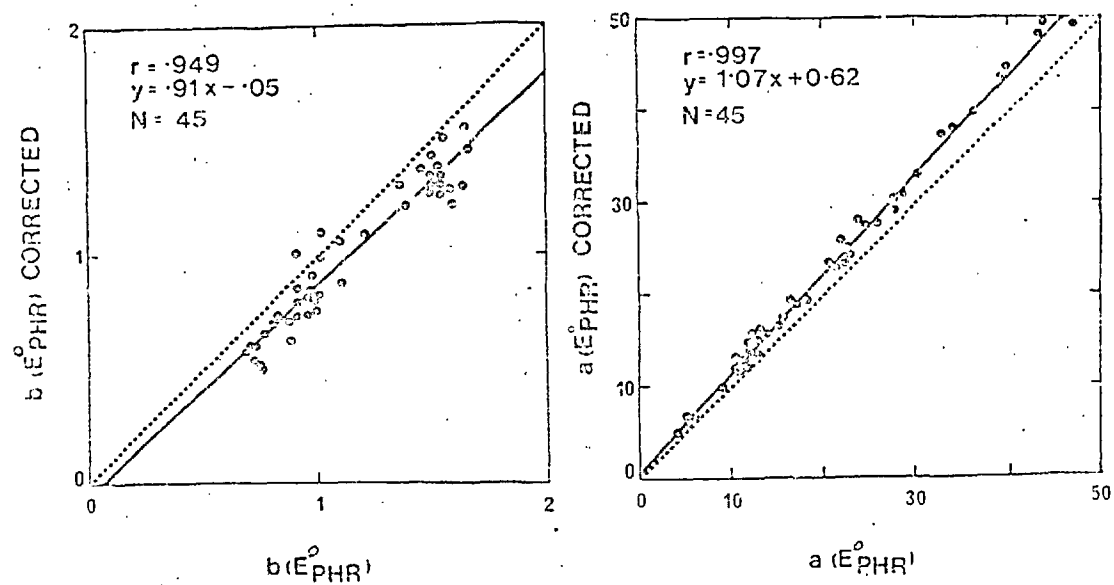


Fig. 12 Relationship between measured and corrected values of b (A) and a (B) in all cats during room air breathing, hypoxia and hypercapnia. Identity is shown by broken lines..

hypercapnia and room air breathing.

In order to estimate the distortion of the phrenic electroneurogram caused by the "moving averager," we have used a computer program as described in the Appendix I. In Fig. 12A the corrected values of the constant b are plotted against the corresponding measured values. It can be seen that our "moving-average" technique involved an overestimate of b which averaged about 10%. Figure 12B gives a plot of the corrected values of the constant a (equation 2) against the measured ones. The latter were slightly lower than the corrected values, by an average of about 7% over the entire range of experimental values. Thus, inter-animal differences in the shape of E_{PHR} are present even when allowance is made for instrumental distortion of the phrenic signal.

These inter-animal differences in shape of E_{PHR} were not due to variability in electrical coupling of the recording system to the C_5 phrenic root. Indeed, in a number of cats we have repeatedly repositioned the phrenic root on the recording electrodes and found that this procedure did not affect the shape of E_{PHR} (b remained unchanged). In many cases, however, repositioning of the nerve on the electrodes resulted in a substantial change in the amplitude (constant a) of the signal.

Although in the present study we have used a constant dose of sodium pentobarbital, it can be argued that different

animal susceptibility to the anesthetic could have been the cause of the observed inter-animal differences in the shape of E_{PHR} . As it is going to be discussed in Chapter IV, increasing doses of sodium pentobarbital affects the amplitude (constant a) but not the shape (constant b) of the phrenic electroneurogram.

Although our measurements of phrenic activity were made from a nerve root, they probably reflect the total activity of the phrenic nerves. Indeed, in each cat the relationship between E_{PHR}^O recorded from the C_5 root and Pdi^O was fixed, i.e. was the same during hypoxia and hypercapnia as during room air breathing.

The shape of both transdiaphragmatic and tracheal occlusion pressure waves also did not change substantially with changes in chemical respiratory drive, while the rate of rise of the waves increased with both hypoxia and hypercapnia. Previous reports have shown that CO_2 inhalation does not affect the shape of the tracheal occlusion pressure wave in cats anesthetized with pentobarbital sodium (23) and in men anesthetized with methoxyflurane (6).

As for phrenic neurogram, the shape of the Pdi^O and P_T^O waves varied between animals (Table 1). This variability was related to the inter-animal differences in the shape of the phrenic neurogram, as shown by the highly significant correlation coefficients ($P < .001$) between the values of b

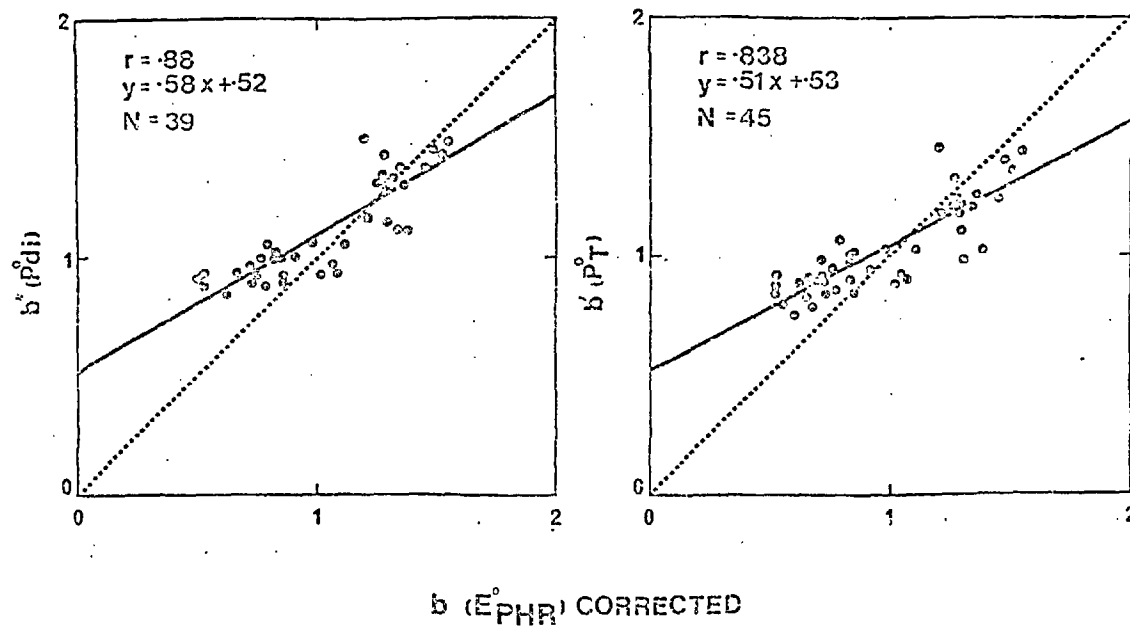


Fig. 13 Plots of b'' (A) and b' (b) against corrected values of b . Results for all cats during room air breathing, hypoxia and hypercapnia. Identity is shown by broken lines.

and both b'' and b' (Fig.11). A highly significant correlation ($P < .001$) was also found between the corrected values of b and both b'' and b' (Fig.13). Thus, it appears that different animals have intrinsic differences in the morphology of the phrenic neurogram which are also present in its mechanical transfer functions, namely the P_{di}^O and P_T^O waves.

In each cat the relationship between E_{PHR} and both P_{di}^O and P_T^O was fixed, i.e. was the same during hypercapnia and hypoxia as during room air breathing. This implies a proportionality of increasing activity among the diaphragm and the extra-diaphragmatic inspiratory muscles as respiratory drive increases, and is in line with the conclusions of previous investigators (7,8,16).

The active transdiaphragmatic pressure developed during the occluded inspirations was due in part to increased gastric pressure, the changes in gastric pressure (ΔP_{ga}^O) being again in a fixed relationship with E_{PHR}^O . The increase in gastric pressure during the occluded inspirations implies descent of the diaphragm. As with CO_2 and hypoxia a given P_{di}^O was achieved in a much shorter time than during room air breathing, P_{di}^O at any given value of E_{PHR}^O might be expected to decrease with increasing respiratory drive because of increased pressure losses in the diaphragm due to its force-velocity relationship (12). This, however, was not the case. Consequently, it must be concluded that

the descent of the diaphragm, as inferred from the increase in gastric pressure, did not involve any appreciable shortening of the diaphragmatic muscle fibres. Conceivably, during the occluded inspirations the diaphragm descends causing an increase in gastric pressure, but at the same time the lower rib cage expands such that the diaphragmatic length does not change, i.e. the contraction is isometric. This behaviour implies an increased radius of curvature of the diaphragm and hence, according to the Laplace law, a less effective contraction of the diaphragm in terms of pressure generated. Thus, during the occluded inspiratory efforts the diaphragm appears to have changed its geometry but not its length.

In considering the relationship between $\overset{\circ}{P}_{di}$ and $\overset{\circ}{E}_{PHR}$, it is important to note that the phrenic signal was somewhat distorted by the "moving-averager." As mentioned above, however, within each cat the distortion was similar during hypoxia and hypercapnia as during room air breathing. Hence, it is legitimate to conclude that the relationships in Figs. 8 and 9 are qualitatively valid, i.e. within each cat there is a fixed relationship between $\overset{\circ}{P}_{di}$ and phrenic electrical activity.

Our results show that in general $\overset{\circ}{\Delta P}_{ga}$ represented only a small fraction of the active transdiaphragmatic pressure developed during occluded inspirations (Fig. 10). Accordingly, most of $\overset{\circ}{P}_{di}$ was due to changes in pressure on the thoracic

side of the diaphragm. Since not only the amplitude but also the shape of the tracheal occlusion pressure waves were very close to those of $\overset{\circ}{P_{di}}$ (Fig. 11C), $\overset{\circ}{P_T}$ and $\overset{\circ}{P_{di}}$ represent essentially equivalent indices of neuromuscular inspiratory drive.

The present results open the question as to which of the above inspiratory output signals should be used in studies of control of breathing. Under the present experimental conditions, the three above output variables were essentially equivalent indices of CIA, in the sense that the relationship of $\overset{\circ}{E_{PHR}}$ with $\overset{\circ}{P_{di}}$ and $\overset{\circ}{P_T}$ was in each cat fixed. Whether a fixed relationship between $\overset{\circ}{E_{PHR}}$, $\overset{\circ}{P_{di}}$ and $\overset{\circ}{P_T}$ is also found in cats under experimental conditions different from the present, and/or in other species under the same or different conditions, remains as yet to be determined.

It has been previously proposed that the respiratory response to various stimuli be quantitated in terms of the airway occlusion pressure developed at a fixed time from the onset of inspiration (6,8,23). The validity of this approach is supported by the present results. It should be noted, however, that in our cats there was considerable inter-animal variability in the shape of the tracheal occlusion pressure waves, and hence comparisons between cats using the above index ($\overset{\circ}{P_T}$ at fixed time) are problematic.

In this connection, it is important to stress that the waveform of the phrenic neurogram, together with that of its mechanical transforms $\dot{P}_{di}^0$ and $\dot{P}_T^0$ must affect the shape of the spirogram. Thus, in studies of control of breathing the shape of the neuromuscular driving inputs must be taken into account.

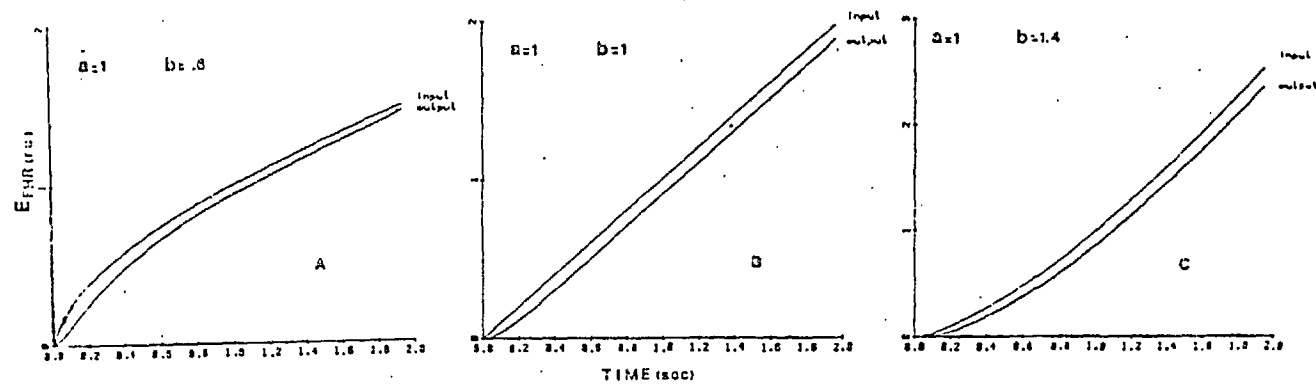


Fig. 14 Plots of simulated input and output phrenic neurograms (E_{PHR}) for three input waveforms (b in equation 6 of .6, 1.0, 1.4) with a fixed value of the constant $a = 1$

II.5. APPENDIX I.

Though the "moving average" technique of the present study is widely used (2,7-9,20), it clearly introduces some distortion to the phrenic signal. To investigate the magnitude of such distortion, the process of passing a signal through an electrical circuit consisting of resistance and capacitance with a time constant (τ) of 100 ms, was reconstructed mathematically. Assuming that the input signal is a power function of time (t) of the type at^b the governing equation in this circuit is:

$$E'(t) = at^b - \frac{1}{\tau} E(t) \quad (5)$$

where at^b is the input and $E(t)$ the output of such a circuit. The solution takes the form of an infinite series:

$$E(t) = at^{b+1} \left[\frac{1}{b+1} - \frac{1}{(b+1)(b+2)} \left(\frac{t}{\tau}\right) + \frac{1}{(b+1)(b+2)(b+3)} \left(\frac{t}{\tau}\right)^2 - \dots + \frac{1}{(b+1)(b+2)\dots(b+n+1)} \left(\frac{t}{\tau}\right)^n \right] \quad (6)$$

In the case of $b=1$, this solution (6) becomes :

$$E(t) = a\tau \left[(t-\tau) + \tau e^{-\frac{t}{\tau}} \right] \quad \text{and in the case of}$$

$b=2$

$$E(t) = a\tau \left[t^2 - 2\tau t - 2\tau^2 e^{-\frac{t}{\tau}} \right]$$

Fig.14. illustrates solutions (output) of equation 6 for three different b 's.

It follows that a numerical scheme can be established in order to compare measured data with the predicted ones obtained from equation 6, using a minimizing technique such that the

following equation is minimum:

$$= \sum_{i=1}^n \frac{1}{2} y_i - E(t_i)^2 \quad (7)$$

where y_i is a measured value at time t_i , and $E(t_i)$ is the corresponding theoretical input value. Based on the above analysis a computer was programmed to calculate the "true" (corrected) a and b 's.

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CHAPTER III

PHRENIC ACTIVITY, RESPIRATORY
PRESSURES, AND VOLUME CHANGES
IN CATS

III.1. INTRODUCTION

Although in recent years there has been considerable interest in the study of the breathing pattern, so far little attention has been paid to detailed analysis of the configuration of the spirogram. In the study described in detail in Chapter 11, we have found that the morphology of the time course of efferent phrenic activity shows considerable inter-animal differences which are reflected in the tracheal and transdiaphragmatic occlusion pressure waveforms (15). Accordingly, similar inter-animal differences should be found in the morphology of the spirogram.

In the present study we first develop a model for predicting the variations in the inspiratory volume-time profile for different inspiratory driving pressure waveforms. Next, using experimental data obtained on cats breathing room air, hypercapnic and/or hypoxic mixtures we determine the transform functions of efferent phrenic activity and of inspiratory driving pressures into volume changes. Finally, we determine the relationships between two recently proposed indices of central inspiratory activity, namely the rate of rise of phrenic activity (5) and of airway occlusion pressure (16), with pulmonary ventilation and mean inspiratory flow.

III.2. MODEL PREDICTIONS

III.2.1. Assumptions. In Chapter II we have shown that in cats, during airway occlusion at end-expiratory

lung volume, the rising part of the airway (tracheal) and transdiaphragmatic pressure waves can be approximated by a power function of the general type:

$$P = aT^b \quad (1)$$

where P is pressure, T is time (sec), b is a dimensionless index of the shape of the curve and a is the pressure developed 1 second after the onset of inspiration. Our first assumption is that the occluded pressure waveform also applies to the inspiratory driving pressures obtained during unoccluded inspirations. Next, we assume the respiratory system (rs) as a linear system with only one degree of freedom, the forces opposing changes in lung volume being represented by an effective linear resistance ($R'rs$) and elastance ($E'rs$), where $R'rs$ includes both the passive flow resistance of the total respiratory system and (if present) the flow-related pressure losses due to the force-velocity relationship of the inspiratory muscles, and $E'rs$ represents both the passive elastance of the total respiratory system and the volume-related pressure losses due to the force-length and geometrical arrangement of the inspiratory muscles (13).

III.2.2. Calculations. From the above premises, a numerical solution of the function relating driving pressure with volume (V) and instantaneous flow ($\dot{V}$) can be obtained as described in the Appendix. II. In the model predictions illustrated below we chose values for $R'rs$ and $E'rs$ of

Fig.15 From top to Bottom: Time course of changes in driving pressure (P), lung volume (V), instantaneous flow ($\dot{V}$) and mean inspiratory flow ($\bar{\dot{V}}$) computed for different driving pressure waveforms (b in equation 1 mounting to .8, 1.0 and 1.4) and a value for constant a in equation 1 of 5 cmH₂O. For further explanation see text.

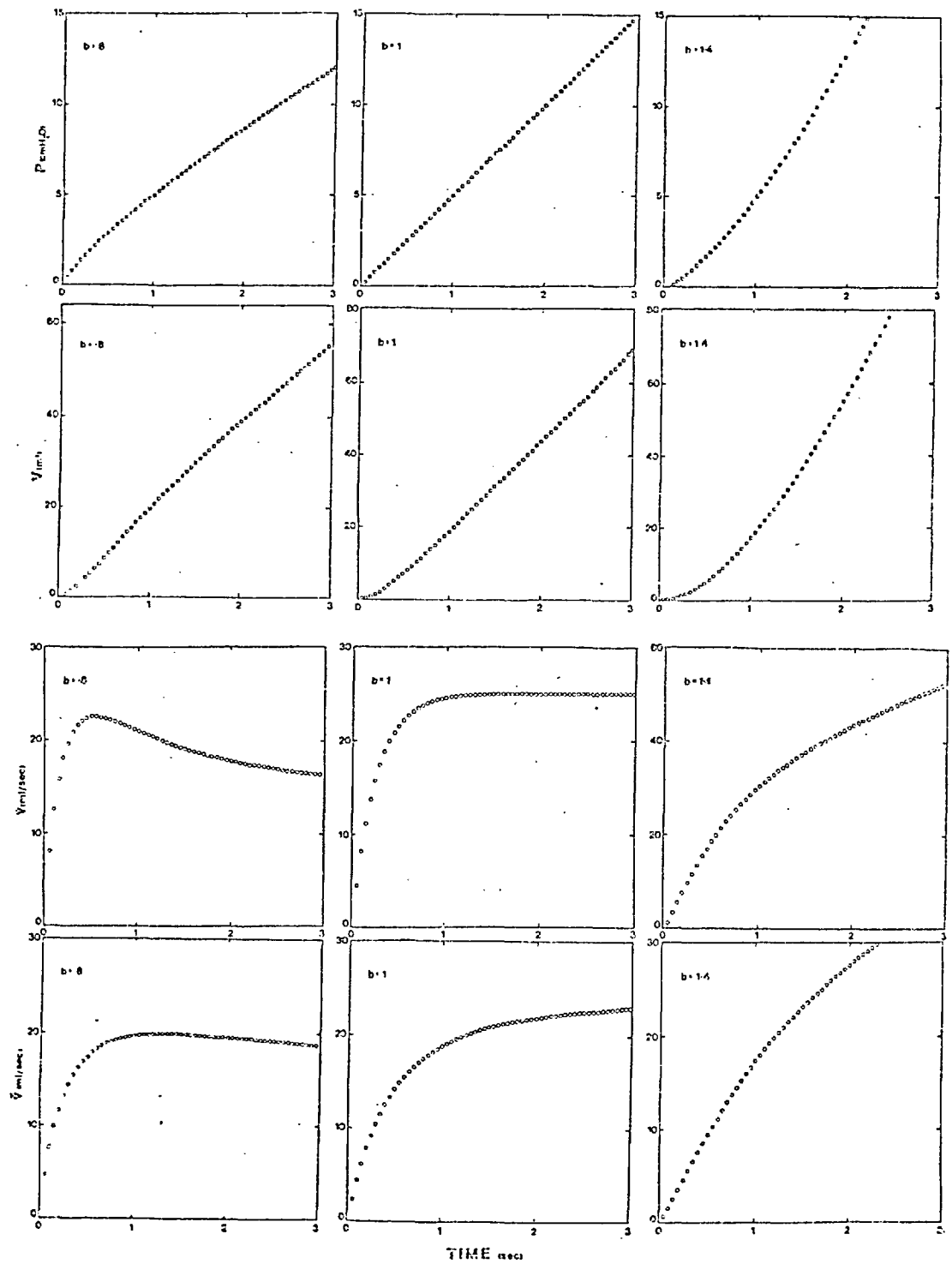


Figure 15.

.05 cmH₂O/ml/s and .2 cmH₂O/ml, respectively (the time constant amounting to .25s). These are not far from the experimental values obtained in the cats of the present study. We chose values of b in equation 1 ranging between .8 and 1.4 which cover the experimental range of our cats (15).

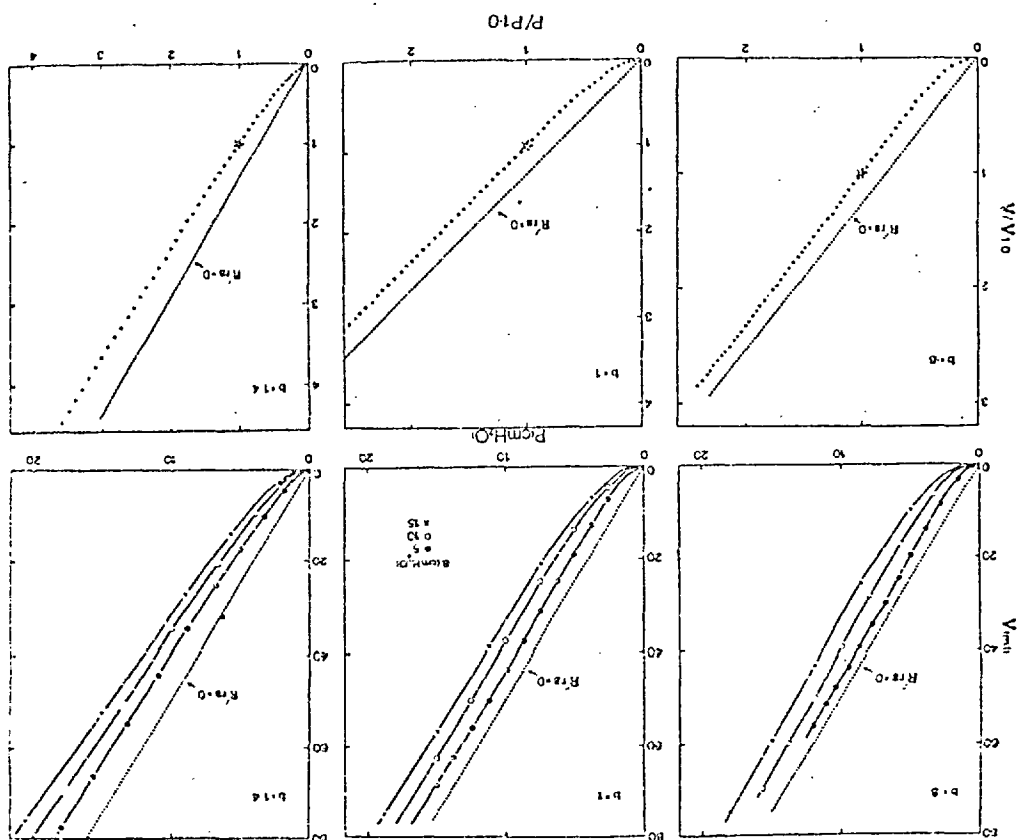
Fig.15(top) illustrates the relationship between driving pressure and inspiratory duration (T_I) for three different values of b , namely .8, 1 and 1.4. In each instance a (the pressure at 1s) was 5 cmH₂O, which is within the range of experimental values obtained in our cats breathing room air (15). Also shown in Fig.15 are the computed volume-time and instantaneous flow-time profiles. For $b=1$ (linear pressure-time profile) $\dot{V}$ increases progressively until it reaches a plateau at about 1 sec, the slow initial increase in $\dot{V}$ being due to the time constant of the system. With $b=.8$, $\dot{V}$ increases during the first .5s and thereafter progressively declines. For $b=1.4$, $\dot{V}$ continuously increases with time. These $\dot{V}$ -time relationships are of course reflected in the profiles of the corresponding spirograms.

Fig.15(bottom) shows the relationship of mean inspiratory flow ($\bar{\dot{V}}$) with inspiratory time for the different driving pressure waveforms. $\bar{\dot{V}}$ was computed by dividing the volume achieved at any given time (say V at .5, 1, 1.5s) by the corresponding time (.5, 1, 1.5s). For $b=1$, $\bar{\dot{V}}$ increases with time, rapidly at first (up to about 1s) and

Fig. 16 Top: Relationship between changed in volume (V) and driving pressure (P) for different driving pressure waveforms ($b = .8, 1.0$ and 1.4) and various driving pressure amplitudes ($a = 5, 10$ and $15 \text{ cmH}_2\text{O}$). Lines labelled $R'rs = 0$ indicate pressure expended to overcome $E'rs$. The horizontal distance between dotted and solid lines represents pressure spent to overcome $R'rs$.

Bottom: Same relationships as above, but V and P expressed as a fraction of the corresponding values obtained 1 s after the onset of inspiration ($V/V_{1.0}$ and $P/P_{1.0}$, respectively). A unique relationship is obtained for each value of b (dotted lines).

Figure 16



slower later on. This reflects the fact that as time progresses the initial loss in $\dot{V}$ due to the time constant makes a progressively smaller contribution to the overall mean flow. With $b=.8$, $\bar{\dot{V}}$ increases up to about 1.3s, and then gradually declines. Between about 1 and 1.8s, $\bar{\dot{V}}$ exhibits a near plateau. For $b=1.4$, $\bar{\dot{V}}$ increases continuously and markedly with inspiratory time. Clearly, for $b=1.4$, $\bar{\dot{V}}$ is highly T_I -dependent for all inspiratory durations. For b values of .8 and 1, $\bar{\dot{V}}$ is highly T_I -dependent (i.e. changes substantially) only at T_I 's lower than 1s. These predictions show that changes in T_I can per se alter the mean inspiratory flow, i.e. for a given value of the constant a in equation 1 a variety of $\bar{\dot{V}}$ values can be obtained depending on T_I and b . Changes in E 'rs and R 'rs will, of course, also affect the $\bar{\dot{V}}$ vs. T_I relationships.

Our model also predicts that the relationship between driving pressure (P) and changes in volume (V) varies with the magnitude of the constant a in equation 1 (Fig.16top). When P and V , however, are normalized (e.g. for the respective values obtained at 1s namely $P_{1.0}$ and $V_{1.0}$) the curves for any value of b are superimposed (Fig.16 bottom). The shape of these functions, however, differs with the value of the constant b . This implies that for a given applied pressure waveform (fixed b) and fixed E 'rs and R 'rs values, an increase in the amplitude of the driving pressure wave (increased a) will result in a proportional increase in the

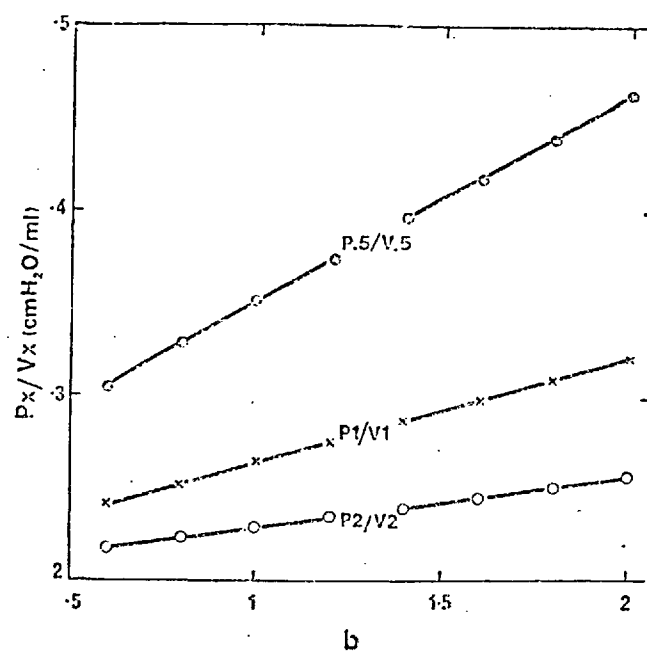


Fig. 17 Relationships of $P.5/V.5$, $P_{1.0}/V_{1.0}$ and $P_{2.0}/V_{2.0}$ with constant b of equation 1. Note that these relationships are independent of the value of the constant a .

amplitude of the spirogram. In other words, under these conditions the ratio of $P_{.5}/V_{.5}$, $P_{1.0}/V_{1.0}$, and so on will be independent of the magnitude of a . Nevertheless, the magnitude of these ratios will differ from different values of b (Fig.17).

Clearly, the relationship of Figs.15-17 will vary quantitatively for values of E 'rs and R 'rs different from those chosen in the present calculations.

III.2.3. Limitations Our model does not take into account the termination of inspiration which during spontaneous breathing is not instantaneous but at the end of inspiration there is a gradual rather than instantaneous decrease of inspiratory flow to zero. Second, our model does not take into account inertial forces. In spite of these and other limitations, the predictions based on this simple model appear to be useful for explaining many of the features of control of breathing found experimentally in the present study.

III.3. METHODS

The present studies were carried out in conjunction with those discussed in Chapter II. The same supine cats (anesthetized with 35 mg/kg of pentobarbital sodium, i.p.) were studied with the same equipment.

Briefly, "moving average" phrenic activity (E_{PHR}), changes in lung volume (V), airflow ($\dot{V}$), and esophageal (P_{es}), gastric (P_{ga}) and tracheal (P_T) pressures were measured while the cats inhaled room air, hypercapnic and hypoxic gas mixtures. All measurements were made under steady state conditions. During the CO_2 runs, 60 percent O_2 was added to

eliminate hypoxic drive. In the hypoxic runs end-tidal P_{CO_2} (P_{ACO_2}) was kept constant by adding CO_2 to the inspired gas. In all cats, the end-expiratory lung volume did not appear to change with either hypoxia or hypercapnia (15). Minute ventilation ($\dot{V}_E$) was calculated as the product of tidal volume (V_T) and frequency of an average of 10-20 breaths. Inspiratory (T_I) and total (T_{TOT}) breath durations were obtained from the flow signal over the same breaths. Mean inspiratory flow was computed by dividing V_T by T_I .

In addition to the measurements described in detail in the previous Chapter (II) we have also measured the tracheal, gastric and esophageal pressures during relaxation of the respiratory muscles at different lung volumes. In the anesthetized cats, following inflation of the lungs there was a period of apnea (Hering-Breuer inflation reflex) during which the relaxation pressures were measured. As previously reported by Pengelly et al (13) for supine cats, during relaxation P_{ga} was more positive than P_{es} , the difference decreasing with increasing lung volume. This behaviour has been attributed to elastic tension within the diaphragm (13). Net or active transdiaphragmatic pressure, $P_{di}(\text{mus})$ developed at different lung volumes was computed by subtracting the transdiaphragmatic pressure during relaxation from the total transdiaphragmatic pressure obtained during at a corresponding lung volume/active breathing (13). The difference between active and relaxed P_{ga} will henceforth be referred to as ΔP_{ga} . During active breathing we also

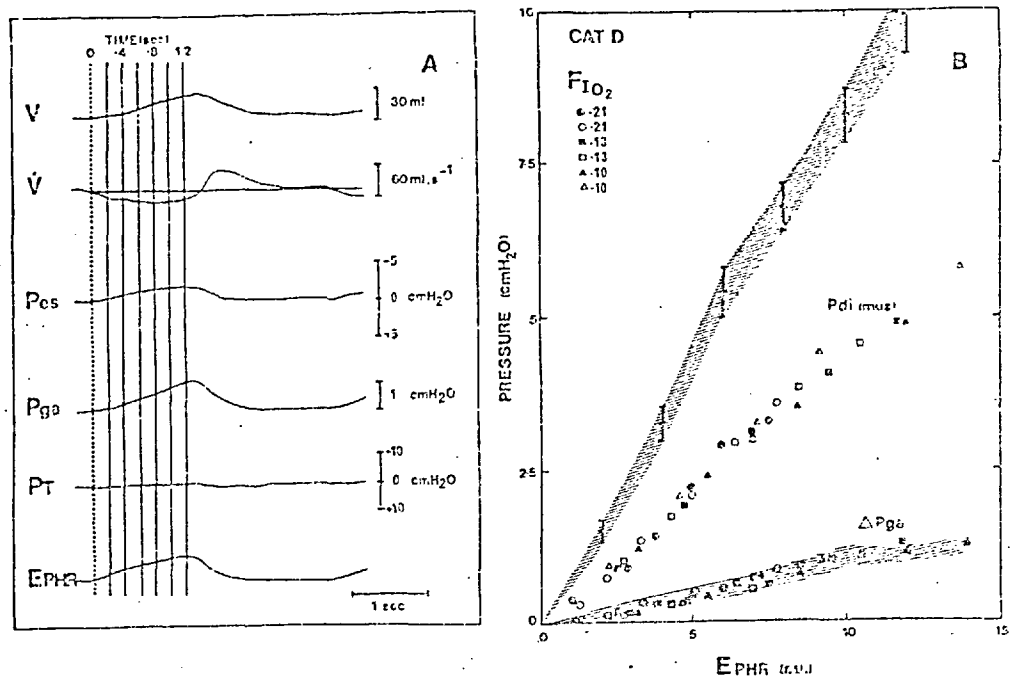


Fig. 18. A: Record obtained in cat D during room air breathing.

Onset of phrenic activity is indicated by vertical broken line. At times indicated by solid vertical lines $P_{di}(mus)$, ΔP_{ga} and E_{PHR} were determined and plotted in B together with similarly obtained data from 5 additional breaths at various inspired O_2 concentrations. The hatched areas

indicate the relationships ($\pm 1SD$) between $P_{di}(mus)$ and E_{PHR} (top) and ΔP_{ga} and E_{PHR} (bottom) obtained in the same cat during efforts with airways occluded at end-expiration

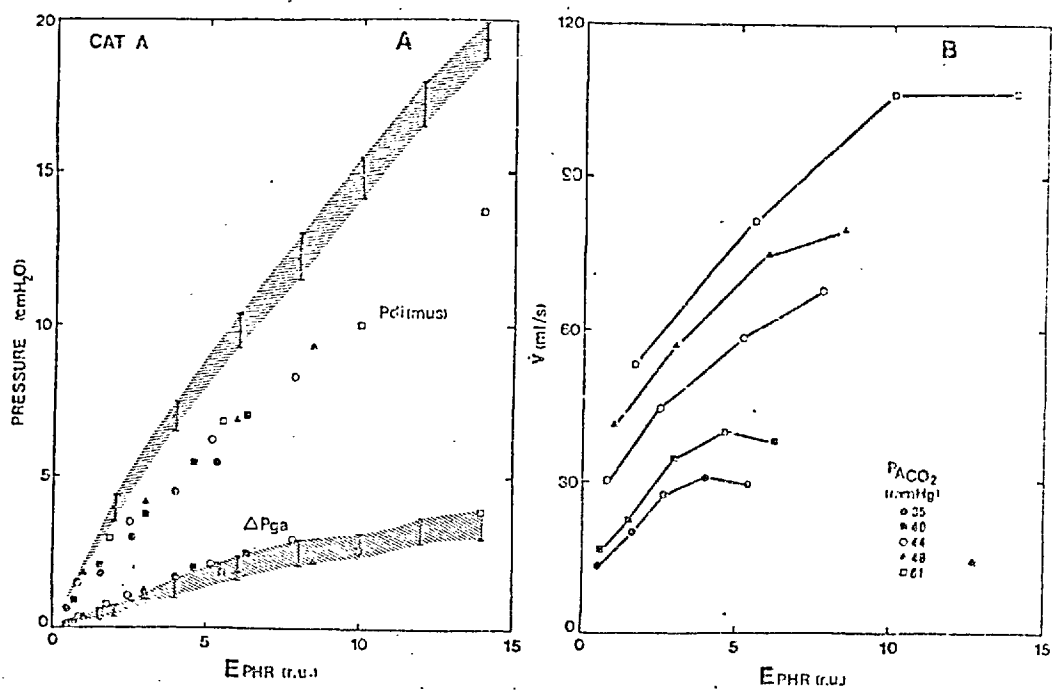


Fig.19.A: Relationships of $P_{di(mus)}$ and ΔP_{ga} with $EPHR$ at various values of P_{ACO_2} . Hatched areas as in Fig. 18B.
 B: Corresponding relationships between instantaneous flow ($\dot{V}$) and $EPHR$. Cat A.

measured in our cats the pulmonary flow resistance (R_l) according to Mead and Whittenberger (9).

III.4. RESULTS

Fig.18A shows a record obtained in cat D during room air breathing. Onset of phrenic activity is indicated by the vertical broken line. The solid vertical lines indicate .2s intervals from the onset of phrenic activity where measurements of $P_{di}(\text{mus})$, ΔP_{ga} and E_{PHR} were made, and plotted as shown in Fig.18B, together with similarly obtained data from 5 additional breaths at various values of $F_{I_{O_2}}$. Each breath is represented by a different symbol. It can be seen that with increasing hypoxic drive $P_{di}(\text{mus})$, for a given E_{PHR} , did not change appreciably inspite of the fact that mean inspiratory flow (V_T/T_I) increased as $F_{I_{O_2}}$ was lowered (from a value of 15 ml/s during room air breathing to 32 ml/s with $F_{I_{O_2}} = .1$). This suggests that the pressure losses due to the force-velocity relationship of the diaphragm were negligible. The relationship between ΔP_{ga} and E_{PHR} also did not show systematic changes with decreasing $F_{I_{O_2}}$, suggesting that, at any given value of E_{PHR} , the descent and configuration of the diaphragm were similar at all values of $F_{I_{O_2}}$. Similar results were found in all cats during both hypoxic and hypercapnic stimulation of breathing. An example of the latter is shown in Fig.19A. In this cat the mean inspiratory flow increased from value of 24 ml/s during room air breathing ($P_{ACO_2} = 35$ mm Hg) to 85 ml/s at the highest P_{ACO_2} (61 mm Hg). The

corresponding relationships between instantaneous flow ($\dot{V}$) and E_{PHR} are shown in Fig.19B.

The fixed relationship between E_{PHR} , $P_{di}(\text{mus})$ and ΔP_{ga} implies a proportional increase in activity among all inspiratory motor inputs (diaphragm and intercostal/accessory muscles) with increasing CO_2 and hypoxic drive. This is in agreement with the results of previous studies on cats and rabbits subjected to various inhaled CO_2 concentrations (4,10).

As shown in Figs.18 and 19 at any given value of E_{PHR} , $P_{di}(\text{mus})$ was substantially greater during the inspiratory efforts made with airways occluded at end-expiratory lung volume than during the unoccluded inspirations. As ΔP_{ga} was similar in the two conditions, the difference between occluded and unoccluded transdiaphragmatic pressure was mainly due to a reduction in the pressure developed on the thoracic side of the diaphragm during the unoccluded breaths.

In order to assess the nature of this difference in pressure between occluded and unoccluded breaths, the following analysis was made. First, we assume that the inspiratory neural drive is the same during the occluded and corresponding unoccluded inspirations. This assumption is justified for E_{PHR} which was in all of our cats identical under the two conditions (15). Second, we assume that P_T^O (i.e., the tracheal pressure developed during inspirations with airways occluded at end-expiratory lung volume) represents the driving pressure available for producing changes in lung volume. This assumption appears to be justified by our finding that, at any given

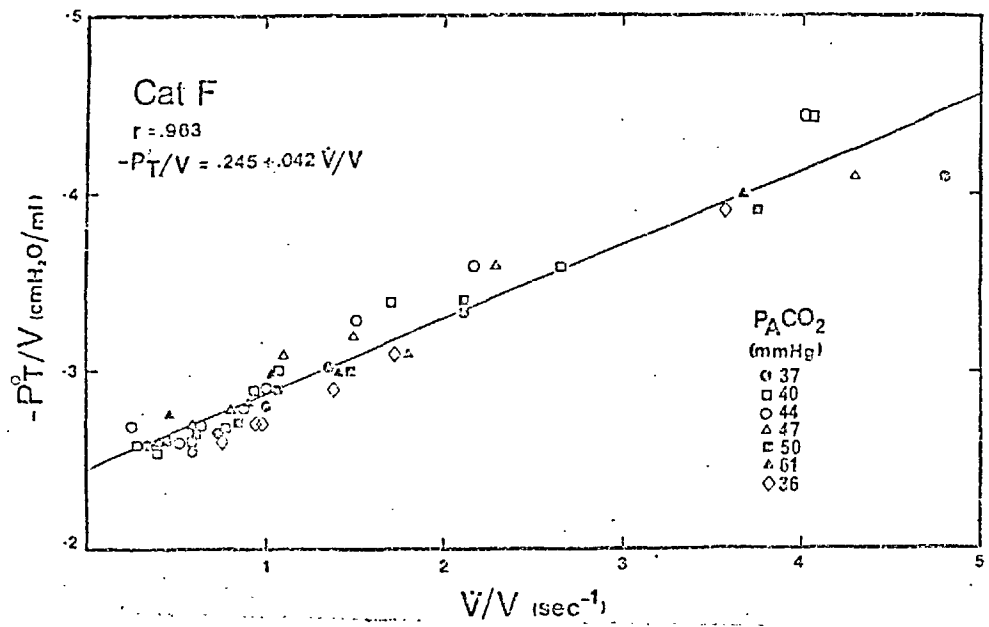


Fig.20. Relationship between $-P_T^O/V$ and $\dot{V}/V$ in cat F at various $P_A CO_2$ values.

E_{PHR} value, ΔP_{ga} was essentially the same during the unoccluded and occluded inspirations.

Third, we assume that the effective elastance (E'_{rs}) and resistance (R'_{rs}) of the respiratory system are linear. Taking the sign of the pressures into account, the relationship between the driving pressure and ^{the} pressures which are dissipated to produce changes in lung volume is given by (1):

$$-P_T^O = E'_{rs}V + R'_{rs}\dot{V} \quad (2)$$

where $E'_{rs}V$ and $R'_{rs}\dot{V}$ are, respectively, the static and dynamic components of the opposing pressures.

By dividing equation 2 by V :

$$-P_T^O/V = E'_{rs} + R'_{rs}\dot{V}/V \quad (3)$$

Fig.20 shows a plot of $-P_T^O/V$ vs. $\dot{V}/V$ for a cat subjected to various inspired CO_2 concentrations (different symbols). Each data point represents values obtained at .2s intervals from the onset of phrenic activity. $\dot{V}/V$ was computed from simultaneous measurements of instantaneous flow and volume during the unoccluded breaths; $-P_T^O/V$ was computed from measurements of V on the breath immediately preceding the occluded inspiration from which P_T^O was derived. In each instance, phrenic activity was the same during the occluded and corresponding unoccluded inspirations. It can be seen that the results fit equation 3, the relationships being essentially the same at all P_{ACO_2} values. Similar results were found in all cats. The correlation coefficient (r)

Table 2 Mean values ($\pm$ SD) of passive and effective elastance, resistance and time constant (τ) for eight cats.

PASSIVE			EFFECTIVE*		
Ers	Rl**	τ	E'rs	R'rs	τ'
(cm H ₂ O/ml)	(cm H ₂ O/ml/s)	(s)	(cm H ₂ O/ml)	(cm H ₂ O/ml/s)	(s)
.132 $\pm$.016	.033 $\pm$.006	.25 $\pm$.07	.251 $\pm$.043	.040 $\pm$.015	.16 $\pm$.03

*Computed according to equation 3.

**The flow resistance of the equipment amounted to .015 cmH₂O/ml/s.

varied between .91 and .98 in the 8 cats. In the cats subjected to both hypoxia and hypercapnia, no appreciable difference in the relationship between $-P_T^O/V$ and $\dot{V}/V$ was found. The average values ($\pm$ SD) of E'rs and R'rs obtained in the eight cats from this analysis are given in Table 2 together with the corresponding values of passive (relaxed) elastance of the total respiratory system (Ers) and pulmonary flow resistance (Rl). In all cats the latter did not change appreciably with either hypoxia or hypercapnia. The values of R'rs (0.40 cm H₂O/ml/s) on the average were slightly higher than those of Rl (.033 cm H₂O/ml/s). If individual cats are considered, only in one of them (D) was R'rs (.064 cmH₂O/ml/s) substantially higher than Rl (.034 cm H₂O/ml/s). The reason for this is not clear. It is possible that in this cat our assumption that the inspiratory neural drive is the same during the occluded and corresponding unoccluded inspirations was not valid, at least with respect to the extra-diaphragmatic inspiratory muscles. In fact, according to Bradley (2) in some pentobarbital anesthetized cats the rate of rise of integrated EMG from the inspiratory intercostal muscles is at times greater during loaded than unloaded inspirations. If this was the case in cat D, P_T^O was an overestimate of the actual driving pressure obtained during the unoccluded inspirations, and this could have resulted in an overestimate of R'rs.

According to Brody and Dubois (3), the passive resistance of the chest wall in cats amounts to .003 cm H₂O/ml/s. If this is added to our values of Rl in order to obtain the

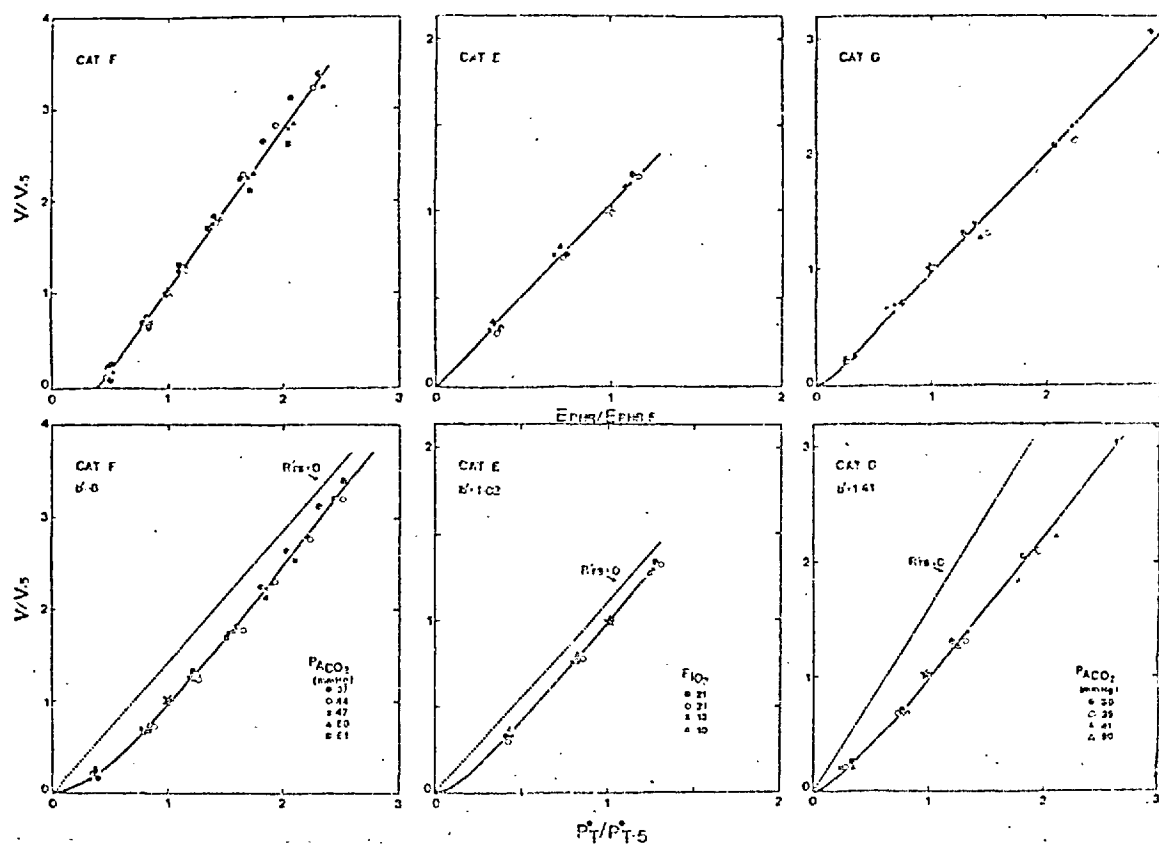


Fig.21. Relationship between $V/V.5$ and $EPHR/EPHR.5$ (top), and $V/V.5$ and $P_T^O/P_T.5^O$ (bottom) in 3 cats with different shapes of tracheal occlusion pressure waves, the shape index b' (equation 4) ranging from .8 to 1.41. Results obtained at different values of $PACO_2$ and FI_{O_2} are shown.

resistance of the total respiratory system (R_{rs}), the difference with our measured values of R'_{rs} becomes negligible, except for cat D. This further supports the notion that in our cats the dynamic pressure losses due to the force-velocity relationship of the inspiratory muscles were negligible. By contrast, the values of E'_{rs} were in all of our cats markedly greater than those of E_{rs} , presumably reflecting decreased effectiveness of the inspiratory muscles as pressure generators with increasing lung volume (8,13)

Fig.21 shows for three cats the relationship between volume (V) and E_{PHR} (top), and volume and P_T^O (bottom), all variables being expressed as a fraction of the corresponding values achieved .5s after the onset of phrenic activity, namely $V_{.5}$, $E_{PHR.5}$ and $P_{T.5}^O$. In each cat results obtained at different values of P_{ACO_2} or F_{IO_2} are shown. It can be seen that the relationships did not change appreciably with increased hypoxic or hypercapnic drive. Similar results were found in all cats.

In the previous Chapter(II) it was shown that the morphology of the inputs driving the ventilatory pump (i.e. the configuration of the phrenic neurogram and of the tracheal and transdiaphragmatic occlusion pressure waves) was in our cats essentially unaffected by CO_2 and hypoxia. The present results showed that the effective elastance and resistance of the respiratory system can also be considered as constant. Accordingly, results as shown in Fig.21 are

Fig22. From top to bottom: Time course of tracheal occlusion pressure (P_{T}^O), volume (V), instantaneous flow ($\dot{V}$) and mean inspiratory flow ($\bar{\dot{V}}$) in 3 cats with different morphology of the tracheal occlusion pressure waves, the shape index b' (equation 4) ranging between .8 and 1.41. Results obtained during room air breathing. The broken lines indicate relationships computed using individual values of $E'rs$, $R'rs$, a' and b'

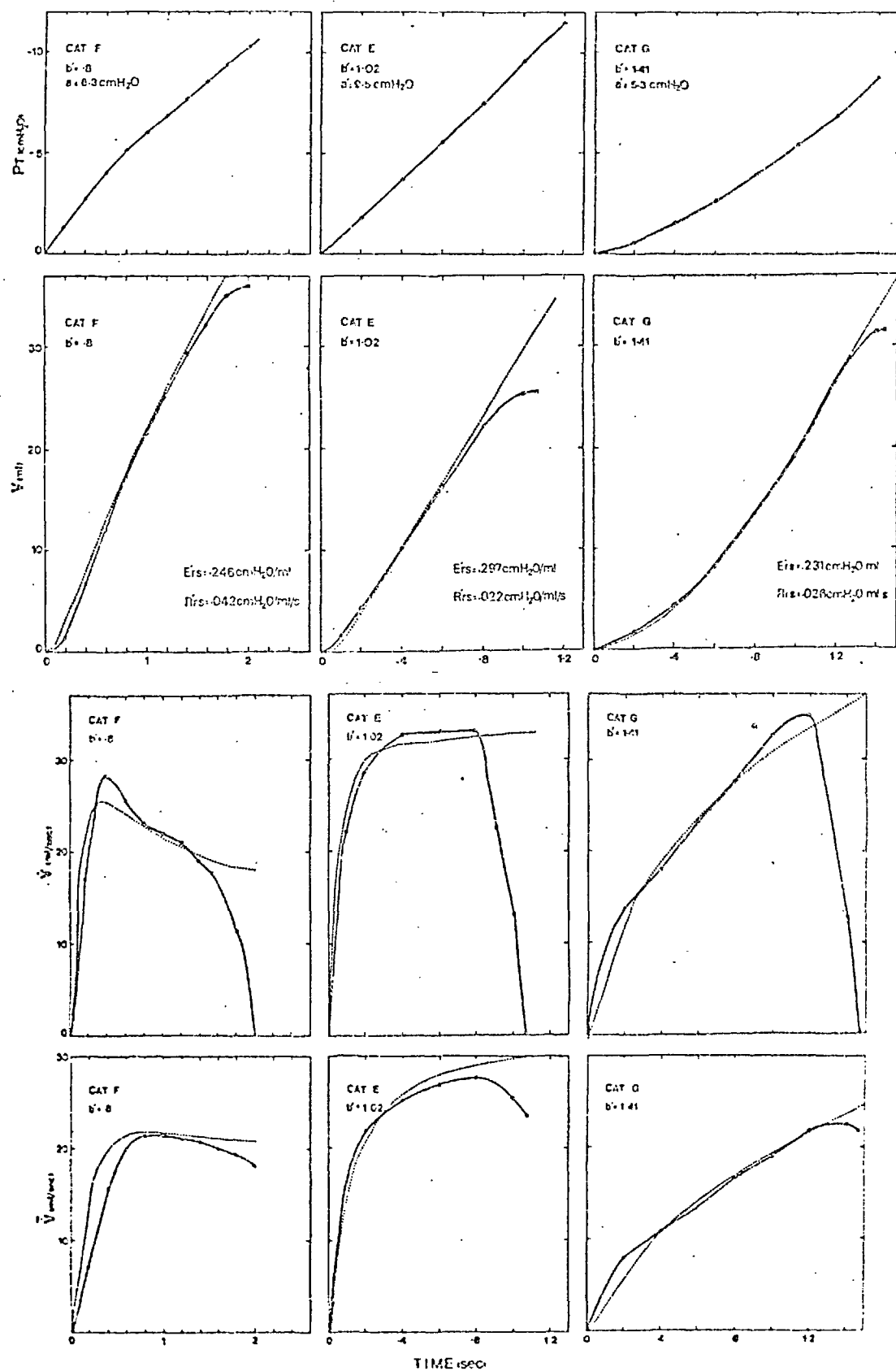


Figure 22

not surprising, and are in accordance with our model predictions (Fig.16 bottom).

Our model predicts that the morphology of the spirogram and pneumotachogram depends on the driving pressure waveform (Fig.15). In our cats, the rising part of the tracheal occlusion pressure wave can be described by a power function of the form (12, 15):

$$P_T^O = a'T^{b'} \quad (4)$$

where T is time in seconds, a' is the tracheal pressure developed 1s after the onset of the occluded inspiration, and b' is a dimensionless constant describing the shape of the wave.

Fig.22 shows inspiratory spirograms and pneumotachograms obtained in 3 cats with different morphology of the tracheal occlusion pressure wave, the values of b' ranging from .8 to 1.41. It can be seen that the observed patterns are qualitatively in agreement with our predictions (Fig.15). This was the case in all animals studied. The agreement between predicted and observed results is quantitatively improved by using in our predictions the experimental values of E' 's and R' 's (broken lines in Fig.22). Also shown in Fig.22 are the observed relationships between $\bar{V}$ and inspiratory duration (T_I). Again, a good agreement between prediction and experimental observation is seen. It should be noted that the theoretical model does not take into account the gradual decline in airflow (and related events) which takes place

Table 3. Regression equations between various ventilatory variables in 8 cats during hypercapnic and/or hypoxic stimulation of breathing, together with b' values (equation 4) Chapter 11

CAT	b'	$V_{.5} = K + m P_{T.5}^O$			$\dot{V}_E = K_1 + m_1 P_{T.5}^O$			$V_T/T_I = K_2 + m_2 P_{T.5}^O$			$\dot{V}_E = K_3 + m_3 (V_T/T_I)$		
		K (ml)	m (ml/cmH ₂ O)	r	K ₁ (ml/min)	m ₁ (ml/min/cmH ₂ O)	r	K ₂ (ml/sec)	m ₂ (ml/sec/cmH ₂ O)	r	K ₃ (ml/min)	m ₃	r
A	1.29	-1.6	4.0	.984	158**	205	.994	3.5	8.5	.994	76***	24	.999
B	.90	1.9	2.8	.984	68	133	.974	4.2	5.1	.982	-55	26	.982
C	.89	2.2	2.3	.974	405*	99	.989	12.1*	3.9	.987	98***	26	.999
D	.90	-2.8	3.6	.996	136	120	.960	2.8	5.4	.960	76	22	.999
E	1.02	1.3	2.8	.999	125**	144	.999	3.2	4.9	.998	36	29	.998
F	.80	-0.8	3.0	.991	24	140	.947	-0.8	6.1	.975	39	23	.976
G	1.41	0.9	3.1	.997	460***	145	.991	15.0***	5.9	.992	100***	25	.999
H	.95	0.1	2.5	.990	46	135	.994	-1.2	5.5	.996	74	25	.998
Mean	1.02	.15	3.0		178	140		4.9	5.7		56	25	
SD	0.21	1.76	.56		164	30		5.8	1.3		50	2	

Significance level (P): * < .05; ** < .01; *** < .001.

The values of b' (eq. 4) are from Chapter 11

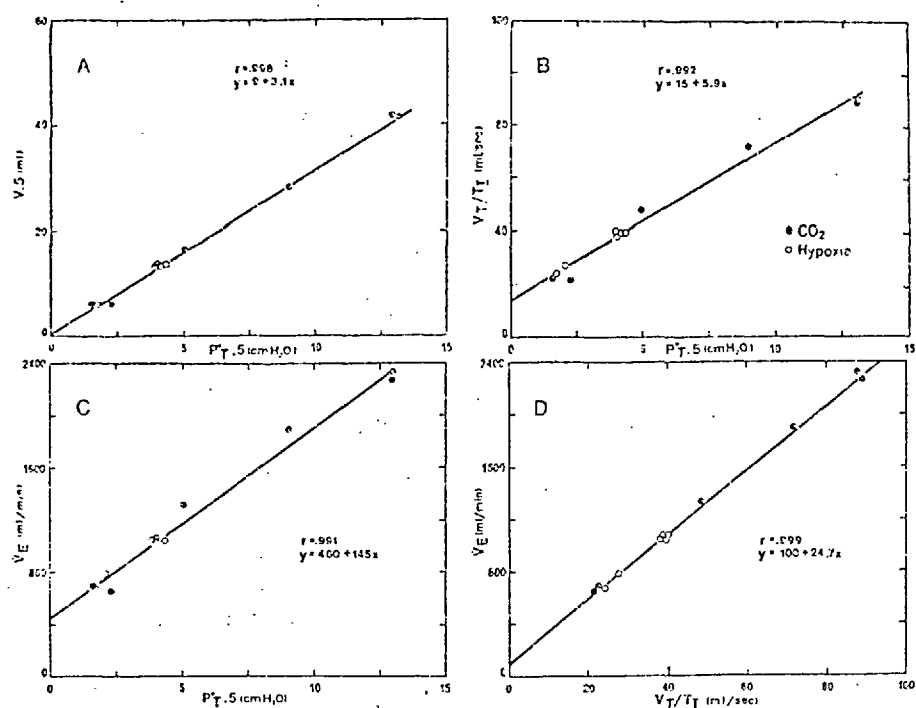


Fig.23. Relationships between $V.5$ and $P_{T,5}^O$ (A), V_T/T_I and $P_{T,5}^O$ (B), $\dot{V}_E$ and $P_{T,5}^O$ (C); $\dot{V}_E$ and V_T/T_I (D). Results in cat G during hypoxic (open circles) and hypercapnic (filled circles) stimulation of breathing.

toward the end of inspiration (Fig.22).

The results in Fig.21 imply that with increasing respiratory drive $V_{.5}$, $V_{1.0}$ and so on increase in direct proportion with the corresponding values of E_{PHR} and $P_{T.5}^O$. A plot of $V_{.5}$ against $P_{T.5}^O$ obtained during hypoxia and hypercapnia in cat G is shown in Fig.23A. A linear relationship is obtained with an intercept close to the origin of the co-ordinates. Similar results were found in all cats, the individual regression equations of $V_{.5}$ vs. $P_{T.5}^O$ being given in Table 3. A significance test for the intercept of $V_{.5}$ at $P_{T.5}^O = 0$ was carried out for all cats. In no case the intercept reached a significance level of .05. Thus, in each cat $V_{.5}$ and $P_{T.5}^O$ were equivalent indices of central inspiratory activity. The slopes of these regressions for the 8 cats ranged between 2.3 and 4.0 ml/cmH₂O. According to our model predictions (Fig.17), part of this variability could be attributed to inter-animal differences in the shape of the tracheal occlusion pressure waves. No significant correlation was however found between the reciprocal values of the slopes (1/m) and the corresponding shape indices (b') of the tracheal occlusion pressure waves (Table 3). Thus, the observed inter-animal differences in the relationship between $V_{.5}$ and $P_{T.5}^O$ must reflect in part inter-animal differences in effective elastance and resistance (Table 2).

Fig.23C shows the relationship between minute ventilation ($\dot{V}_E$) and $P_{T.5}^O$ for cat G. It can be seen that at $P_{T.5}^O = 0$ the regression line intercepted the y-axis at $\dot{V}_E = 460$ ml/min.

This implies that in this cat $\dot{V}_E$ and $P_{T.5}^O$ were not equivalent indices of respiratory output, i.e. with increased respiratory drive $\dot{V}_E$ changed proportionately less than $P_{T.5}^O$. The individual regression functions for $\dot{V}_E$ vs. $P_{T.5}^O$ are given in Table 3. A significance test for the intercept of $\dot{V}_E$ at $P_{T.5}^O = 0$ showed that in 4 cats it reached a significance level.

Fig.23B illustrates the relationship between overall mean inspiratory flow, obtained by dividing the tidal volume (V_T) by inspiratory duration (T_I), with $P_{T.5}^O$ in cat G. As for $\dot{V}_E$, the regression function intercepted the y-axis at a relatively high value of V_T/T_I (15 ml/s). Thus, in this cat V_T/T_I and tracheal occlusion pressure were not equivalent indices of respiratory output. This is in line with our model predictions. Indeed, in this cat the shape index (b') of the tracheal occlusion pressure wave (equation 4) was 1.41, and T_I decreased from a value of 1.47s during room air breathing to .86s during hypercapnia. Accordingly, with increasing drive the increase in V_T/T_I should be proportionately less than that in $P_{T.5}^O$ because the decrease in T_I has per se caused a reduction in overall mean inspiratory flow (Figs.15 and 22 bottom). Accordingly, a high y-axis intercept of the V_T/T_I vs. $P_{T.5}^O$ function is obtained. A high y-axis intercept was also found in cat C ($b' = .89$), in which T_I decreased substantially during hypercapnia (from 1.2 to .5s) and furthermore it reached low values (.5s) at

the highest CO_2 drives. At such low values of T_I , mean inspiratory flow becomes highly T_I -dependent (Fig.15). In the other 6 cats the y-axis intercepts were closer to zero because the changes in T_I with chemical stimulation of breathing were very small (cats A,B, E,H)and/or the T_I values never fell below .8s (cats A,D,F,G,H).

Also given in Table 3 are the regression functions for $\dot{V}_E$ vs. V_T/T_I . The intercept of $\dot{V}_E$ at $V_T/T_I = 0$ was positive in 7 cats (range: 28-100 ml/min) and reached a significance level of .001 in 3 of them. Since $\dot{V}_E = (V_T/T_I) \times (T_I/T_{TOT})$, a positive intercept implies that T_I/T_{TOT} decreased with increasing hypercapnic and/or hypoxic drive. This contributed to the discrepancy between $\dot{V}_E$ and $P_{T,5}^O$ as indices of respiratory output. In cat B, on the contrary, the intercept of $\dot{V}_E$ at $V_T/T_I = 0$ was negative (-55 ml/min) indicating that T_I/T_{TOT} tended to increase during hypoxia and hypercapnia. In this connection it should be noted that in the cats subjected to inhalation of both hypoxic and hypercapnic mixtures the various relationships in Table 3 were virtually identical in the two conditions.

III.5. DISCUSSION

Mognoni et al (11) and Pengelly et al (13) reported that in anesthetized cats and dogs and in conscious humans, with constant tetanic electrophrenic stimulation at a fixed

lung volume, the pressure developed by the diaphragm decreased with increasing airflow. They attributed this behaviour to the force-velocity characteristics of the diaphragm. On the other hand, Marshall (8) in similar electrophrenic stimulation experiments on anesthetized cats and dogs found that the pressure developed by the diaphragm did not vary appreciably with changes in airflow. This is in line with the results obtained in the present study. In our spontaneously breathing cats we found that $P_{di}(mus)$, at a fixed E_{PHR} , did not change appreciably with increasing airflow. The reasons for these discrepant results are not clear. On theoretical grounds, relatively greater pressure losses due to the force-velocity relationship would be expected when the breathing movements are produced by contraction of a single muscle (phrenic stimulation) than when breathing involves contraction of both diaphragm and extra-diaphragmatic muscles (spontaneous breathing). In addition, it should be noted that, during electrophrenic stimulation with occluded airways at functional residual capacity, the static pressure developed by the diaphragm required in cats about 150 ms to reach a plateau (11). During unobstructed electrophrenic inspiration a substantial increase in lung volume can occur within the first 150 ms following the application of the electrical stimulus, and this, to some extent, must have affected the results obtained in the electrophrenic studies. The latter should

better have been carried out by applying the stimulus to the phrenic nerves with airways initially closed in order to allow full development of $P_{di}(\text{mus})$ and next by opening the airways to study the dynamic events. Clearly, further studies using the approach of Goldman et al (7) are required to explain our finding that in spontaneously breathing cats the relationship between $P_{di}(\text{mus})$ and E_{PHR} is independent of airflow.

In line with the electrophrenic studies (8,13), we found that $P_{di}(\text{mus})$ decreased with increasing lung volume, as a result of decreased pressure developed on the thoracic side of the diaphragm. Our observation that, at any given value of E_{PHR} , the changes in gastric pressure (ΔP_{ga}) were virtually the same during unoccluded and occluded inspirations are in line with the results obtained in cats with electrophrenic stimulation (13). This indicates that the viscous resistance of the abdominal wall and contents is very small. Furthermore, these findings imply that the pressure losses in deforming ~~ing~~ of the chest wall was virtually the same during occluded and unoccluded inspirations.

Since the relationship between ΔP_{ga} and E_{PHR} was similar during occluded and unoccluded breaths, it follows that the pressure developed on the thoracic side of the diaphragm during the occluded efforts (P_T^O) represents the "effective" (potential) pressure available for producing changes in lung volume. During unobstructed inspiration, P_T^O is

dissipated in part to overcome the flow-resistance and elastance of the passive respiratory system. In addition, there is a volume-related (but not flow-related) loss in pressure which is probably due to changes in geometrical advantage of the inspiratory muscles and/or their length (8,13). As during both occluded and unoccluded inspirations gastric pressure increased in all cats relative to the values obtained during relaxation, it follows that the pressure contributed by the diaphragm probably predominated over that of intercostal/accessory muscles. In some cats, the values of ΔP_{ga} were very small, indicating that the intercostal/accessory muscles acted essentially as fixators of the rib cage. In other cats, however, the values of ΔP_{ga} were more pronounced, and hence the inspiratory intercostal/accessory muscles probably lengthened during inspiration. Nevertheless, the near constancy of the interrelationships between $P_{di}(mus)$, ΔP_{ga} and E_{PHR} during both occluded (15) and unoccluded inspirations made at different respiratory drives suggests that in each cat the contribution of the diaphragm and extra-diaphragmatic muscles was proportionately the same during hypercapnia, hypoxia and room air breathing. This is in agreement with previous reports on cats (4,10).

In the previous Chapter(II) it was shown that in our cats there were substantial inter-animal differences in

the morphology of the phrenic neurogram and of its transform functions, namely the tracheal and transdiaphragmatic occlusion pressure waves. In each animal, however, the morphology of the time-course of these variables did not change appreciably with inhalation of CO₂ and hypoxic mixtures. In the present study we have developed a model which predicts the morphology of the spirogram and pneumotachogram for various driving pressure waveforms (Fig.15). This model also predicts that, for constant morphology of the driving pressure wave and fixed values of effective flow resistance and elastance, the changes in lung volume should be proportional to those in the amplitude of the driving pressure wave (Fig.16). Our experimental data fit both model predictions in the sense that (a) the morphology of the spirograms and pneumotachograms closely approximated that expected on the basis of the shape of the tracheal occlusion pressure waves (Fig.22 and (b) the relationship between $V/V_{.5}$ and both $P_T^0/P_{T.5}^0$ and $E_{PHR}/E_{PHR.5}$ was in each cat essentially the same at all respiratory drives (Fig.21). The latter results imply (a) that in each cat the effective resistance ($R'rs$) and elastance ($E'rs$) of the respiratory system were fixed, and (b) that $V_{.5}$, $E_{PHR.5}$ and $P_{T.5}^0$ were in each cat equivalent indices of central inspiratory activity. The former is in accordance with the results obtained using equation 3.

It has been previously suggested(6) that ratios such as $P_{T.5}^0/V_{.5}$ be used as measures of the "effective inspiratory impedance." According to our model analysis (Fig.17),

at fixed values of flow resistance and elastance, the magnitude of $P_{T.5}/V_{T.5}$ varies with the shape of the driving pressure wave. This should be taken into account when comparing values of "effective inspiratory impedance" between animals with different morphology of driving inputs. With a fixed morphology and constant $E'rs$ and $R'rs$, however, the values of "effective inspiratory impedance" are independent of respiratory drive. These conditions were met in each of our cats, as shown by the fact that the function relating $P_{T.5}^0$ and $V_{T.5}$ was linear, with an intercept not significantly different from zero (Table 3).

While in each of our cats the changes in $V_{T.5}$ elicited by hypoxia and hypercapnia were proportionately the same as those in $P_{T.5}^0$ (or $E_{PHR.5}$), this was not always the case for $\bar{V}_E$ and V_T/T_I . According to our model predictions (Fig.15 bottom) and experimental results (Fig.22 bottom), the mean inspiratory flow is T_I -dependent, the function relating $\bar{V}$ with T_I varying both with the driving pressure waveform and the values of $E'rs$ and $R'rs$. As shown in Figs.15 and 22, the effect of changes in T_I on $\bar{V}$ is highly dependent on the operational range of T_I 's. Since in our cats there was considerable inter-animal variability in both the absolute values of T_I and in the magnitude of the changes in T_I elicited by hypoxia and/or hypercapnia, it is not surprising that the relationship between V_T/T_I and $P_{T.5}^0$ varied considerably from one animal to the other. In

fact, for a given $P_{T.5}^0$ (or $E_{PHR.5}$) different values of V_T/T_I can be obtained depending on the morphology of the tracheal occlusion pressure wave, magnitude of E's and R's, duration of inspiration, and also the pattern of termination of inspiration. The latter is not taken into account in our model predictions. In the present study, however, the termination of inspiration was relatively abrupt.

In several of our cats, T_I/T_{TOT} decreased progressively during increased hypoxic and hypercapnic stimulation of breathing. As a result the changes in $\dot{V}_E$ induced by increased chemical drive were proportionately smaller than those in V_T/T_I (Table 3). Consequently, in these cats the discrepancy between changes in $\dot{V}_E$ relative to those in $P_{T.5}^0$ was greater than that between V_T/T_I and $P_{T.5}^0$. In only one cat (B) T_I/T_{TOT} was found to increase slightly during hypoxia and hypercapnia.

III.6. APPENDIX II

With the simplifying assumptions mentioned previously and an input pressure wave $P=at^b$, volume and flow are related to time by the following non-linear first order differential equation :

$$V + \tau \dot{V} = Cat^b \quad (5)$$

where C is the compliance and τ the product of resistance and compliance, or time constant.

As there is no analytical solution for eq. 5 when b is not an integer, volume and flow at different, equally spaced, time intervals were obtained using a numerical method.

Let V_i and $\dot{V}_i$ be the volume and flow at time t_i and V_{i-1} and $\dot{V}_{i-1}$ the volume flow at time $(t_i - \Delta t)$, by using the trapezoidal approximation for numerical integration:

$$V_i = V_{i-1} + \Delta t (\dot{V}_{i-1} + \dot{V}_i) / 2 \quad (6)$$

Equation 5 may then be written as:

$$V_{i-1} + \Delta t (\dot{V}_{i-1} + \dot{V}_i) / 2 + \tau \dot{V}_i = Cat_i^b$$

which permits to express $\dot{V}_i$ as a function of time and of the previous volume and flow values:

$$\dot{V}_i = (2Cat_i^b - 2V_{i-1} - \Delta t \dot{V}_{i-1}) / (\Delta t + 2\tau) \quad (7)$$

Volume is then derived from flow using equation 6.

Equations 7 and 6 were programmed on a desk computer (Hewlett Packard 9100B) with the initial conditions $V=0$ and $\dot{V}=0$ at time $t=0$. The computation was made with a time step Δt of 2ms, which was seen to ensure a good accuracy for all τ values used in this study. The data were printed every 50 ms. Finally, the numerical solution was compared to the analytical solution for the case $b=1$ and found satisfactory.

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CHAPTER IV

DOSE-EFFECT OF PENTOBARBITAL
SODIUM ON CONTROL OF BREATHING
IN CATS

IV.1 INTRODUCTION

It is well known that pentobarbital sodium, one of the anesthetic agents commonly used in human subjects and in animals, depresses minute ventilation (14,17,22). The present study was designed to investigate the effects of progressively increased depth of pentobarbital anesthesia on: a) the output of the respiratory centers, b) the transdiaphragmatic pressure, c) the excitation-contraction coupling in the diaphragm, d) the mechanical properties of the respiratory system, and e) ventilation and breathing pattern in adult cats.

We recorded phrenic activity in order to investigate the central inspiratory activity (8), and transdiaphragmatic pressure and its relationship with phrenic activity to study the transformation of neural into muscular activity. Breathing pattern was analyzed in terms of tidal volume, respiratory frequency, duration of the respiratory phases and inspiratory flow, as well as in terms of the morphology of the spirogram.

IV.2 METHODS

Six adult cats, weighing 2.8-3.7 kg, were studied breathing spontaneously room air. The animals were initially anesthetized with 35 mg/kg of pentobarbital sodium intraperitoneally, and held supine on a heated operating table. The rectal temperature was continuously monitored and kept between 37 and 38°C. The trachea was intubated

and connected to a pneumotachograph (Fleisch No.00) for measurement of flow ($\dot{V}$). The flow resistance of the system was .015 cmH₂O/ml/s. Changes in lung volume (V) were obtained by electrical integration of the flow signal. Tracheal pressure (P_T) was measured by connecting the tracheal tube to a pressure transducer (Schlumberger H-5035). Esophageal (P_{es}) and gastric (P_{ga}) pressures were measured by means of two latex balloons attached to polyethelene catheters and connected to two identical pressure transducers (Schlumberger H-5020). In one animal, P_{ga} was not measured. The active or net transdiaphragmatic pressure, $P_{di}(mus)$, was obtained from measurements of P_{es} and P_{ga} as previously described Chap.III. The difference between active and relaxed gastric pressure, computed as previously indicated (Chap.III), henceforth be referred to as ΔP_{ga} . The active transdiaphragmatic and gastric pressure changes obtained during efforts with occluded airways at end-expiration will be referred to as P_{di}^0 and ΔP_{ga}^0 , respectively.

Phrenic activity was recorded from the C5 root after the nerve was isolated, cut and placed on bipolar platinum electrodes with its distal end fixed. The nerve preparation was kept in a warm (37-38°C) mineral oil pool. The signal was amplified (Grass Amplifier RRS 107 with a band pass of 50-10,000 Hz), rectified and integrated by an R-C low pass filter with a time constant of 100 ms. By this means the

the moving average of phrenic activity was obtained (E_{PHR}) (6,18). Expired CO_2 concentration was measured with a rapid CO_2 analyzer (Beckman LB-2). All variables were recorded on a pen recorder (Gould Allco EN 68) at a speed of 25 or 50 mm/s.

With the initial dose of 35 mg/kg of pentobarbital (i.p.), a series of airway occlusions were performed at end-expiration, one about every 2-3 minutes. Minute ventilation ($\dot{V}_E$) was calculated as the product of tidal volume (V_T) and frequency (f) of an average of 5-10 breaths preceding each occlusion. Inspiratory (T_I), expiratory (T_E) and total (T_{TOT}) breath durations were obtained from the flow signal over the same breaths. Overall mean inspiratory flow was computed by dividing V_T by T_I . After completion of the measurements with the initial pentobarbital dose, 6 mg/kg of the anesthetic were injected as a bolus in the femoral vein every 15 minutes, until the death of the animal. At each dose, beginning 7 min after each injection, the above measurements were repeated. For technical reasons, in one cat measurements of E_{PHR} were made only at the first 5 out of 11 doses used. At each dose of pentobarbital, airway occlusions were also performed at end-inspiration in order to elicit the Hering-Breuer inflation reflex and obtain values of the passive elastance of the total respiratory system (E_{rs}), lung (E_l) and chest wall (E_w) (19). Airway occlusion at end-inspiration resulted in a period of apnea in each cat, permitting measurement of the relaxation

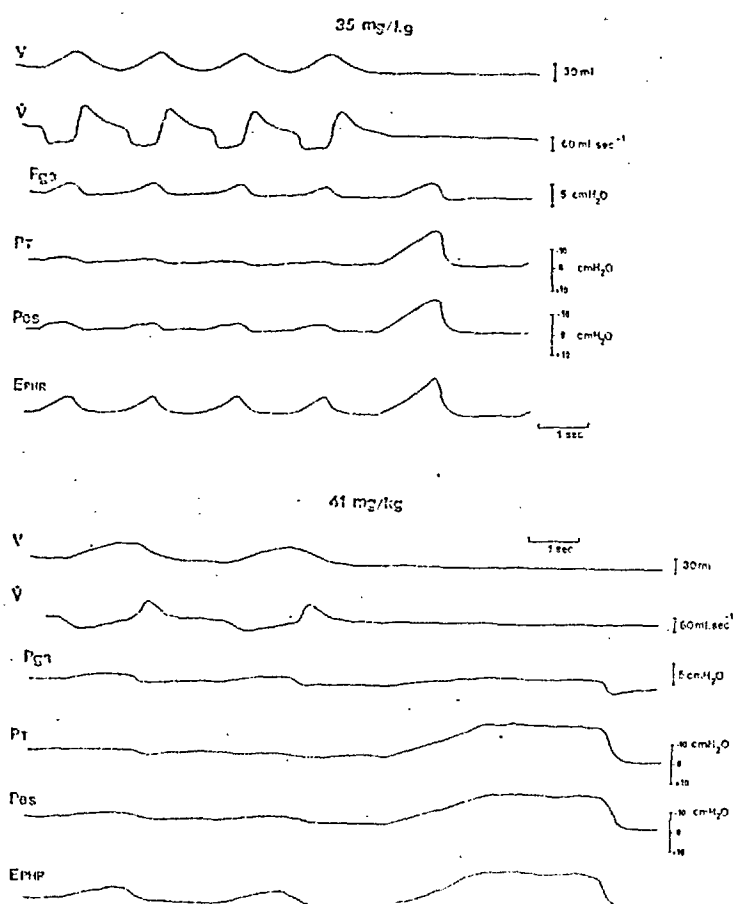


Fig. 24. Tracings obtained in cat 4 at two pentobarbital doses. From top to bottom: volume (V), instantaneous flow ($\dot{V}$), gastric pressure (P_{ga}), tracheal pressure (P_T), esophageal pressure (P_{es}) and integrated phrenic activity (EPHR). In each record a series of unoccluded breaths is followed by an effort against airway occluded at end-expiration.

pressures of the respiratory system. Pulmonary flow resistance (R_l) was computed according to Mead and Whittenberger (10).

IV.3 RESULTS

Figure 24 shows representative tracings obtained in an animal at the initial pentobarbital dose (35 mg/kg i.p.) and 9 minutes after administration of an additional 6 mg/kg dose (i.v.). Each record comprises a series of unoccluded breaths followed by an effort against airways closed at end-expiration. During both occluded and unoccluded breaths, gastric and esophageal pressures remained constant during most of expiration, indicating absence of phasic expiratory muscle activity (1). The end-expiratory values of P_{es} and P_{ga} did not change with depth of anesthesia. Furthermore, the tracheal pressure during the occluded expirations returned to zero (atmospheric) pressure. These results, which were obtained in all animals at all levels of anesthesia, indicate that the end-expiratory lung volume probably did not change with increasing depth of anesthesia, and was representative of the relaxed volume of the respiratory system. A constancy of the functional residual capacity with increasing pentobarbital dose has been previously reported (12).

IV.3.1 Effect of airway occlusion at end-expiration on E_{PHR}

Airway occlusion at end-expiration resulted in a prolongation of inspiration which was more pronounced with

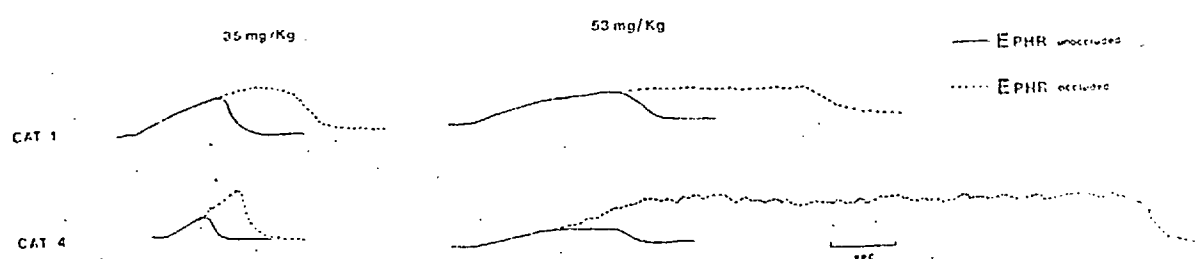


Fig.25. Tracings of phrenic activity (EPHR) during occluded efforts superimposed on that of preceding unoccluded inspirations. Cats 1 and 4 at initial (35 mg/kg) and increased (53 mg/kg) pentobarbital dose.

increasing pentobarbital doses (Fig. 24). The initial parts of occluded and unoccluded E_{PHR} 's were virtually identical. This is shown for two cats in Fig. 25 where the occluded E_{PHR} 's obtained at two levels of anesthesia are superimposed on the preceding unoccluded ones. This initial phase was followed by a variable period during which the unoccluded E_{PHR} gradually deviated from the occluded E_{PHR} before starting to decline rapidly. According to Younes et al (23) this phase represents graded volume-related vagal inhibition of central inspiratory activity (CIA) during the unoccluded inspiration. In all cats this phase was relatively short (mean: .08s; range 0--24 s) at the initial dose of pentobarbital (35 mg/kg). In three cats its duration did not change substantially with increased pentobarbital dose, while in the other three (cats 4-6) its duration increased markedly (e.g. cat 4 in Fig. 25). In agreement with previous reports (4,6,8,18) these results indicate that the phrenic output during the unoccluded breaths does not always reflect the intrinsic CIA, but is partly modulated by vagal volume-related feedback. In 3 cats, this modulation involved only a small part of the inspiration at all levels of anesthesia, and consequently had little effect on the spirogram. In the other 3 cats, however, this phenomenon encompassed a substantial part of inspiration at increased depth of anesthesia, and consequently had a marked effect on the spirogram (see below).

Figure 25 also shows that the shape of the rising part of

the occluded E_{PHR} -time profile varied markedly between cats; in cat 1 exhibiting an upward convexity and in cat 4 an upward concavity. In both cats increasing dose of pentobarbital resulted in a decreasing rate of rise of occluded E_{PHR} , but the shape of the neurogram was preserved.

IV.3.2 Morphology of E_{PHR} , $P_{\text{di}}(\text{mus})$ and P_{T} waves during inspiratory efforts against airways occluded at end-expiration.

When the log values of the rising part of the occluded $E_{\text{PHR}}(E_{\text{PHR}}^{\text{O}})$ wave, measured every 200 ms from the onset of phrenic activity, were plotted against the logarithm of the corresponding time, the $E_{\text{PHR}}^{\text{O}}$ -time relationship became straight, as shown for two cats in Fig.26. These functions are expressed by the equation:

$$\log E_{\text{PHR}}^{\text{O}} = \log a + b \log T \quad (1)$$

where a is the value of $E_{\text{PHR}}^{\text{O}}$ in relative units (r.u.) at one second, b is a dimensionless constant representing the slope of the lines, and T is time in seconds from the onset of phrenic activity.

In all of our cats, at each dose of pentobarbital studied, we found highly significant correlations ($r > .994$) between $\log E_{\text{PHR}}^{\text{O}}$ and $\log T$.

Since the $\log E_{\text{PHR}}^{\text{O}}$ vs. $\log T$ relationship is linear, it follows that $E_{\text{PHR}}^{\text{O}}$ can be described as a simple power function of time, of the form:

$$E_{\text{PHR}}^{\text{O}} = aT^b \quad (2)$$

When the $E_{\text{PHR}}^{\text{O}}$ -time profile is linear, the constant b is equal

TABLE 4. Values of constants in equations 2-4 of six cats at initial pentobarbital dose (35 mg/kg).

	$ES_{PHR} = aT^b$		$P_T^O = a'T^{b'}$		$P_{di}^O = a''T^{b''}$	
CAT	a (r.u.)	b	a' (cmH ₂ O)	b'	a'' (cmH ₂ O)	b''
1	22.3	.74	7.1	.79	-	-
2	18.3	1.23	6.5	1.18	8.7	1.33
3	17.2	.71	8.5	.89	8.7	.90
4	15.5	1.09	15.5	.95	18.0	1.05
5	13.6	.89	12.2	.97	12.5	.93
6	7.3	1.21	4.4	1.15	5.0	1.19
Mean±SD	15.7±5.1	.98±.23	9.0±4.1	.99±.15	10.6±4.9	1.08±.18

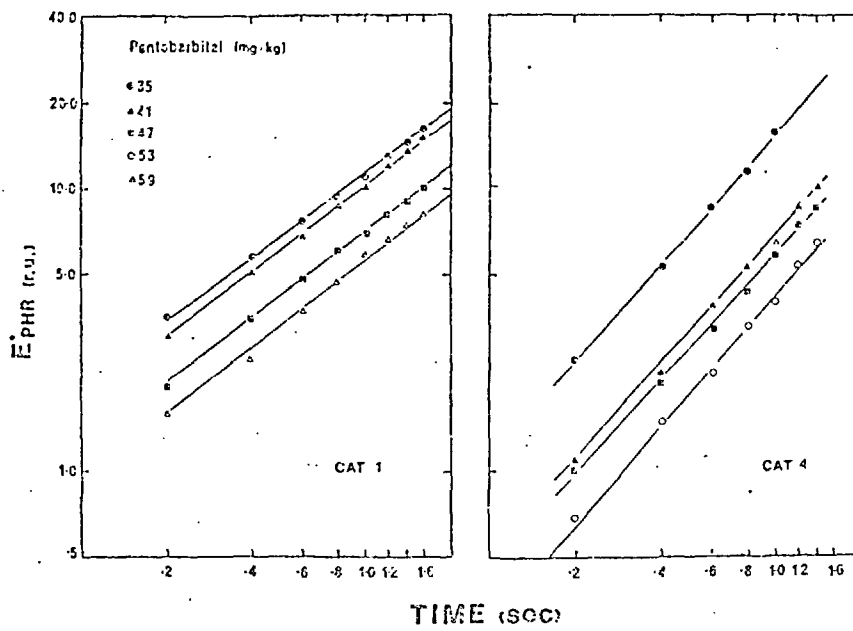


Fig.26. Relationship between $\log E_{PHR}^O$ and $\log$ time in cats 1 and 4 at different pentobarbital doses. Points represent experimental values measured at .2 s intervals from onset of phrenic activity.

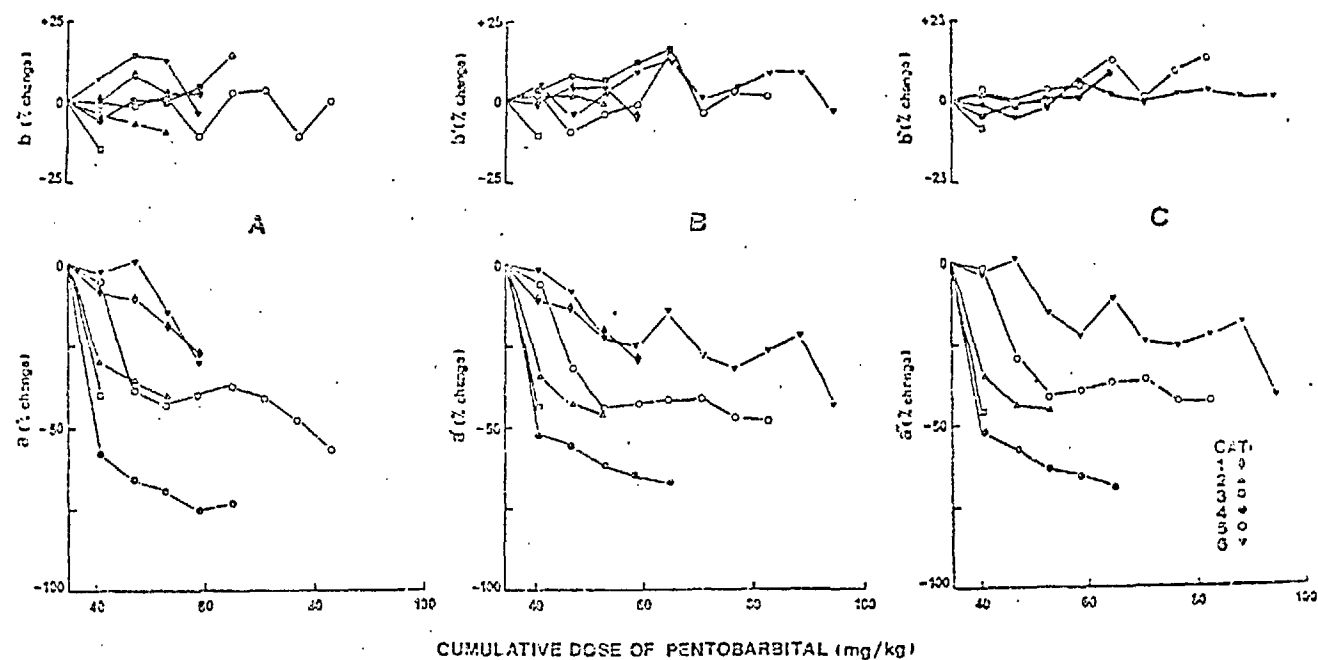


Fig. 27. Top: Changes in values of constants b , b' and b'' (eqs. 2-4), expressed as percent of corresponding values at initial pentobarbital dose (35 mg/kg), as a function of cumulative dose of pentobarbital in 6 cats. Bottom: Similar plots of constants a , a' and a'' .

to 1; when the rising part of the E_{PHR}^O curve has an upward concavity, b is >1 (Fig.25 cat 4); when it is convex upwards b is <1 (Fig.25, cat 1). Therefore, the constant b is a useful index for representing the shape of the E_{PHR}^O wave, while the constant a is an index of the amplitude of the wave.

At the initial dose of pentobarbital (35 mg/kg) the constant b was found to vary from 0.71 to 1.23 between the different animals (Table 4). As shown in Fig.26, with increasing dose of anesthetic the $\log E_{PHR}^O$ vs. $\log T$ relationships were displaced downwards (decrease in constant a) but in a nearly parallel fashion, i.e. the slope of the lines (constant b) remained virtually unchanged. Similar results were obtained in all cats, as shown in Fig.27A(top). Over the whole range of pentobarbital doses studied, b changed less than 15% of its initial value and in a non-systematic fashion. On the other hand, Fig.27A (bottom) shows that the amplitude of E_{PHR}^O at one second (constant a) decreased markedly with cumulative dose of pentobarbital. The dose-effect of pentobarbital on the constant a varied substantially between cats.

Since the occluded and unoccluded E_{PHR} 's were identical, the above conclusions also pertain to the unoccluded E_{PHR} waves, at least up to the point at which the unoccluded E_{PHR} 's deviated from those obtained during the occluded efforts because of graded inhibition of CIA (Fig.25).

With a similar analysis, it was found that the rising

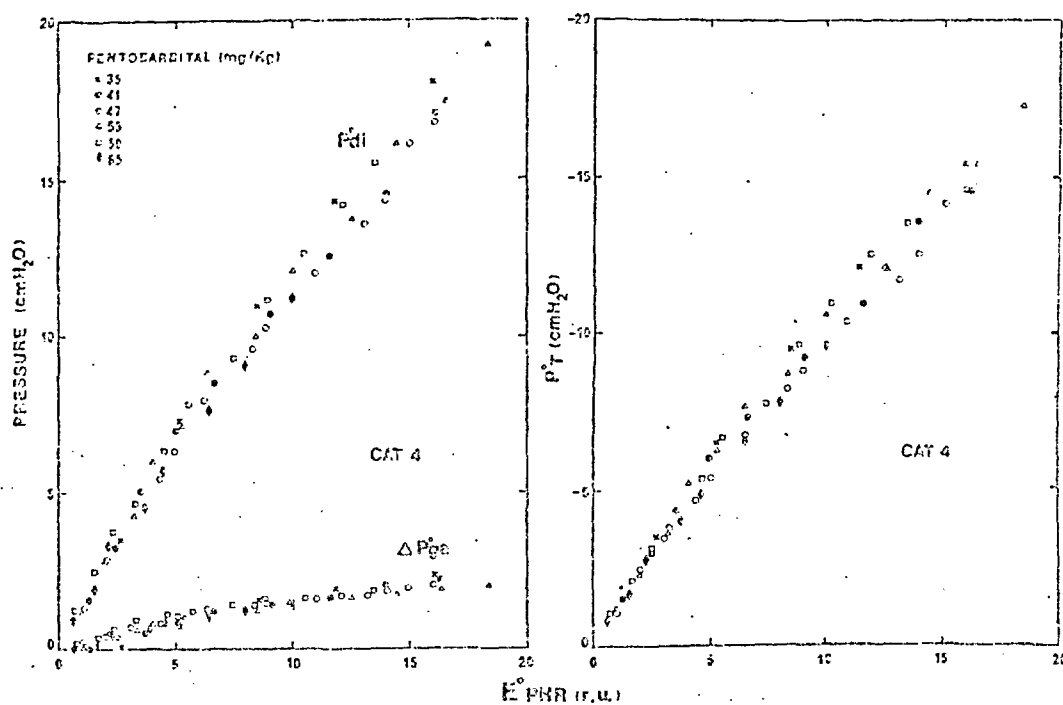


Fig.28. Left: Relationship of P_{di}^O and ΔP_{ga}^O with E_{PHR}^O during six occluded inspirations made at different pentobarbital doses.

Right: Corresponding relationship between P_T^O and E_{PHR}^O .

part of the P_T and P_{di} occlusion waves could also be described as a useful approximation by simple power functions of the same form as eq. 2:

$$P_T^0 = a' T^{b'} \quad (3)$$

$$\text{and} \quad P_{di}^0 = a'' T^{b''} \quad (4)$$

where P_T^0 and P_{di}^0 are the values of P_T and P_{di} at 1 second (cmH₂O), and b' and b'' are the corresponding shape indices. The values of these parameters obtained in the 6 cats at the initial pentobarbital dose are given in Table 4. Figure 27 B and C show the percentage changes of the parameters in eqs. 3 and 4 with cumulative dose of pentobarbital in the six cats. Constants b' and b'' showed relatively small and non-systematic variability, while the values of the constants a' and a'' decreased markedly with increased pentobarbital dose. As for the constant a , the dose effect of pentobarbital on a' and a'' varied markedly between animals.

As for the constant b , the values of b' and b'' varied considerably between animals (Table 4). A significant positive correlation ($P < .01$) was found between the values of b and the corresponding values of b' and b'' . This indicates that the shape of the P_T^0 and P_{di}^0 waves is modulated by the phrenic neurogram. A significant ($P < .01$) correlation was also found between the values of b' and b'' in Table 4.

IV.3.3 Relationship between E_{PHR}^0 and P_{di}^0 .

Figure 28 / shows plots of P_{di} and changes in gastric

pressure (ΔP_{ga}^o) against E_{PHR}^o in cat 4 during a representative series of occluded inspiratory efforts made at different doses of pentobarbital. For each effort, values obtained at .2s intervals from the onset of phrenic activity to its peak are plotted (same symbols). The relationship of both P_{di}^o and ΔP_{ga}^o with E_{PHR}^o was essentially independent of the dose of pentobarbital, ΔP_{ga}^o representing a relatively small fraction of the total pressure developed by the diaphragm. Since the vertical distance between P_{di}^o and the corresponding ΔP_{ga}^o values represents the occluded tracheal pressure (P_T^o), it follows that also the E_{PHR}^o and P_T^o relationship was independent of pentobarbital dose (Fig.28 right).

It is important to note that as the amplitude of the occlusion pressure waves decreased with increasing pentobarbital dose, a given P_{di}^o was achieved in a much shorter time with the initial dose (35 mg/kg) than with the subsequent doses (e.g. in cat 4 at the initial dose it took 0.6s to achieve a transdiaphragmatic pressure of 11 cmH₂O while the corresponding time was 1.8 sec at a cumulative dose of 65 mg/kg). Similarly, a given ΔP_{ga}^o was achieved more rapidly with the initial than with the subsequent doses of pentobarbital. The increase in gastric pressure during the occluded inspirations indicates descent of the diaphragm. If this had involved substantial shortening of the diaphragmatic muscle fibres, P_{di}^o at any given E_{PHR}^o value would be expected to increase with increasing pentobarbital dose

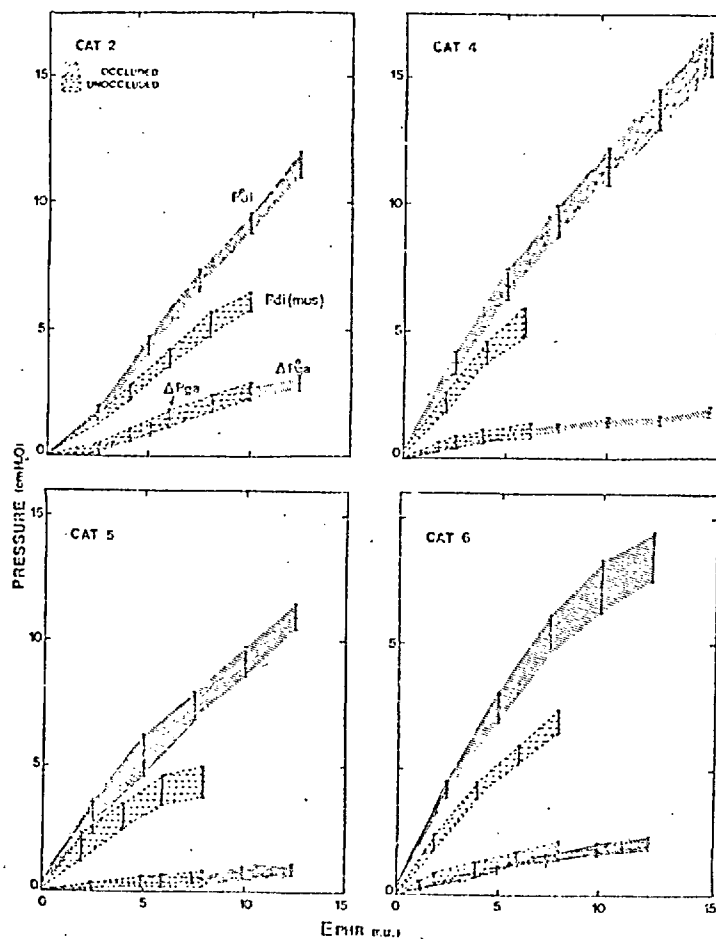


Fig.29. Overall relationships of $\bar{P}_{di}$ and $\Delta \bar{P}_{ga}$ with E_{PHR}^0 in 4 cats. Hatched areas indicate mean ± 1 SD. In each cat data obtained at different pentobarbital doses were pooled. Also shown are corresponding relationships of $\bar{P}_{di}(\text{mus})$ and $\Delta \bar{P}_{ga}$ with E_{PHR} obtained during unoccluded inspirations.

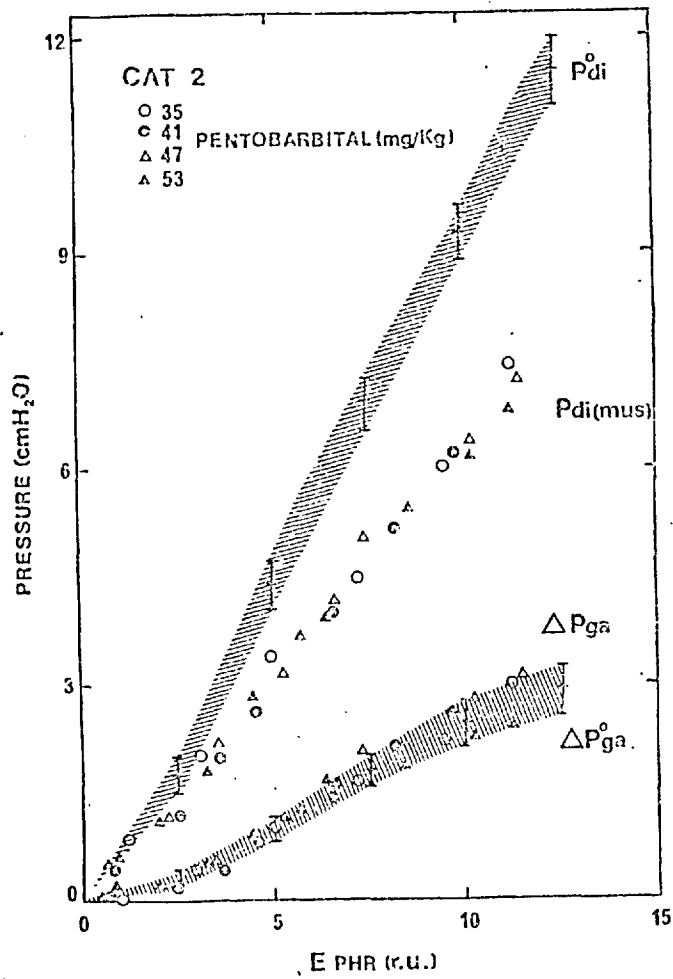


Fig.30. Relationship of $P_{di}(\text{mus})$ and ΔP_{ga} with E_{PHR} in a cat during a series of unoccluded inspirations made at different cumulative doses of pentobarbital. Also shown are corresponding relationships obtained during efforts with airway occluded at end-expiration, the hatched areas indicating mean ± 1 SD.

because of the force-velocity relationship of the diaphragm, i.e. as the rate of rise in gastric pressure decreases with increasing pentobarbital dose, the diaphragmatic pressure losses due to its force-velocity relationship should decrease. As indicated above, this was not the case. Consequently, it must be concluded that the descent of the diaphragm probably did not involve appreciable shortening of its fibres.

Fig.29 shows the overall relationship of $\overset{\circ}{P_{di}}$ and $\overset{\circ}{\Delta P_{ga}}$ with $\overset{\circ}{E_{PHR}}$ in cat 4, together with similar data for three other cats. Average relationships ($\pm$ SD) obtained by pooling all data obtained at the different doses of pentobarbital are shown. Similar results were also obtained on cat 3 which was studied at only two pentobarbital levels. In cat 1, $\overset{\circ}{P_{di}}$ and $\overset{\circ}{\Delta P_{ga}}$ were not available as gastric pressure was not measured. Nevertheless, in this cat (as in all other animals) the relationship between $\overset{\circ}{P_T}$ and $\overset{\circ}{E_{PHR}}$ was not affected by pentobarbital dose.

IV.3.4. $\overset{\circ}{E_{PHR}}$, $\overset{\circ}{P_{di(mus)}}$ and $\overset{\circ}{\Delta P_{ga}}$ during unoccluded breathing.

Figure 30 shows plots of $\overset{\circ}{P_{di(mus)}}$ and $\overset{\circ}{\Delta P_{ga}}$ against $\overset{\circ}{E_{PHR}}$ obtained in a cat during a series of unoccluded inspirations made at 6 different cumulative doses of pentobarbital, each dose being represented by a different symbol. For each dose, the various points represent values measured at .2s intervals from the beginning of inspiration as defined by onset of phrenic activity. It can be seen that during unoccluded breathing the relationship of $\overset{\circ}{P_{di(mus)}}$ and $\overset{\circ}{\Delta P_{ga}}$ with $\overset{\circ}{E_{PHR}}$

was not appreciably affected by increased dose of pentobarbital. Similar results were found in the other cats (Fig.29). Since inspiratory flow decreased with increasing pentobarbital dose, these results indicate that also during unoccluded breathing the dynamic pressure losses in the diaphragm (force-velocity relationship) were negligible.

As shown in Figs.29 and 30 for a given E_{PHR} , the values of $P_{di}(mus)$ were substantially smaller during unoccluded than during occluded inspirations. Since the values of ΔP_{ga} were similar during the occluded and unoccluded inspirations, the reduction in $P_{di}(mus)$ during the unoccluded inspirations was due to a drop in pressure developed on the thoracic side of the diaphragm. The nature of this loss in pressure was assessed as described in detail in the previous Chapter(III). This analysis is based on the following assumptions: (a) that the respiratory system behaves as a linear system with one degree of freedom, whose volume and flow-related pressure losses are given by: $E'rsV + R'rs\dot{V}$, where $E'rs$ and $R'rs$ are respectively the effective elastance and resistance of the system; and (b) that P_T^o represents the effective pressure available for driving the system (i.e. for producing volume changes during unobstructed breathing). From the above, it follows that (1,19):

$$-P_T^o/V = E'rs + R'rs\dot{V}/V \quad (5)$$

where $\dot{V}$ and V are measured during the unoccluded inspirations which precede the occluded effort from which P_T is

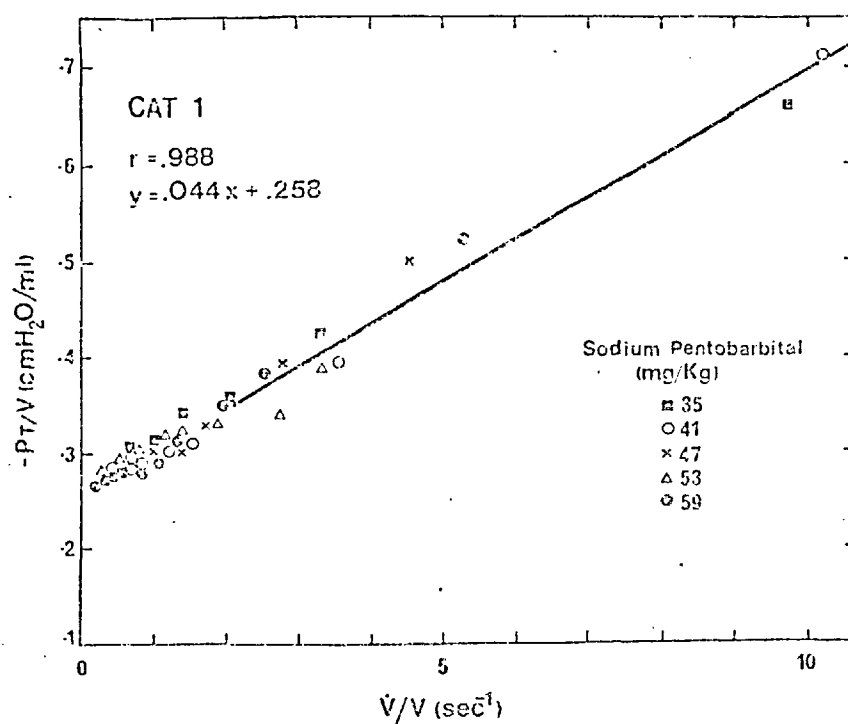


Fig. 31. Relationship between $-P_T^O/V$ and $\dot{V}/V$ (eq. 5) in cat 1 at different pentobarbital doses.

TABLE 5. Values of passive and effective elastance and resistance of respiratory system in 6 cats.

CAT	EFFECTIVE			PASSIVE	
	r	R'rs (cmH ₂ O/ml/s)	E'rs (cmH ₂ O/ml)	Rl* (cmH ₂ O/ml/s)	Ers (cmH ₂ O/ml)
1	.988	.044	.258	.031	.140
2	.903	.044	.185	.034	.124
3	.934	.047	.299	.044	.124
4	.867	.026	.261	.024	.155
5	.907	.024	.247	.026	.145
6	.824	.049	.253	.034	.135
Mean		.039	.250	.032	.137
SD		.011	.037	.007	.012

*Including resistance of equipment (.015 cmH₂O/ml/s).

TABLE 6. Average values (.SD) of mechanics data in six cats at initial and terminal doses of pentobarbital.

Pentobarbital	Ers	Ew (cmH ₂ O/ml)	El	Rl* (cmH ₂ O/ml)
Initial dose (35 mg/kg)	.137 ±.012	.057 ±.01	.080 ± .010	.032 ±.007
Terminal dose (41-95 mg/kg)	.142 ±.016	.062 ±.02	.079 ± .008	.029 ±.006

*Including flow resistance of equipment (.015 cmH₂O/ml/s)

taken. Implicit in this analysis is that all variables are measured over the range where the occluded and unoccluded E_{PHR} 's are identical, as shown in Fig.25.

Fig.31 shows a plot of $-\dot{P}_T^0/V$ vs. $\dot{V}/V$ in cat 1. A linear relationship is obtained which is essentially independent of pentobarbital dose. The intercept of the regression at $\dot{V}/V = 0$ represents $E'rs$ and the slope $R'rs$ (equation 5). Similar results were found in all cats. The individual values of $E'rs$ and $R'rs$, computed from regressions as shown in Fig.31, together with the values of R_l and Ers are given in Table 5. The passive flow resistance of the total respiratory system (Rrs) for our cats can be estimated by adding to our measured values of R_l the passive flow resistance of the chest wall, which in cats amounts to about .003 $cmH_2O/ml/s$ (2), yielding an average Rrs value of .035 $cmH_2O/ml/s$. This value is not substantially different from our average value of $R'rs$ (.039 $cmH_2O/ml/s$). This indicates that in our cats the pressure losses due to the force-velocity relationship of the inspiratory muscles were effectively nil. The values of R_l and Ers in Table 5 pertain to measurements made at the initial pentobarbital dose (35 mg/kg i.p.). Increased pentobarbital dose, however, had no effect on R_l and Ers , as well as on Ew and El (Table 6).

As shown in Table 5, the values of $E'rs$ were in all cats considerably greater than those of Ers , reflecting decreased effectiveness of the inspiratory muscles as pressure

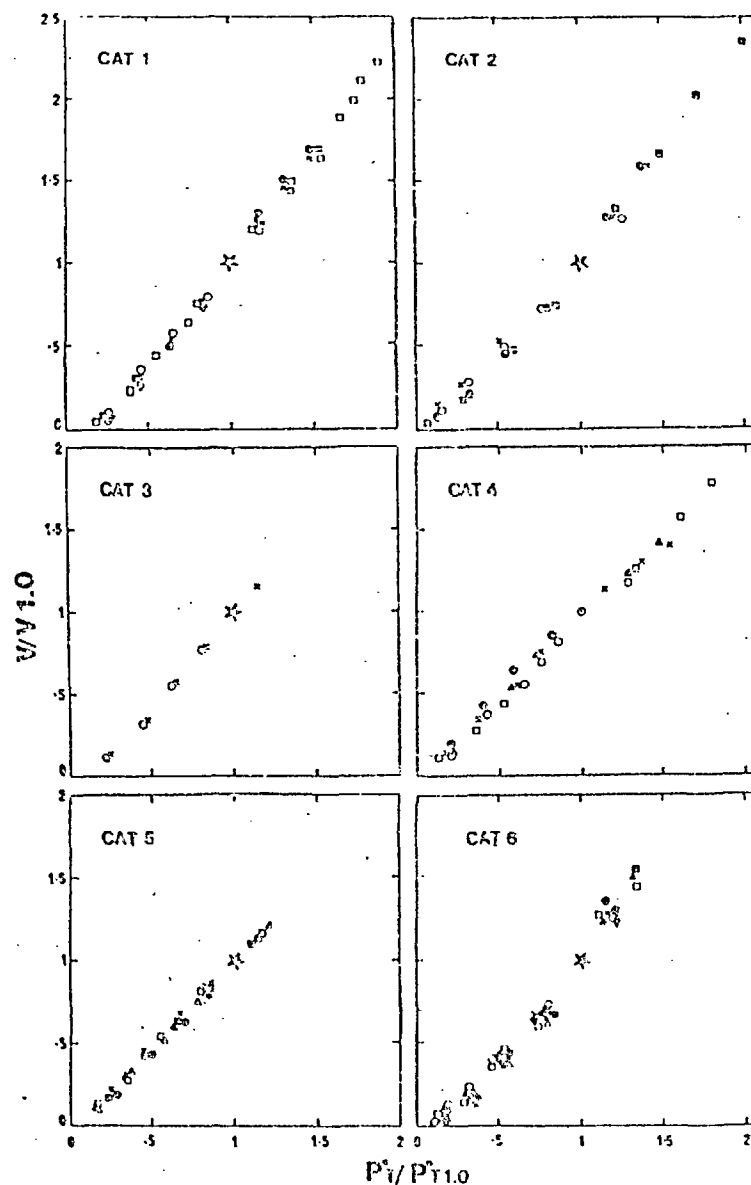


Fig. 32. Relationship between $V/V_{1.0}$ and $P_T^O/P_{T1.0}^O$ in 6 cats at various doses of pentobarbital (different symbols). Points represent values obtained at .2s intervals from the onset of phrenic activity up to onset of graded volume-related inhibition of CIA.

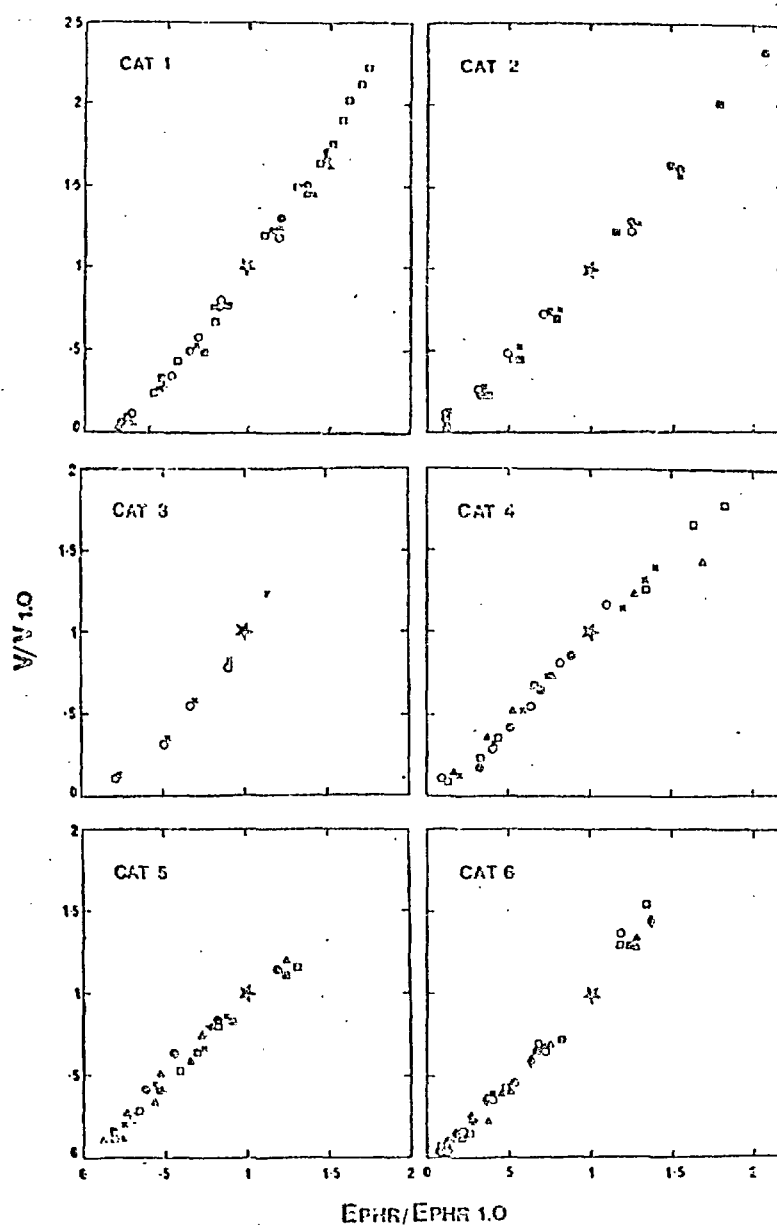


Fig.33. As Fig.32, but $E_{PHR}/E_{PHR\ 1.0}$ instead of $P_T^O/P_{T\ 1.0}^O$

generators with increasing lung volume (9,16).

The results in Fig.31 and Table 5 imply that, over the range of E_{PHR} 's where the occluded and unoccluded phrenic activity was identical (Fig.25), the decrease in rate of rise of volume resulting from increased pentobarbital dose was proportionately the same as that in P_T^O . This is shown in Fig.32 where changes in volume are plotted against P_T^O , both variables being expressed as a fraction of the corresponding values achieved 1s after the onset of phrenic activity ($V_{1.0}$ and $P_{T1.0}^O$, respectively). Similar results were obtained when $V/V_{1.0}$ is plotted against $E_{PHR}/E_{PHR1.0}$ (Fig.33).

IV.3.5. Morphology of the spirogram.

The morphology of the spirograms differed markedly between cats, reflecting inter-animal differences in the profile of inspiratory driving inputs (Fig.25). As with the initial pentobarbital dose there was relatively little partial inhibition of CIA, during most of inspiration the volume-time profiles reflected the shape of the intrinsic CIA waveforms, namely that of E_{PHR}^O and of its mechanical transforms P_{di}^O and P_T^O . In the three cats in which the duration of partial inhibition of inspiration remained unchanged by pentobarbital dose (e.g. cat 1 in Fig.25), the shape of the spirograms remained unvaried. In cats 4-6, however, with increased pentobarbital dose the partial inhibition of inspiration encompassed a substantial fraction

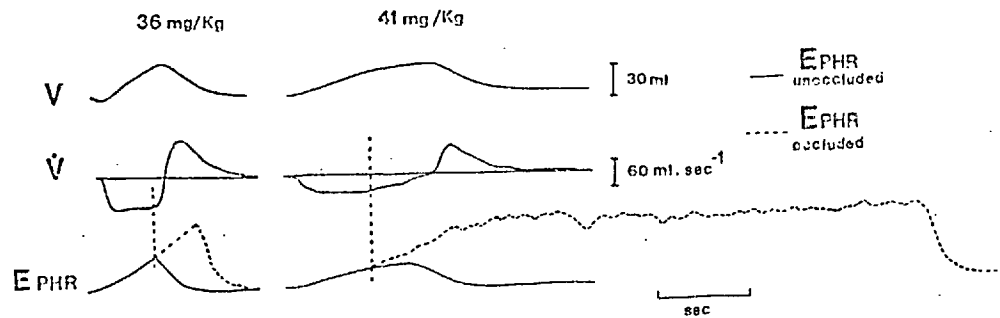


Fig. 34. Tracings of changes in volume (V), flow ($\dot{V}$) and phrenic activity (EPHR) in cat 4 at two pentobarbital doses. EPHR's with occluded airway (broken lines) are superimposed on the EPHR's of corresponding unoccluded inspirations. At the higher pentobarbital dose, the graded inhibition of CIA (as seen by the gradual downward deviation of unoccluded from occluded EPHR) encompassed a substantial fraction of inspiration. As a result, $\dot{V}$ decreased gradually and the inspiratory volume-time profile changed from nearly linear at the initial pentobarbital dose (35 mg/kg) to markedly curvilinear (convex upward) at 41 mg/kg.

TABLE 7. Values of spirometric variables and PACO_2 in six cats at initial dose of pentobarbital (35 mg/kg).

CAT	$\dot{V}_E$ (ml/min)	V_T (ml)	f (cpm)	T_I (sec)	T_{TOT} (sec)	T_E (sec)	V_T/T_I (ml/sec)	T_I/T_{TOT}	PACO_2 (Torr)
1	614	28.5	21.5	1.33	2.79	1.46	21.5	.477	32.0
2	658	35.0	18.8	1.32	3.19	1.87	26.5	.413	30.0
3	819	33.3	24.6	1.20	2.44	1.24	27.8	.491	30.5
4	1249	35.2	35.5	.69	1.69	1.00	51.0	.408	32.5
5	901	30.2	29.9	.92	2.01	1.09	32.5	.462	32.0
6	471	25.1	18.8	1.51	3.19	1.68	16.6	.470	38.5
Mean	785	31.2	24.8	1.16	2.55	1.39	29.3	.454	32.6
SD	273	4.0	6.7	0.30	0.62	0.34	12.0	.035	3.1

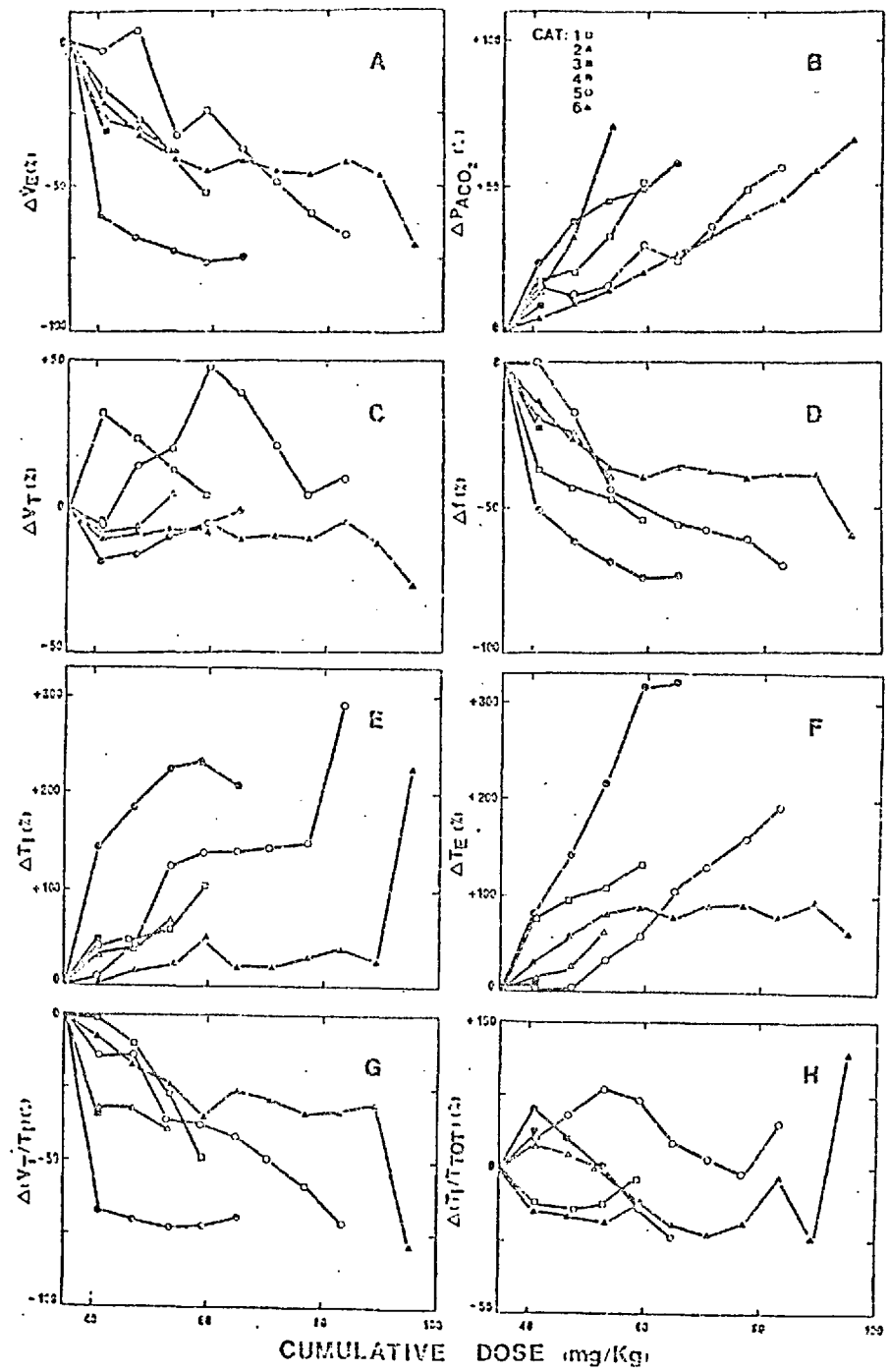


Fig.35. Relationship of various spirometric variables and end-tidal P_{CO_2} (P_{ACO_2}) with cumulative dose of pentobarbital in 6 cats.

of inspiration, and consequently both the shape of the unoccluded E_{PHR} wave and of the spirogram were affected. This is shown for cat 4 in Fig.34. With the initial pentobarbital dose (35 mg/kg i.p.) volume increased approximately linearly with time (constant $\dot{V}$) over most of inspiration,

With an additional i.v. dose of 6 mg/kg, partial inhibition of inspiration occurred early in inspiration, resulting in a progressively decreasing rate of rise of E_{PHR} and volume. In fact, at this dose of pentobarbital (41 mg/kg) the spirogram exhibited a curvature with an upward convexity. Similar results were found in cats 5 and 6. In cat 6 with the initial pentobarbital dose the inspiratory volume-time profile was concave upward and became concave downward with increased anesthetic level.

IV.3.6 Dose-effect of pentobarbital on $\dot{V}_E$ and V_T/T_I .

Table 7 provides the values of pulmonary ventilation and of other spirometric variables, together with end-tidal P_{CO_2} , in the six cats at the initial dose of pentobarbital (35 mg/kg). Increasing dose of pentobarbital resulted in a progressive decrease in $\dot{V}_E$ and increase in P_{ACO_2} (Fig.35). The decrease in minute ventilation was due to a consistent decrease in respiratory frequency (f) while the response of V_T was variable. The decrease in f was due both to prolongation of T_I and T_E . These did not change proportionately, as shown by the variable T_I/T_{TOT} response to increasing

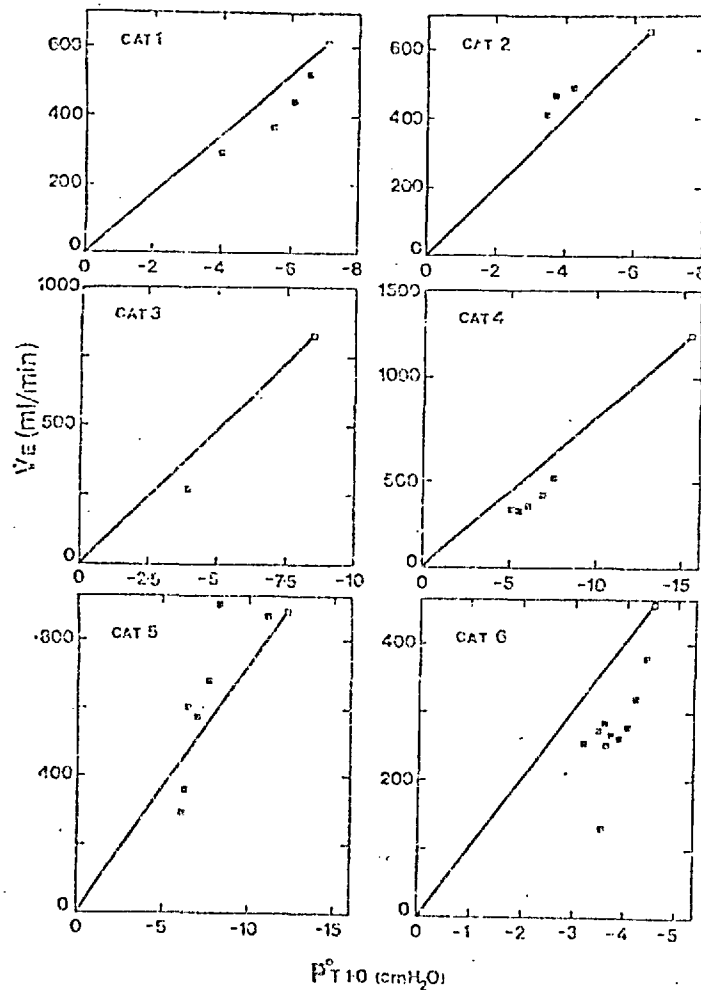


Fig.36 . Relationship between $\dot{V}_E$ and $P_{T1.0}^O$ for the 6 cats.

The squares represent average values obtained at different doses of pentobarbital, the open squares representing the values obtained at the initial pentobarbital dose (35 mg/kg). Lines joining open squares with origin of co-ordinates indicate relationships that would obtain if with increasing anesthetic dose $\dot{V}_E$ and $P_{T1.0}^O$ changed in direct proportion.

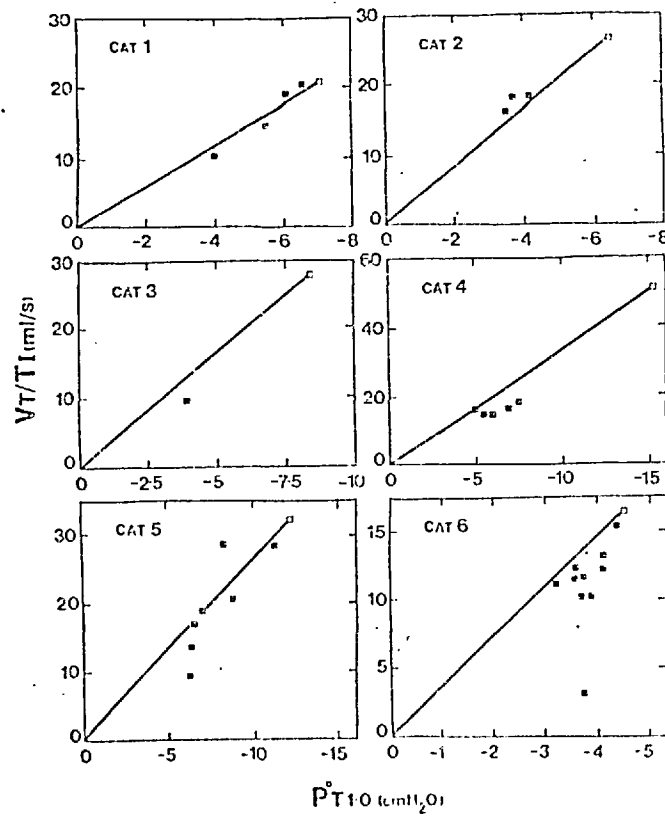


Fig. 37. As Fig. 36, but V_T/T_I instead of $\dot{V}_E$.

pentobarbital dose both within and between animals. The overall mean inspiratory flow (V_T/T_I) tended to decrease with pentobarbital dose, the dose-effect varying between cats.

Fig. 36 shows a plot of $\dot{V}_E$ (a measure of the overall output of the respiratory system) against $P_{Tl.0}^O$ (an index of CIA) for the 6 cats. The individual points represent mean values obtained at each pentobarbital dose studied, the results obtained at the initial dose being represented by open squares. The reduction in $\dot{V}_E$ with increasing pentobarbital dose was not proportionate to that in $P_{Tl.0}^O$. This is shown by the fact that the points obtained at the higher pentobarbital levels deviated from the line joining the open squares (initial dose) with the origin of the coordinates. Similar results were found in terms of the relationship between V_T/T_I and $P_{Tl.0}^O$ (Fig. 37).

IV.4 DISCUSSION

As pointed out in Chapter II, the device used in the present study for measurement of E_{PHR} distorts somewhat the phrenic signal. Although corrections could have been made to allow for such distortion, we felt that this was not necessary within the framework of the present report. Indeed, in each cat the morphology of the time course of occluded E_{PHR} did not change appreciably with pentobarbital dose. Accordingly, the instrumental

distortion of the phrenic signal was nearly constant in each cat. Furthermore, according to our previous estimates (Chap. II) the error introduced in our measurements of the constants a and b (equation 2) was of the order of only about 10%. Thus, while quantitatively our E_{PHR} values involve some error, from the practical standpoint these errors appear to be too small to alter the basic arguments of this Chapter.

In agreement with previous data we found that there are inter-animal differences in the morphology of the time-course of E_{PHR}^o . Within each cat, however, the shape of the latter did not change substantially with increasing pentobarbital dose, whereas the rate of rise of E_{PHR}^o decreased.

In three of the cats, the morphology of the time-course of unoccluded E_{PHR} also did not change substantially with pentobarbital dose. These were the cats which exhibited little volume-related graded inhibition of CIA. In the other three cats, however, with increasing dose of the anesthetic there was a prolonged phase of graded lung volume-related vagal inhibition of central inspiratory activity (23) which resulted in marked shape changes of the unoccluded E_{PHR} -time profile. Thus, while the morphology of the intrinsic CIA, as reflected by the occluded E_{PHR} , is not modified by pentobarbital dose, with increasing anesthetic depth in some cats the time-course of unoccluded E_{PHR} can be reflexly altered. These reflex modifications in phrenic output result in changes of the morphology of the spirogram, and hence

are important in terms of ventilatory output.

As previously found in cats subjected to hypercapnia and hypoxia we found that the morphology of the time-course of occluded transdiaphragmatic and tracheal pressure waves is modulated by the phrenic neurogram, as indicated by a significant correlation between the respective shape indices. Pentobarbital dose had no systematic effect on the shape of the Pdi and P_T occlusion pressure waves. The latter is in agreement with previous reports (12,13).

In all cats, the relationship between the active trans-diaphragmatic pressure (contraction) and phrenic activity (excitation) during efforts with airways occluded at end-expiration was the same at all pentobarbital doses. This implies that pentobarbital had no effect on diaphragmatic excitation-contraction coupling. In this connection it should be noted that during the occluded efforts, at any given E_{PHR}, the changes in gastric pressure were essentially the same at all pentobarbital doses, suggesting that the geometry of the diaphragm was fixed. Hence, the mechanical advantage of the diaphragm in converting tension into pressure was probably similar at all levels of the anesthetic.

In studies on isolated frog nerve-muscle (sartorius) preparations, Thesleff (20) found that neuromuscular transmission begins to be impaired at a concentration of pentobarbital of 0.15-0.20 mg/ml. Neglecting clearance of the drug and assuming that water represented 600 ml/kg of body

weight (3), the highest concentration of pentobarbital in our cats would amount to about .05 mg/ml of body water. This value is considerably lower than the critical concentration required to affect neuromuscular transmission, as reported by Thesleff. To our knowledge no such data are available for the cat diaphragm.

In lightly pentobarbital anesthetized cats (30 mg/kg), respiratory activity is present in the following inspiratory muscles: diaphragm, external intercostals and interchondrals ~~and also~~; in addition there may be some activity in the internal intercostals (4). According to Duron (5) in decerebrate cats with deepening of pentobarbital anesthesia the order of disappearance of activity is: external intercostals, internal intercostals, interchondrals and diaphragm. This general behaviour has been previously proposed by Miller (11), and appears to occur in humans anesthetized with halothane (21). Surprisingly, in our cats, we found that the relationship between $\overset{O}{P}_{di}$, $\overset{O}{P}_T$, $\overset{C}{AP}_{ga}$ and $\overset{O}{E}_{PHR}$ was not affected by pentobarbital dose (Figs. 19 and 20). This implies that the derecruitment of the various muscles which occurs with increasing anesthetic depth does not perceptibly affect, at any given $\overset{O}{E}_{PHR}$, the pressures generated on both thoracic and abdominal side of the diaphragm. This behaviour is more consistent with a proportional decrease in activity among all inspiratory muscles with increasing anesthetic depth than with the selective derecruitment of

of different muscles as described by Miller (11) and Duron (5). Indeed, selective derecruitment of the external intercostals and interchondrals should result in a reduction of P_T^O and increased ΔP_{ga}^O for a given value of E_{PHR}^O because a lesser contribution of the extra-diaphragmatic muscles should result in decreased pressure developed on the thoracic side of the diaphragm and, at the same time, a proportionately greater contribution of the diaphragm should cause greater descent of the latter (hence increased ΔP_{ga}^O). Clearly, further studies are required where the activity of the various respiratory muscles is measured together with P_{di}^O , P_T^O and ΔP_{ga}^O .

In Chapter II it was shown that in cats the relationships of P_{di}^O , P_T^O and ΔP_{ga}^O with E_{PHR}^O are also unaffected by hypercapnia and hypoxia, indicating that with respect to its effects on CIA pentobarbital mimics specifically the effects of reductions in the input from the chemoreceptors. As pointed out by von Euler (7), one action of pentobarbitone is to enhance the GABA-mechanisms for inhibition (15), and topical applications of pentobarbitone and of GABA on the chemoceptive areas of the ventral surface of the medulla causes a depression of respiration similar to hypocapnia.

In agreement with the results on cats subjected to hypoxia and hypercapnia (19), we found that also during the unoccluded breaths there is a fixed relationship between active transdiaphragmatic pressure and E_{PHR} independent of

the dose of pentobarbital. Since inspiratory flow decreased with increasing pentobarbital dose, these results indicate that pressure losses due to the force-velocity of the diaphragm were negligible in our cats. This notion is further supported by our finding that during spontaneous breathing the effective flow-resistance of the respiratory system is not appreciably different from the passive flow resistance of the respiratory system. Nevertheless, during the unoccluded breaths the active transdiaphragmatic pressure developed at any given value of E_{PHR} was smaller than the corresponding values attained during occluded inspirations, indicating that during the unoccluded breaths there is a volume-related (but not flow-related) loss in active transdiaphragmatic pressure. This loss probably reflects decreased effectiveness of the diaphragm as a pressure generator with increasing lung volume (9,16,19). In fact, the effective elastance of the respiratory system measured during active breathing was lower than the elastance of the relaxed (passive) respiratory system.

As for cats subjected to hypoxia and hypercapnia (19), we found that the active change in gastric pressure was, for any given E_{PHR} , approximately the same during the occluded and unoccluded inspirations. This being the case, it follows that the occluded tracheal pressure represents the net pressure available to produce changes in lung volume

during unobstructed breathing, with the provision that this is only valid within the time domain where the occluded and unoccluded E_{PHR} 's are identical (i.e. up to onset of graded volume-related inhibition of CIA). In fact, within these limits the changes in lung volume were proportionately the same as those in P_T^0 in all cats (Fig. 32). This proportionality is to be expected in view of the fact that neither the shape of the tracheal occlusion pressure waves nor the elastance and flow resistance (both passive and effective) changed with depth of pentobarbital anesthesia.

In each of our cats, E_{PHR}^0 , P_{di}^0 and P_T^0 , as well as unoccluded E_{PHR} and V (up to onset of graded inhibition of CIA), provided equivalent indices of central inspiratory activity, in the sense that the depression in rate of rise of phrenic activity with increasing pentobarbital dose was associated with a proportionate decrease in rate of rise of the other variables. This, however, was not the case for either $\dot{V}_E$ or V_T/T_I . In fact, in all of our cats the depression of V_T/T_I with increased pentobarbital dose was not proportionately the same as that in $P_{T1.0}^0$ (Fig. 37).

As previously pointed out V_T/T_I depends on the morphology of the tracheal occlusion pressure wave, on the duration of inspiration, on E 'rs and R 'rs, and (if present) also on graded volume-related vagal inhibition of CIA. In three of our cats the latter affected only a small fraction of inspiration at all pentobarbital levels. These three

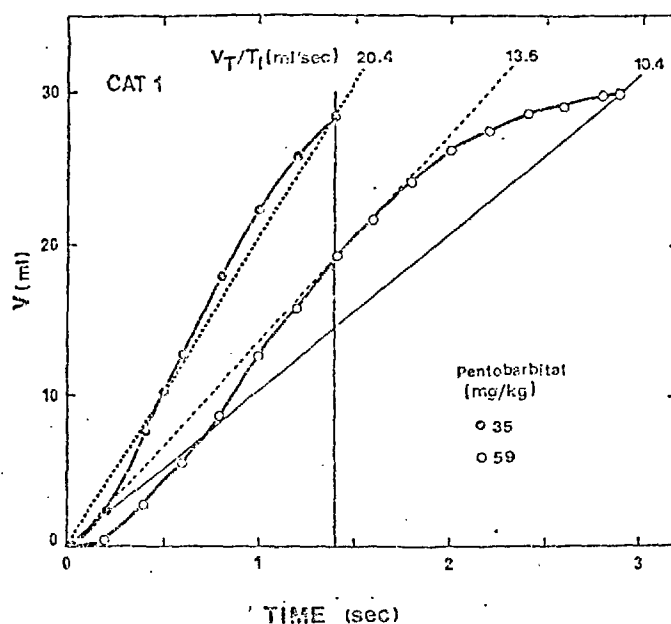


Fig. 38. Inspiratory limbs of spirograms in cat 1 at two doses of pentobarbital. The lines joining the origin of the co-ordinates with the end-inspiratory points represent the overall mean inspiratory flow (V_T/T_I). The broken line intercepting the spirogram obtaining at the higher pentobarbital dose (open circles) at T_I obtaining at the lower dose (filled circles) represents the V_T/T_I that would be expected at the higher anesthetic dose if there was no prolongation of inspiration. For further explanation see text.

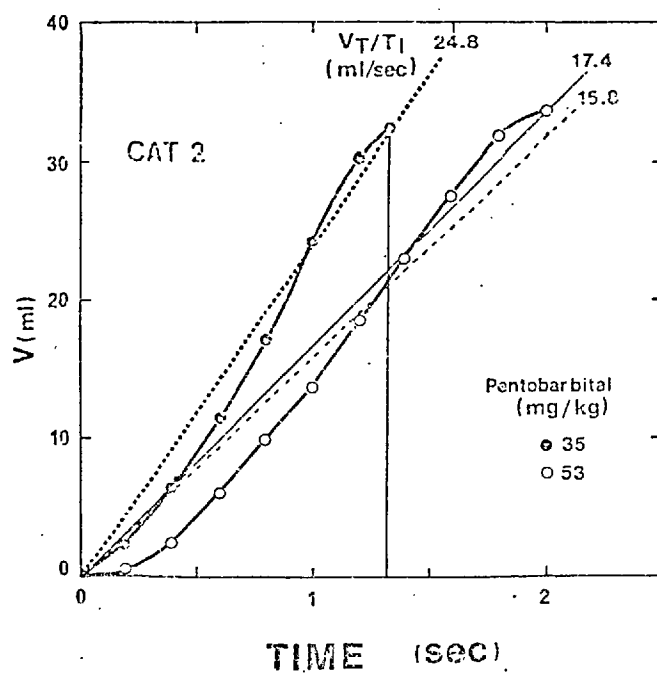


Fig.39. Results as in Fig.38 in cat 2. In this animal the prolongation of T_I with increased pentobarbital dose (53 mg/kg) resulted in an increase in V_T/T_I relative to that expected in the absence of prolongation of T_I relative to that obtaining at the lower anesthetic dose (35 mg/kg). For further explanation see text.

cats will be discussed first. In cat 1, the tracheal occlusion pressure wave was characterized by an upward convexity ($b'=.79$). This was reflected in the inspiratory volume-time profiles, as shown in Fig.38 where results obtained at initial (35 mg/kg) and higher (59 mg/kg) pentobarbital dose are shown. It can be seen that in this cat V_T/T_I decreased at the higher anesthetic dose in part because of the reduced rate of rise of volume resulting from decreased rate of rise in driving pressure, and in part because of prolongation of duration of inspiration. Indeed, in the absence of a prolongation in T_I , V_T/T_I at the higher dose should have amounted to 13.6 ml/s instead of the observed value of 10.4. Analogous results were obtained in cat 3. Thus, in these two cats V_T/T_I tended to decrease more than $P_{T1.0}^0$. In cat 2, in which b' was greater than 1.0, the opposite was seen, the prolongation of T_I with increasing anesthetic depth resulting in a proportionately smaller drop in V_T/T_I than in $P_{T1.0}^0$ (Fig.39). In the other three animals (cats 4-6), in which graded volume-related vagal inhibition of CIA encompassed a large fraction of inspiration with increased pentobarbital dose, V_T/T_I in general decreased proportionately more than $P_{T1.0}^0$. As graded inhibition was variable, the V_T/T_I vs. $P_{T1.0}$ relationship in these cats also shows marked variability. Thus, the changes in V_T/T_I occurring with increasing pentobarbital dose are not representative of changes in CIA.

Since $\dot{V}_E = (V_T/T_I) \times (T_I/T_{TOT})$, the variable inter and

intra-animal T_I/T_{TOT} response to anesthetic depth (Fig. 35) further complicates the relationship between $\dot{V}_E$ and CIA. Clearly, in studies of control of breathing V_T/T_I and $\dot{V}_E$ cannot always be taken as representative measures of central inspiratory activity.

Recently, Webber and Peiss (22) have studied the dose-effect of pentobarbital on breathing pattern in cats. In agreement with the present results they found that increased dose of the anesthetic results in a consistent reduction of breathing frequency while tidal volume is less affected. Similar observations have been made by Murphy (12). Webber and Peiss (22) found that the decrease in f was due to a more marked prolongation of T_I relative to T_E , leading to increased T_I/T_E ratio. In the present study, as well as in the investigation of Murphy (12), this was not always the case. In fact, in two of our cats the T_I/T_E ratio was lower at the higher pentobarbital doses than with the initial one. Thus, apneustic breathing (increased T_I/T_E ratio) does not always occur with increased depth of pentobarbital anesthesia. In all cats, however, the terminal respiratory arrest was immediately preceded by a prolonged inspiratory apneusis.

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CHAPTER V.

THE RATE OF CHANGE OF MOUTH
OCCLUSION PRESSURE DURING
EXERCISE

V.I. INTRODUCTION

It has been suggested that mouth pressure during a brief period of occlusion of the airway at the beginning of inspiration could be a simple and useful index of central inspiratory drive and that it could be used to estimate the sensitivity of the respiratory centres to different stimuli (9). This suggestion is based upon observations by Lourenço, Cherniack, Malm and Fishman (6), who showed that phrenic nerve activity was a simple function of the force of isometric contraction of the diaphragm during obstructed inspiration in experimental animals. Similar findings have been described in human subjects by Altose, Kelsen, Stanley, Levinson, Cherniack and Fishman (1). These workers related the electrical activity of the diaphragm to the pressure developed at the mouth in 0.1 s from the beginning of inspiration ($P_{0.1}$) during obstruction. Previously, Whitelaw et al. (9) showed that the rate of change of mouth pressure over a period of 0.1-0.2 s of inspiratory obstruction was closely correlated with end-tidal CO_2 and pulmonary ventilation. Mouth occlusion pressure has also been shown to increase during hyperventilation induced by exercise (3). However, this was not studied systematically. We have studied the initial rate of change of mouth occlusion pressure in more detail during progressive and steady-state exercise and assessed the use of this ratio as an index of inspiratory drive during exercise.

Table 8a: Some of the physical characteristics and results of tests of lung function in the nine male subjects used in the experiments.

Subject	Age (years)	Wt. (kg.)	Hg. (cm)	R_{aw} (kPa l ⁻¹ s)	Vtg (ml)	$sGaw$ (kPa ⁻¹ s ⁻¹)	FRC (ml)
A.Y.	41	72	180	0.034	4625	6.36	4410
A.M.	27	64	176	0.165	3570	3.095	3150
N.S.	29	70	178	0.048	3360	6.22	3050
M.L.	24	73	184	0.091	4300	2.55	4000
G.T.	37	75	168	0.079	3420	3.701	3000
S.S.	28	69	176	0.103	2540	3.82	2300
S.A.	34	74	178	0.131	2910	2.62	2950
D.H.	28	70	183	0.103	4000	2.54	3850
R.M.	27	73	183	0.055	4500	4.04	4300

Table 8b: Some of the physical characteristics and results of tests in lung function in the nine male subjects used in the experiments.

Subject	FEV _{1.0} (ml)	FVC (ml)	RV (ml)	TLC (ml)	IC (ml)	Smoking Habits
A.Y.	3550	4400	2760	7160	2750	-
A.M.	4000	4750	1400	6150	3000	-
N.S.	4050	4550	1150	5700	2650	-
M.L.	4350	4700	1400	6600	2600	-
G.T.	3800	4750	1000	5800	2800	Pipe
S.S.	3300	4200	1050	5500	3200	Cigarettes
S.A.	3450	4500	1250	5750	2800	Cigarettes
D.M.	4100	4600	1370	6100	2250	Cigarettes
R.M.	4500	5250	2550	7800	3500	Cigarettes

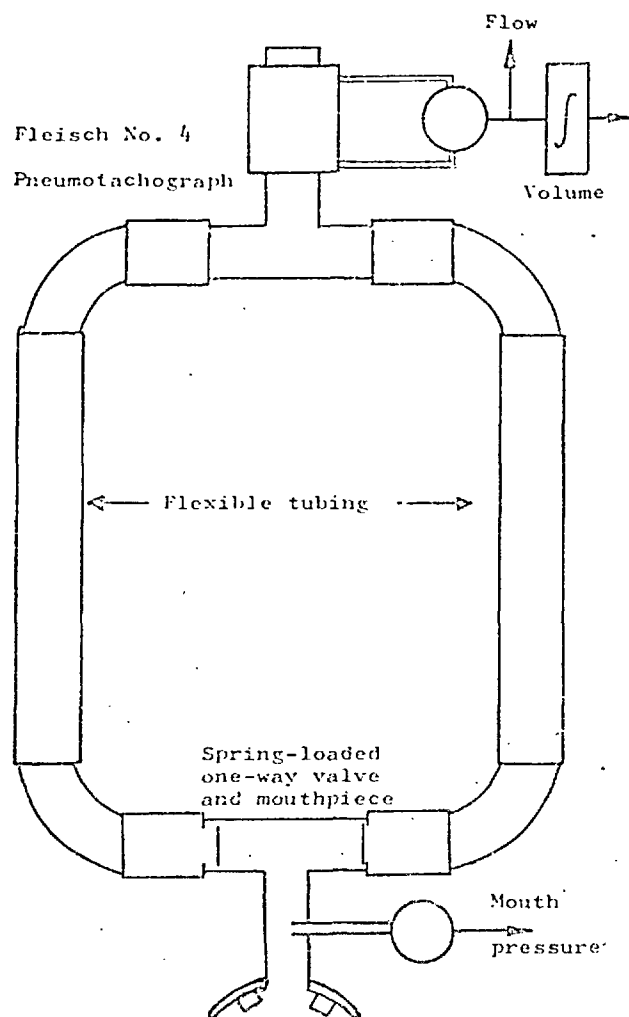


Fig. 40 Diagram of apparatus used

V.2. SUBJECTS AND METHODS

V.2.1. Subjects

Nine healthy young men were studied. Their physical measurements and estimates of lung function are shown in Table 8a,b. All lived an active life, though none was in physical training. Four were cigarette smokers and one smoked a pipe the remaining four were non-smokers. Two were aware of the purpose of the study and had had some practical experience of the investigation.

V.2.2. Measurement of Mouth Occlusion Pressure

The rate of change of mouth occlusion pressure was measured by a method described by Matthews and Howell (6). The apparatus is shown diagrammatically in Fig.40. The subjects breathed through the mouthpiece into a valve (P.K. Morgan 71522), which separated inspired and expired gas to avoid rebreathing. Flexible tubing connected the valve through a Y-piece to a heated pneumotachograph (Fleisch no. 4), which allowed inspired and expired flow rates to be measured. The flow signals were integrated with respect to time to give tidal volume. The resistance to gas flow of the whole assembly was less than $0.2 \text{ kPa l}^{-1} \text{ s}$ at a gas-flow of 2 litres/s. Continuous measurements of CO_2 concentrations at the mouth made by a rapid CO_2 analyser (Hartmann-Braun, URAS 4) failed to reveal any evidence

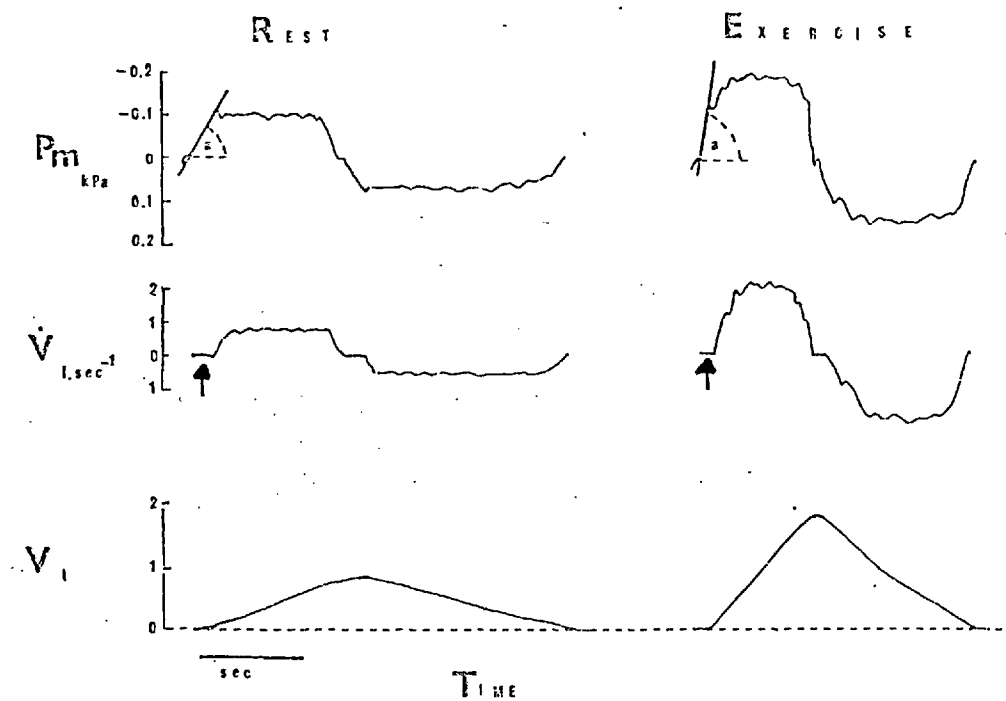


Fig. 41 Construction used for estimating dP/dt from original tracing of mouth pressure (P_m , upper trace). Middle trace: gas flow; lower trace: tidal volume

of rebreathing of expired gas throughout the experiments.

Mouth pressure was measured continuously by a photoelectric pressure transducer (Mercury Electronics, M 2/555).

Obstruction at the mouth was achieved by the small delay in opening of the spring-loaded valve. During this brief obstruction mouth pressure fell before the valve opened (Fig. 41). The opening pressure of the valve, measured continuously, was found to be about 0.1 kPa during quiet breathing and moderate exercise. However, moisture accumulating in the valve increased the opening pressure by the end of the exercise. This increase was found to be about 0.2-0.25 kPa in eight out of nine subjects in both forms of exercise. The ninth subject showed an opening pressure of 0.4 kPa at the last minute of the progressive exercise. The duration of the occlusion was not constant but depended upon the rate of change of pressure at the mouth, varying from about 0.040 s at high rates to about 0.200 s at low rates, measured from the flow trace (arrow in Fig. 41).

The frequency response of the system was tested by applying a square wave of pressure at the mouthpiece. The rise time of the mouth pressure signal was less than 10 ms to 95% of the total response.

V.2.3. Discussion of the Method

The great advantage of using a valve instead of a mechanically operated shutter is that the interruption to flow is very brief, almost noiseless and undetected by the subject. It does not therefore modify the pattern of breathing and makes it possible to measure the initial slope of the pressure (dP/dt) on every breath.

One objection to the use of the valve may be that the time of occlusion is too brief to allow pressure equilibration throughout the lung. However, Mead and Whittenberger (7) estimated the time of equilibration to be about 0.018 s in healthy subjects. In our experiments the shortest duration of occlusion was about three times this value.

Another objection may be that the opening pressure of the valve by the end of the exercise test is high enough to be an effective inspiratory resistive load (4). However, the opening pressure in the last minute was less than 0.25 kPa in eight subjects. Even in one subject where the pressure rose to about 0.4 kPa he was not aware of any load at the mouth.

Finally, the relationship between the neural input to the inspiratory muscles and the muscle tension measured as dP/dt , is linear only if we assume that the drop of the pressure is produced during isometric contraction of the muscles. This drop is about 0.1 kPa

(pressure required to open the valve) and it follows that the change in lung volume due to this is of the order of 0.1%. At a lung volume of 3.5 litres this is about 3.5 ml and is therefore considered small enough to justify the assumption of isometricity.

V.2.4 Procedure

Each subject performed a controlled progressive exercise test on a bicycle ergometer. During the test he breathed through the mouthpiece of the apparatus and wore a nose-clip. The test started with a recording of resting ventilation (flow, tidal volume and mouth pressure) for at least 2 min. Exercise was begun at a level of 60 W and a cycling speed of 60 rev./min. This load was maintained for 1 min and then was increased successively by 20 W increments at the end of each minute to the maximum load which could be tolerated short of complete exhaustion. At this point the subject stopped pedalling but continued breathing through the mouthpiece for 2 min. Recordings were made for the last 15 s of each minute during exercise and at intervals of 15 s during recovery. On the following day the subject performed a steady-state exercise lasting 6 min at a load of 60% of the final load of the progressive test. Recordings were made at rest, every 15 s during the first minute of exercise and at the

end of every minute thereafter, and again every 15 s during the first 2 min of recovery.

V.2.5. Calculation of Results

Fig.41 is a sample trace of a single breath at rest and during exercise. To measure the rate of change of the mouth occlusion pressure (dP/dt) a tangent was drawn coinciding with the initial part of the pressure trace, where it was approximately linear. The value of dP/dt was estimated from the slope of this line (tangent of a: Fig.41). Mean dP/dt was calculated from five successive breaths at rest and at each level of exercise.

The tidal volume (V_T) of the same breaths, together with the time of inspiration (T_I) and the total time of the complete breathing cycle (T_T) were measured and averaged over the five breaths. The ventilation was measured as the product of tidal volume and respiratory frequency over the same five breaths. Since the pneumotachograph was heated, no temperature correction was needed.

V.2.6 Statistical Methods

Standard methods have been used to calculate values for the correlation and regression coefficients. The significances of the differences between the slopes of the regression lines were calculated by estimating the variances of each value of the regression coefficient and from these the standard error of the

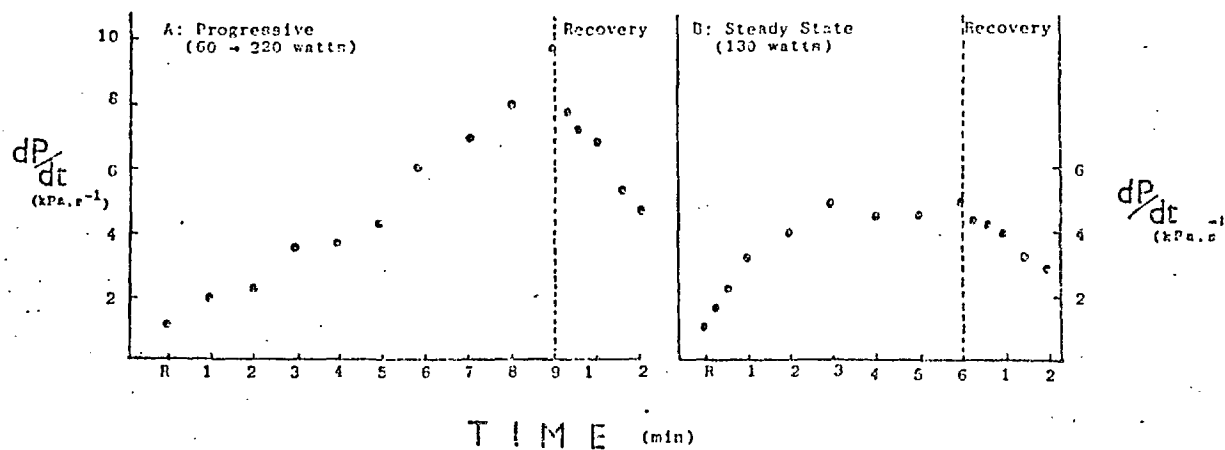


Fig. 42 A: dP/dt during exercise with progressively increased load (60 → 220 W) and recovery.
 B: dP/dt during steady-state exercise at constant load (130 W) and recovery. (Data from a typical subject).

differences between them. The actual techniques for these calculations are fully described by Smart (8).

V.3 RESULTS

At rest the value of dP/dt varied between individuals from 0.704 kPa/s to 1.408 kPa/s. The mean value was 1.0357 (SD 0.184) kPa/s in the nine subjects. In only one subject was there a significant difference between the values obtained on the 2 days of experiment. These values agree reasonably well with other published data from use of a similar method (6). dP/dt increased immediately after the beginning of exercise and dropped abruptly at the termination of exercise. This drop was more apparent at the end of progressive exercise (Fig. 42). Thereafter, for the 2 min of recovery, dP/dt decreased progressively (Fig. 42).

During progressive exercise dP/dt continued to increase progressively up to the end of the exercise. During steady-state exercise after the initial increase, dP/dt continued to rise progressively until the second or third minute, thereafter remaining almost constant (Fig. 42).

V.3.1 Response of dP/dt to the Workload

During progressive exercise there was a very close correlation between the work load and dP/dt . The correlation coefficient (r) was between 0.8734

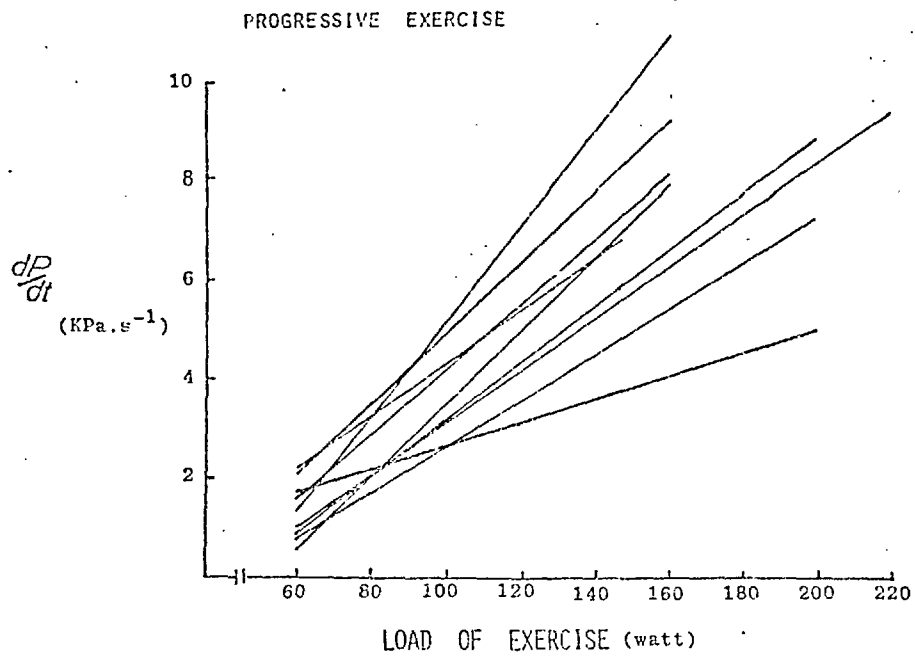


Fig. 43 Regression lines of dP/dt against load of exercise in all subjects during progressive exercise.

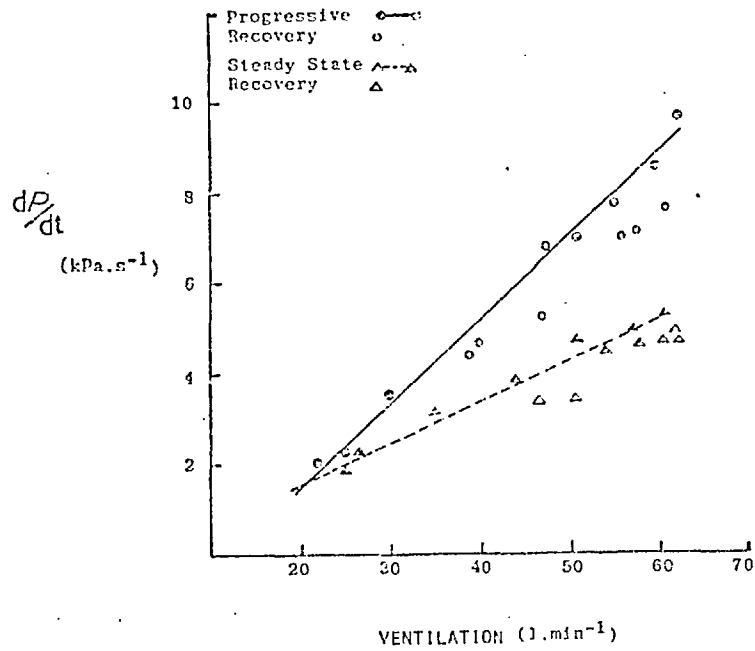


Fig. 44 Plot of dP/dt against ventilation during progressive exercise and recovery and during steady-state exercise and recovery in one subject. Regression lines are only from data during progressive or steady-state exercise

and 0.9909, highly significant in all subjects ($P < 0.001$). The coefficients of linear regression varied between the subjects from 0.0208 to 0.0916 $\text{kPa s}^{-1} \text{W}^{-1}$. Fig. 43 shows the calculated regression lines for all subjects.

V.3.2. dP/dt and Ventilation

During exercise, whether with progressively increasing work loads or with a single load, there was a very close correlation between dP/dt and ventilation.

The range of correlation coefficients (r) for all subjects under both conditions of exercise was 0.8015 - 0.9798, all highly significant ($P < 0.01$). The coefficients of linear regression varied between subjects from 4.932 to 15.345 kPa/l in the progressive exercise test and from 4.381 to 11.370 kPa/l in the steady-state test. There was a difference between the regression coefficients in the same subject during the two types of exercise, which was highly significant in six out of nine subjects. In those six individuals the regression line for progressive exercise was steeper than that for steady-state exercise. A typical example is shown in Fig. 44. The values of dP/dt during recovery from both forms of exercise were closely related to ventilation ($r = 0.671 - 0.986$). The number of observations available for estimating r in each case was only five, so that in only 12 of 17

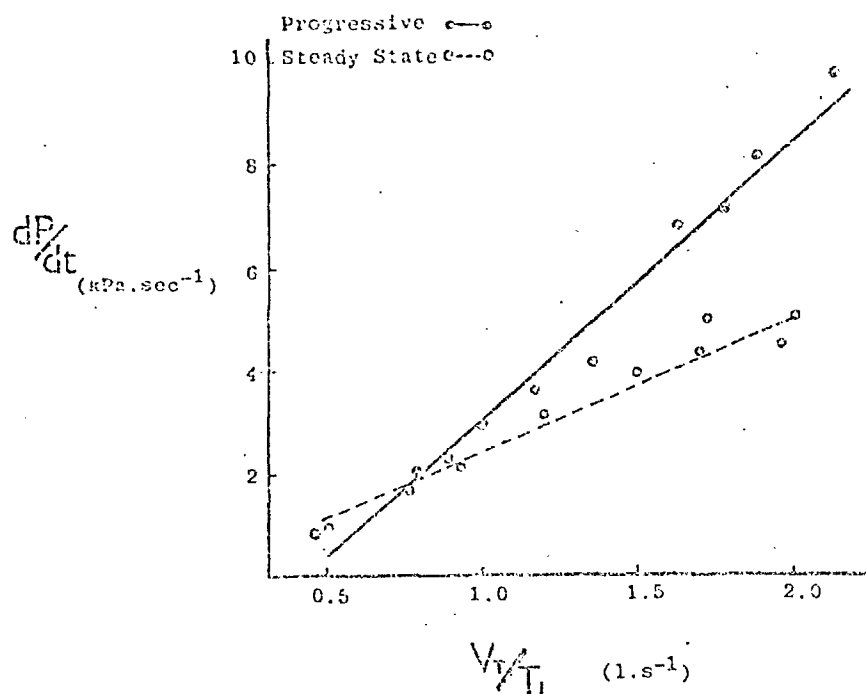


Fig. 45 Plot of $\frac{dP}{dt}$ against $\frac{V_T}{T_I}$ in one subjects during progressive and steady-state exercise.

experiments were the values statistically significant ($P < 0.05$).

The slope of the linear relationship of dP/dt to $\dot{V}_E$ during recovery was not significantly different from the slope obtained from the preceding exercise. Furthermore, the slope during recovery from progressive exercise was not significantly different from the slope during recovery from steady-state exercise in the same individual.

V.3.3. dP/dt and V_T/T_I

Following a suggestion by Milic Emili that the ratio V_T/T_I could also be regarded as an index of inspiratory drive we have compared this ratio with dP/dt in each of our subjects. We found a highly significant correlation both for progressive exercise and steady-state exercise (r between 0.7573 and 0.9759). The coefficient of linear regression in the two forms of exercise was statistically significantly different in six out of nine subjects, and again the slope of the regression line during progressive exercise was steeper than that during steady-state exercise in the same subject. A typical example is shown in Fig.45.

V.3.4. Pattern of Breathing during Progressive and Steady-State Exercise

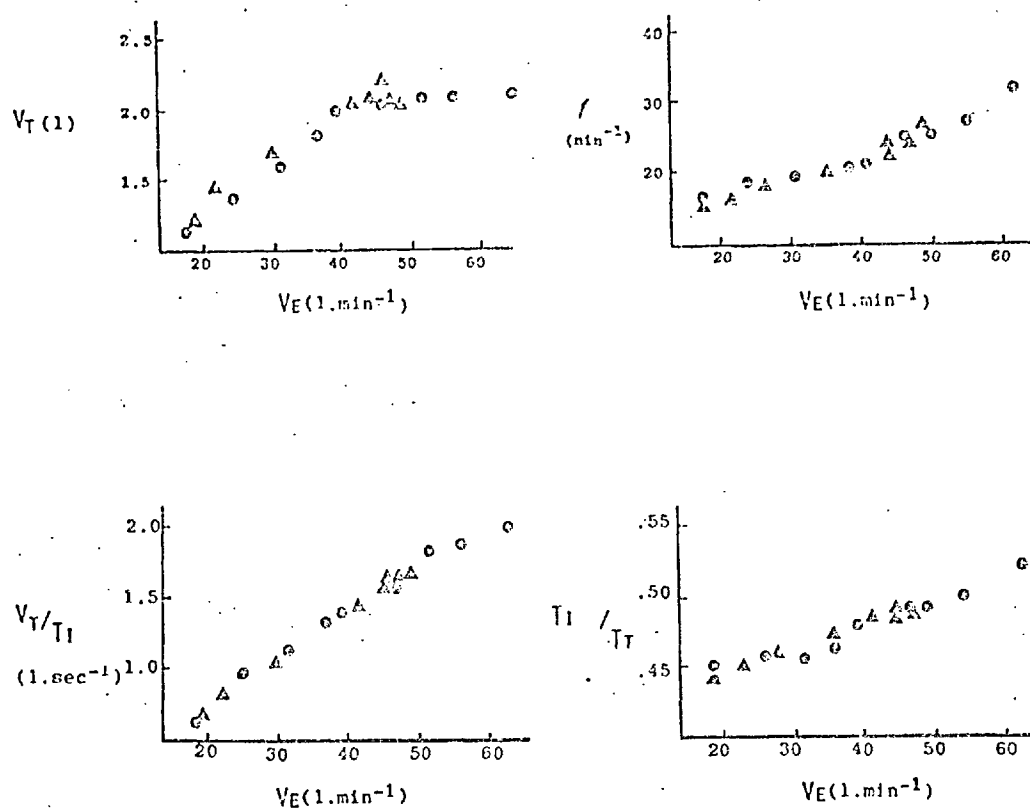


Fig. 46 Plots of tidal volume (V_T), frequency (f), V_T/T_I and T_I/V_T against ventilation in one subjects during progressive (○) and steady-state (△) exercise.

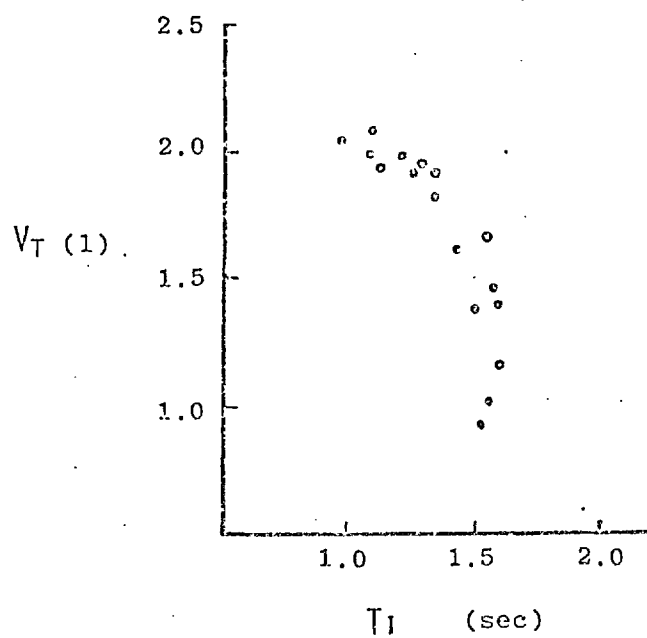


Fig. 47 Plots of V_T against T_I in one subject during progressive (•) and steady-state (o) exercise.

Minute ventilation may be expressed either as

$$\dot{V}_E = V_T \times f$$

or

$$\dot{V}_E = \frac{V_T}{T_I} \times \frac{T_I}{T_T}$$

We plotted V_T , f , V_T/T_I and T_I/T_T against ventilation during progressive and steady-state exercise to investigate the pattern of breathing. These plots failed to reveal any difference in the pattern of breathing between the two types of exercise in all subjects. An example of these plots in the same subject is shown in Fig. 46. In addition, tidal volume (V_T) was plotted against the time of inspiration (T_I) (2) in the two forms of exercise. This plot showed no difference between progressive and steady-state exercise in all subjects (Fig. 47).

V.4 DISCUSSION

Published data have evaluated the use of mouth occlusion pressure as an index of the neural output from the respiratory centres during hyperventilation stimulated by hypercapnia or hypoxia. In our experiments we used exercise to increase ventilation and the results presented here are in agreement with the hypothesis that dP/dt represents an index of the

central inspiratory drive. We found a linear relationship between progressively increasing work loads and dP/dt with a highly significant correlation coefficient in all our subjects. If the work load at each level of progressive exercise represents an index of the level of stimulation of the respiratory system, this correlation indicates that input and output of the respiratory centres are in agreement.

At the beginning and end of exercise changes in the value of dP/dt occurred within 5-10 s. This indicates that dP/dt follows closely a sudden change in ventilatory stimulus, i.e. the start or termination of exercise.

dP/dt was also found to correlate well with ventilation in both forms of exercise and during recovery. It is most interesting to find that the slopes of the dP/dt to $\dot{V}_E$ were significantly steeper during progressive than during steady-state exercise in six out of nine subjects. This suggested that less 'drive' is needed to produce the same amount of ventilation during steady-state than progressive exercise.

We do not think that this difference was an artifact due to the increase in the opening pressure of the valve as it became wet, because the opening pressure was similar in the two forms of exercise. The difference was still apparent in subsequent tests

performed by two individuals and could not therefore be due to familiarity with the apparatus. It may have been due to factors affecting either the pattern of breathing or the mechanical efficiency of the respiratory system.

Different patterns of breathing (e.g. slow, deep or rapid, shallow breathing) may produce the same minute ventilation but dP/dt for each pattern would be different. We studied the pattern of breathing and found no difference between steady-state and progressive exercise for the same level of ventilation. It therefore seems probable that a change in the physical properties of the respiratory system affected its mechanical efficiency and resulted in this difference. During steady-state exercise the respiratory system had time to adopt an optimal way of producing the required ventilation, whereas during progressive exercise there may not be enough time for this adaptation before the demand for higher ventilation occurred.

Finally, we have found a similar relationship between dP/dt and the ratio V_T/T_I and that between dP/dt and ventilation. We cannot explain these discrepancies by the model which we have applied in the anesthetized animals, since conscious men react to the whole breath occlusion and therefore the morphology of the driving pressure ~~wave~~ cannot be determined.

Since both V_T/T_I and V_E are affected by the mechanical properties of the system (resistance and compliance) as well as we have shown by the shape of the driving pressure wave, we believe that the rate of change of mouth occlusion pressure, which is presumably independent of these properties, must be a better index of central inspiratory drive.

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CHAPTER VI

CONCLUSIONS

This thesis is concerned with the respiratory "centres" output (controlling signal) and its final transformation to airflow. The various factors that affect the signal as it is translated from neural activity into driving pressure and from pressure into changes in lung volume are discussed.

It was shown that in anesthetized cats (35 mg/kg pentobarbital) changes in CIA, as monitored by the rate of change in the phrenic electrical activity, during hypercapnia or hypoxia are followed by proportional changes in the driving pressures and in most cases by equivalent changes in spirometric variables ($\dot{V}_E$, V_T/T_I). This increase in rate of rise of the various measurements of respiratory output was achieved without changing the time profile (shape) of these variables.

On the other hand, it was found that the morphology of the neural signal driving pressure waves and the spirogram was substantially different between cats. Within each animal however, the similarities in the shape of the various respiratory "outputs" were striking. Thus, it is concluded that under the experimental conditions of the present study the different inter-animal morphologies in outputs represent an intrinsic function of generation of the controlling signal. In addition, since a

similar morphology was seen in the spirogram (end-result) it follows that the time profile of the signal was not lost at the various mechanical translations.

Similar conclusions concerning the shape of the signals can be drawn from the experiments during increased depth of anesthesia where, apart from an enhancement of partial inhibition of central inspiratory activity similar results were obtained. From these experiments it is also concluded that neither the neuromuscular junction nor the effectiveness of the respiratory muscles to produce pressure were impaired by the increase anesthesia till the death of the animal.

In addition, it was shown that the potentially available pressure during inspiration was dissipated to overcome the passive resistance and elastance of the system, and in an additional volume-related pressure loss. The latter indicates the fact that with increased lung volume the inspiratory muscles became less effective pressure generators because of changes in their length and/or their configuration. On the other hand, in our cats little if any, pressure is lost as a result of the force-velocity relationship of the inspiratory muscles.

During light anesthesia (35 mg/kg of pento-barbital sodium), with increased respiratory drive induced by hypercapnia or hypoxia the changes in minute ventilation ($\dot{V}_E$) and mean inspiratory flow (V_T/T_I) were in many cases proportional to these in central inspiratory activity (CIA) as assessed by phrenic electroneurogram or airway occlusion pressure. In other animals, however, this was not the case. With increased level of anesthesia $\dot{V}_E$ and V_T/T_I were not directly proportional to CIA in any of the cats. To explain these findings a theoretical model was developed which takes into account the shape of the pressures that drive the respiratory system. This model explains many of the features found experimentally in our cats. It also clarified the reason why in many instances the changes in CIA and $\dot{V}_E$ or V_T/T_I were not proportional.

From these studies it is concluded that the morphology of the time course of neural and respiratory driving pressure waves must be taken into consideration in studies of control of breathing.

In the human studies similar discrepancies between rate of rise of mouth occlusion pressure and $\dot{V}_E$ or V_T/T_I also found. In this case it is difficult to interpret the findings since the shape of the time course of respiratory driving pressures cannot be determined in conscious men. This emphasizes

the fact that mechanical properties of the respiratory system, such as resistance and elastance, are not the only factors influencing the spirometric output. The shape of the respiratory driving pressure waves is an additional important one.