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Ann Maureen Nielsen
Iowa State University

NIELSEN, ANN MAUREEN

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Iowa State University PH.D. 1980

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Reflex respiratory responses to specific airway occlusions during normoxic, hypoxic, hyperoxic and differential lung ventilation

Ann Maureen Nielsen

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Members of the Committee:

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TABLE OF CONTENTS

LIST OF FIGURES

Page

Page

LIST OF TABLES

ABBREVIATIONS

AIRFLOW

$I\text{-}\dot{F}^R$, $I\text{-}\dot{F}^L$	Inspiratory airflow (L/min). Superscript denotes right (R) and left (L) airways.
$E\text{-}\dot{F}^R$, $E\text{-}\dot{F}^L$	Expiratory airflow (L/min). Superscript denotes right (R) and left (L) airways.

ELASTANCE

$E_{dyn}{}^R$, $E_{dyn}{}^L$	Dynamic elastance (cm H_2O/L) of the right (R) and left (L) lung.
$E_{qs}{}^R$, $E_{qs}{}^L$	Quasi-static elastance (cm H_2O/L) of the right (R) and left (L) lung. Only applies to an occluded lung during a given maneuver.

OCCLUSIONS

RLO-EE, RLO-EI LLO-EE, LLO-EI BLO-EE, BLO-EI	Right lung (RLO), left lung (LLO) or both lungs (BLO) occluded at end-expiration (EE) or end-inspiration (EI).

PRESSURE

$I\text{-}P_{AW}{}^R$, $I\text{-}P_{AW}{}^L$	Inspiratory airway pressure (cm H_2O) of right (R) and left (L) lung.
$E\text{-}P_{AW}{}^R$, $E\text{-}P_{AW}{}^L$	Expiratory airway pressure (cm H_2O) of right (R) and left (L) lung.
P_{ES}	Esophageal pressure (cm H_2O) used as an estimate of pleural pressure referenced to atmospheric pressure.
PAP	Pulmonary arterial blood pressure (mm Hg).
RVP	Right ventricular systolic blood pressure (mm Hg).
AoP	Systemic blood pressure (mm Hg) measured in aortic arch.
p_aO_2, p_aCO_2	Partial pressure (mm Hg) of oxygen and carbon dioxide in arterial blood.

$P_{\bar{v}}O_2$, $P_{\bar{v}}CO_2$	Partial pressure (mm Hg) of oxygen and carbon dioxide in mixed venous blood samples obtained from the pulmonary artery or right ventricle.
ET-pO_2, ET-pCO_2	Partial pressure (mm Hg) of oxygen and carbon dioxide in end-tidal gas samples. Values have been corrected for body temperature and saturation.

TIME

T_I, T_{IO}	Inspiratory duration (sec or msec as indicated in text) of control and first effort occluded breaths.
T_E, T_{EO}	Expiratory duration (sec or msec as indicated) of control and first effort occluded breaths.
T_A	Apneic duration (sec) measured from the onset of occlusion at peak inspiration to the onset of the first inspiratory effort.
T_I'	Inspiratory duration (sec) of the breath during which the occlusion was actually set.
T_{TOT}, T_{TOT}^0, T_{TOT}^1	Total respiratory cycle duration (sec) of the control, occluded and first effort breaths.

VOLUME

V_T^R, V_T^L, V_T	Tidal volume (ml) of the right, left or total lung.
$\dot{V}_E$	Minute ventilation (L/min). Values have been corrected to BTPS.

MISCELLANEOUS

CIA	Central inspiratory activity.
Diff. Vent., DV	Differential ventilation where left lung breathes 100% nitrogen and right lung breaths 90-100% oxygen. Also referred to as unilateral hypoxia.

F_IO_2, F_IN_2	Fractional concentration of inspired oxygen and nitrogen.
FRC	Functional residual capacity, i.e., end-expiratory lung volume.
I-OS	Inhibitory-off switch.
PIR	Pulmonary irritant receptors.
PSR	Pulmonary stretch receptors.
RVX, LVX, BVX	Right, left and bilateral vagotomy.
SSBP	Steady state breathing pattern.

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"If the sky falls, have clouds for breakfast"

One more breakfast at Sambo's (3:34 a.m.) with my newly acquired friends in Madison without whom this paper would never have appeared in print. Julie Gunderson and Carolyn Birr were so eager to type this manuscript that I actually found them arguing about who would type Appendix A. Furthermore, they have confirmed my suspicions that there are good people wherever you go; even outside of Ames, Iowa.

Prior to printing, this work was the product of many hours of assistance from my committee which I hope someday I will be able to return. Bob Carithers is responsible for scrounging up most of the necessary equipment and for adjusting my attitude every now and then. Dr. Dyer was the first of many to redirect my energy and help me to "...stop banging my head against the wall..." about fiber picking. And Charlie Drewes, thank you for all the hours of encouraging me to "...ask someone...don't try to recreate the wheel...." I could ALWAYS (and probably will always) turn to Mary Helen Greer for explanations about how, why and what--thank you for never rolling your eyes at some of my misconceptions. I'm sure there will be many more. Dr. Cholvin, you never once were too busy to stop and show or explain something to me or to refer me to a proper source. One of these days I will understand blood flow regulation. As I stated in my M.S. Thesis, you are

responsible for encouraging me to remain in graduate school in the first place.

During my graduate education I have had 16 ± 2 (Mean ± SD) nervous breakdowns per week about research and teaching and anything else that wasn't being worried about. Dick Engen has seen me through every one, always seeming to know just the right remedy for a particular seizure.

If I had to dedicate this paper to someone very special I would have to name Bud Maakestad whose gentle hug now and then as well as his shear genius with plexiglass, epoxy and solder resulted in Figure 5, far from a Rube Goldberg. Furthermore, his home is my adopted home in Ames, complete with Ursula's constant encouragement and wisdom.

If I have not thanked my parents or told them how much I love them for their patience, it would surely be too late by now. Whether I fail or succeed, I know I will always have my family. This gives me a great deal of self-confidence and optimism.

Sincerely,

Ann

ABSTRACT

Experiments were conducted to assess the influence of changes in alveolar oxygen tension with and without concomitant changes in arterial oxygen tension on respiratory responses to occluding the left and/or right airway(s) at specific times during the respiratory cycle. Thirty-eight anesthetized dogs were intubated with a double-lumen endobronchial divider which allowed independent ventilation of the left and right lungs. Steady state breathing patterns (volumes, airflows, airway pressures and timing of the inspiratory and expiratory phases) and reflex responses during bilateral normoxia, hypoxia and hyperoxia (all isocapneic) were studied to evaluate the contribution of peripheral chemoreception input to control of respiration. A fourth test gas experimental condition termed differential ventilation allowed the left lung to breathe 100% nitrogen while the right lung breathed 90-100% oxygen. This procedure was used to partition the roles of alveolar versus arterial O_2 tension on lung volume reflexes. Data obtained from differentially ventilated dogs, when compared with reflexes induced during hypoxia and hyperoxia, support the hypothesis that mechanisms which 'sense' changes in the concentration of alveolar O_2 participate in breathing pattern control. Like the CO_2-pulmonary reflex, oxygen chemoreception appears to act by altering pulmonary stretch receptor discharge. However, the observation of a significant ventilatory response to differential ventilation (normal systemic oxygenation) in bilaterally vagotomized dogs further suggests the possibility that

intrapulmonary oxygen chemoreception is mediated by extravagal mechanisms which could include a humoral component. The contribution from vagal and extravagal mechanoreceptors in mediating these reflexes was evaluated by comparing pre- and post vagotomy responses to occlusions set at peak inspiration and end-expiration. Data obtained from unilateral airway occlusions revealed that the respiratory response to total airway occlusion was not a simple summation of left and right lung responses. These results suggest that: 1) pulmonary vagal afferents are not strictly ipsilateral, 2) central integration of volume feedback is not simply additive and 3) extravagal sensory input provides a substantial contribution in control of the breathing pattern.

INTRODUCTION

Numerous investigations concerning the neural, chemical and mechanical mechanisms underlying rate and depth conrol of the respiratory cycle have been performed. Unfortunately most of these studies have been designed to detail only one of these components without regarding input from the others. Actually neuronal output of the brainstem respiratory center(s) represents central integration of: 1) vagal and extravagal feedback relaying chemical and mechanical information from the periphery, 2) intrinsic spontaneous neuronal activity, 3) tonic non-feedback afferent activity, and 4) humoral factors.

Measuring each input-output relationship separately was required in order to obtain information as to how the central nervous system interprets specific afferent input and how these inputs (mechanical and chemical) are interrelated. The present study was designed: 1) to evaluate the contribution of the left and right to total lung reflex respiratory responses to infinite elastic loading, i.e., airway occlusion, 2) to compare the nature of these responses during loading and unloading of peripheral chemoreceptors by altering arterial oxygen tension, 3) to assess the vagal and extravagal mechanoreceptor contributions to these reflexes, and 4) to investigate the possibility that alveolar oxygen tension alters these phasic lung-volume related pulmonary reflexes.

The technical ease of manipulating sensory activity coursing from the periphery to the brainstem has led to the use of 'loaded' breathing as a tool for studying respiratory pattern regulation. Mechanical loads were imposed by occluding one or both airways at end-expiration (EE) or end-inspiration (EI) of anesthetized dogs fitted with a cuffed endobronchial divider. This enabled assessments of phasic versus tonic pulmonary stretch receptor (PSR) afferent effects on respiratory pattern control. Similar experiments performed in bilaterally vagotomized dogs were used to evaluate the contribution by extravagal mechanical afferents on breathing pattern control. Unilateral occlusion in intact dogs and respiratory responses to bilateral occlusion in unilaterally vagotomized dogs were tested in order to determine the nature of central integration, i.e., non-linear verses additive. Unilateral vagotomy was also used to ascertain whether or not pulmonary vagal innervation is strictly ipsilateral and to evaluate the contribution of left and right lung reflex respiratory responses to infinite elastic loads.

It has been shown that conventional peripheral chemoreceptors exert an effect on the breathing pattern which is opposite that resulting from stimulation of pulmonary stretch receptors. In addition to peripheral and central chemoreceptor involvement in pattern regulation, a CO_2-pulmonary reflex arising from the lungs has been described in dogs (Banzett et al., 1978) and repeatedly demonstrated in avian species (Fedde and Peterson, 1970). Based on these reports it is tenable that changes in alveolar oxygen, independent of alterations in arterial oxygen tension, could contribute to rate and depth control of the

breathing cycle. Physiological evidence for the existence of intrapulmonary oxygen chemoreceptors was first provided by Dawes and Comroe (1954) and indeed it has become well-established that hypoxia causes pulmonary vasoconstriction by intrapulmonary mechanisms (Daly and Hebb, 1966; Laros, 1971). However, the role of intrapulmonary oxygen chemoreceptors in regulating the respiratory pattern has not been previously addressed.

Changes in inspired oxygen (both lungs F_IO_2 = 0.1, 0.2 or 1.0) were used in the present study to assess the combined effects of parallel changes in alveolar and arterial chemoreceptor inputs on bulbopontine respiratory output. To isolate the effects of local alveolar oxygen tension without alterating peripheral chemoreceptor input the animals were differentially ventilated (left lung with 100% nitrogen and right lung with 90 - 100% oxygen). This preparation has lungs which are normally innervated and spontaneously breathing. Normoxia is established during differential ventilation. Therefore, peripheral chemoreceptor input should be identical to that which is present during room air ventilation. Changes in local oxygen tension of the hypoxic and/or hyperoxic lung, if detected by intrapulmonary oxygen chemosensitive receptors, could interact with phasic and tonic vagal volume feedback mechanisms, extravagal afferents, and/or possibly humoral factors such that reflex responses to airway occlusions as well as steady state breathing patterns would be altered.

LITERATURE REVIEW

Introduction

The Hering-Breuer inspiratory-inhibiting and expiratory-exciting reflexes have been extensively studied during the last 100 years. These vagally mediated, phasic lung volume reflexes were originally hypothesized by Breuer (1868) and Hering (1868) to underlie regulation of the respiratory cycle pattern, i.e., rate and depth. These reflexes can be elicited: 1) by mechanical loading via, e.g., partially or completely obstructing the airways at different lung volumes or 2) by artificially inflating the lung with a predetermined volume or tracheal pressure at specific times during the breathing cycle.

The reflex respiratory response of decreased frequency and increased tidal volume to airway obstruction (resistive loading) as well as the increased frequency and reduced tidal volume response to external elastic loading are well-documented (Bland et al., 1967; Freedman et al., 1972; Freedman, 1974). It is also well-known that 'threshold' inflations applied during inspiration cause an 'all-or-none' premature inhibition of inspiration and an apneic period of variable duration while inflations applied during expiration result in graded lengthening of expiration related to the volume of inflation (Clark and von Euler, 1972). However, the responses during expiration are less clear cut. Inflations applied during the last 20-30% of expiration appear to have no effect and if the

inflation is applied very rapidly may actually produce drastic shortening of expiration (Knox, 1973).

The review which follows examines current models of ventilatory control and factors which contribute to regulation of the rate and depth of breathing. Specific emphasis is placed on the inspiratory-inhibiting reflex and timing of inspiration and expiration. A discussion of afferent (vagal and extravagal), central (bulbopontine) and efferent (phrenic) components which have been implicated in the reflex arc of respiratory rhythmicity is presented. The contribution of a tonic humoral drive to breathe is reviewed since phasic lung volume reflexes are superimposed upon such a drive even during room air ventilation. Several approaches for quantitatively evaluating ventilatory control mechanisms will be discussed emphasizing the importance of effector mechanisms, i.e., mechanical properties of the respiratory apparatus in determining a given response. Animal status (conscious versus anesthetized and open versus closed-chest) and species specific responses will be included since they are imperative considerations in designing experiments and interpreting results aimed at evaluating ventilatory control mechanisms.

Proposed Models of Ventilatory Control

It has been proposed that the breathing pattern is adjusted to maximize output of the respiratory muscle effort needed to effect adequate alveolar ventilation with the minimal amount of work

(Rohrer, 1925; Otis et al., 1950) or force (Mead, 1960). In other words, the breathing pattern is dependent on respiratory system mechanics, i.e., resistance and compliance.

With regard to the breathing pattern Milic-Emili and Cajani (1957) and Hey et al. (1966) have described unique relationships between mean ventilation and the mean tidal volume and frequency in intact man. However, the mechanisms underlying these relationships are not fully understood.

A widely used working model of ventilatory control proposed by von Euler et al. (1970) states that the respiratory cycle characteristics are set by a bulbopontine pattern generator regulating the duration of inspiration. This central pattern generator may interact with vagal mechanisms relaying volume, rate of change of tidal volume and transmural pressure information from the lungs (Adrian, 1933; Larrabee and Knowlton, 1946; Davies et al., 1956; Widdicombe, 1964). The magnitude of tidal volume may therefore be determined by a combination of the two processes; one which sets the rate of volume change (chemical drive) and a second which regulates the duration of the volume change. The model of von Euler et al. (1970) partially explains the Hey relationships (Hey et al., 1966) in terms of neural circuitry and indirectly implies that lung mechanics do play an important role in respiratory pattern regulation. A more detailed discussion of this model will be presented later in this review.

Neuronal Networks Underlying Respiratory Pattern Regulation

Bulbopontine mechanisms

Studies based on intracellular recordings from different neuronal networks within the bulbopontine brainstem areas have contributed to current concepts regarding neural control of respiration as depicted schematically in Figure 1. Spontaneous central inspiratory activity (CIA) which appears to be synchronous with phrenic output arises from Type α neurons in the dorsal respiratory group of the Nucleus Tractus Solitarius and impinges on closely associated Type β neurons. These β neurons also receive vagal afferent information from pulmonary stretch receptors (PSR) which together with CIA activity is relayed to inhibitory off-switch (I-OS) neurons[1]. When the sum of CIA plus vagal volume feedback coursing to the I-OS reaches some apparent threshold the I-OS inhibits inspiration by terminating phrenic motor activity. The I-OS may also receive tonic facilitory activity coursing from the pontine pneumotactic center located in the Nucleus Parabrachialis Medialis and Kölliker-Fuse Nucleus (Bertrand et al., 1974). The bulbopontine neuronal pools are

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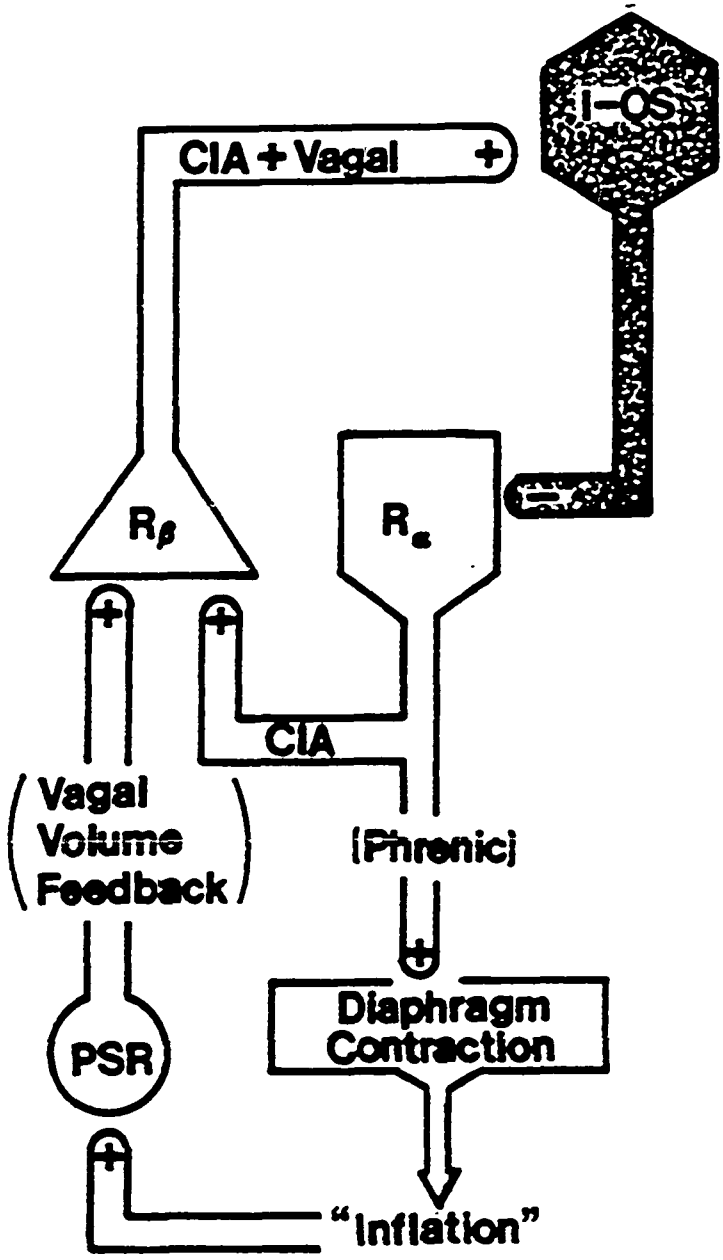
[1]The classification used in the figures and text is from Baumgarten and Kanzow (1958). Another classification of these cells has been presented by von Euler et al. (1973). The I-V cells are analogous with the Type β neurons which receive both vagal and CIA input. The type α cells are referred to as I-S neurons since they have spinal axons but do not receive vagal input. von Euler also suggests that the I-V efferents represent the I-OS mechanism. In other words, the I-V neurons terminate inspiration either by a central pattern generator mechanism or by reflex vagal volume feedback, or a combination of the two.

Figure 1. Schematic representation of neural circuitry postulated to be directly involved in respiratory phase-switching.

Excitatory (+) and inhibitory (-) connections are denoted. Central inspiratory activity (CIA) and phrenic output drawn as diverging pathways arising from Rα-neurons in *Nucleus Tractus Solitarius*. CIA as well as pulmonary stretch receptor (PSR) afferent vagal activity impinges on and is integrated by Rβ-neurons. Outflow from Rβ neurons courses to the inhibitory-off switch (I-OS) neurons. The I-OS output inhibits Rα-neurons thereby completing a classical negative feedback system. Forebrain, pneumotactic, hypothalamic, chest wall, and chemoreceptor inputs are not shown.


I–OS
CIA + Vagal
+
R_β
R_α
+
+
CIA
Vagal
Volume
Feedback
[Phrenic]
+
PSR
Diaphragm
Contraction
+
"Inflation"

functionally, although not anatomically, represented in the simplified model diagrammed in Figure 1. Phase switching between inspiration and expiration may actually involve at least eight types of respiratory neurons which respond specifically to mechanical and/or chemical stimuli (Folgering and Smolders, 1979).

Vagal mechanisms

It is presently held that slow adapting pulmonary stretch receptors are primarily, although not solely, responsible for mediating the inflation reflex by responding to changes in transpulmonary pressure or volume (Guz and Trenchard, 1971a). There is physiological evidence that vagal afferent innervation of a lung is exclusively ipsilateral (Klassen et al., 1951; Guz et al., 1966a). Single fiber nerve recordings have revealed that these receptors fire at a rate that is closely proportional to the square root of lung volume (Clark and von Euler, 1972). However, pulmonary stretch receptor sensitivity can be altered by anesthesia, carbon dioxide and temperature which complicates the interpretation of their role in reflex responses to mechanical loading.

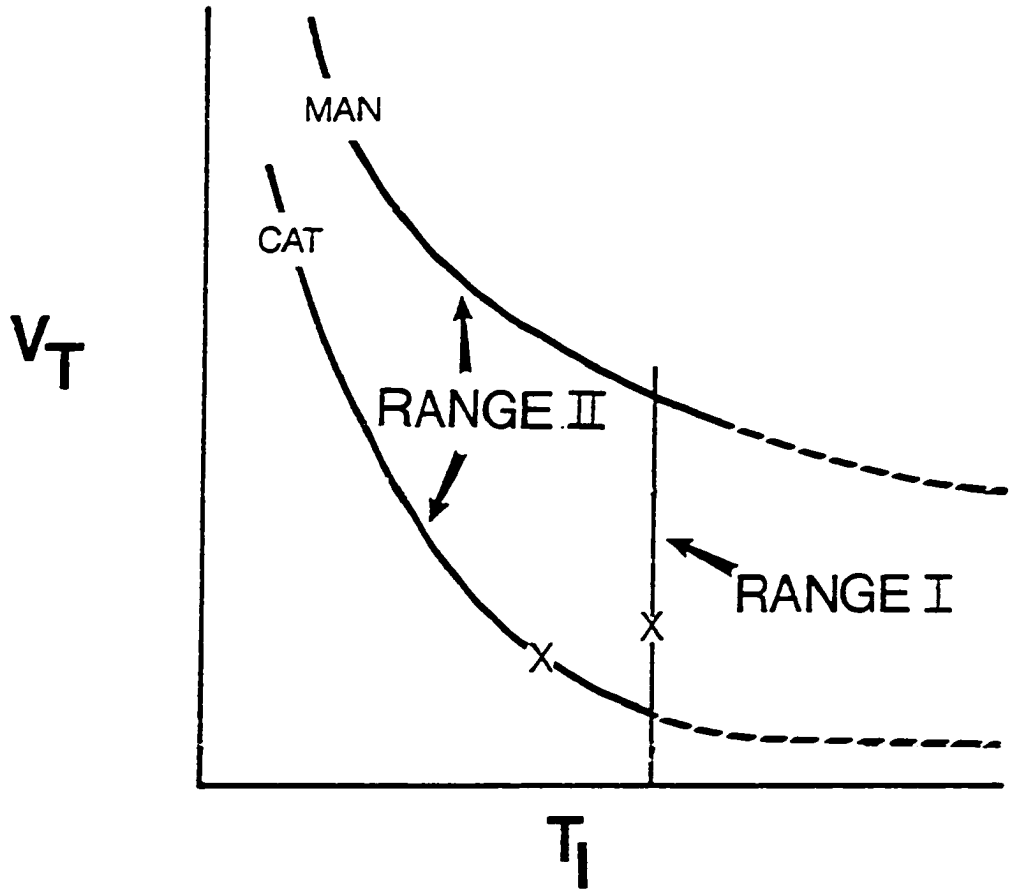
Miserocchi and Sant'Ambrogio (1974) categorized pulmonary stretch receptors into at least two groups. Type I PSR are located mainly in the larger airways. They contribute most of the afferent vagal feedback in the normal tidal range with increasing PSR discharge corresponding to increasing transpulmonary pressures up to about 10-12 cm H_2O. Further increases in pressure do not result in

increased activity. On the other hand, Type II PSR which are located in the small airways show increasing discharge with increasing pressure over a very large pressure-volume range with no detectable plateau. Thus, as lung volume increases, i.e., transpulmonary pressure increases; the contribution by Type II PSR impulses to the total PSR afferent activity progressively increases. It follows from this that knowledge of the pressure generated against an occluded airway is an important consideration in describing the strength and mechanisms of phasic lung volume reflexes and will be discussed later.

Clark and von Euler (1972) quantitatively described the inspiratory-inhibitory effect of the vagal feedback mechanism by an inspiratory volume-time characteristic (V_T-T_I) as shown in Figure 2 and a time dependent relationship of expiratory time (T_E) on inspiratory time (T_I). Their results were obtained from breath-by-breath analysis during progressive rebreathing in paralyzed and artificially ventilated, anesthetized cats and conscious humans. The relationship between tidal volume and inspiratory duration represents the threshold sensitivity curve of the respiratory centers for the volume-related vagal feedback arc. The V_T-T_I relationship is divided into two responses. Range I includes tidal volume increases which are not associated with changes in inspiratory time and Range II is curvilinear with increases in tidal volume being associated with decreases in inspiratory duration. Range I, considered the volume-independent portion represents the

Figure 2. Relationship between inspired volume and inspiratory duration for man and cat.

Solid lines represent tidal volumes (V_T) and inspiratory durations (T_I) obtained during rebreathing experiments. Dashed lines are V_T-T_I extrapolations obtained during elastic loading. The crosses (x) indicate position of typical tidal volume and inspiratory duration during eupneic breathing. It can be seen that man normally operates in Range I where T_I is independent of tidal volume. Conversely, the eupneic pattern in cats is controlled by Range II determinants, i.e., Hering-Breuer mechanisms.


MAN
CAT
RANGE II
RANGE I
V_T
T_I

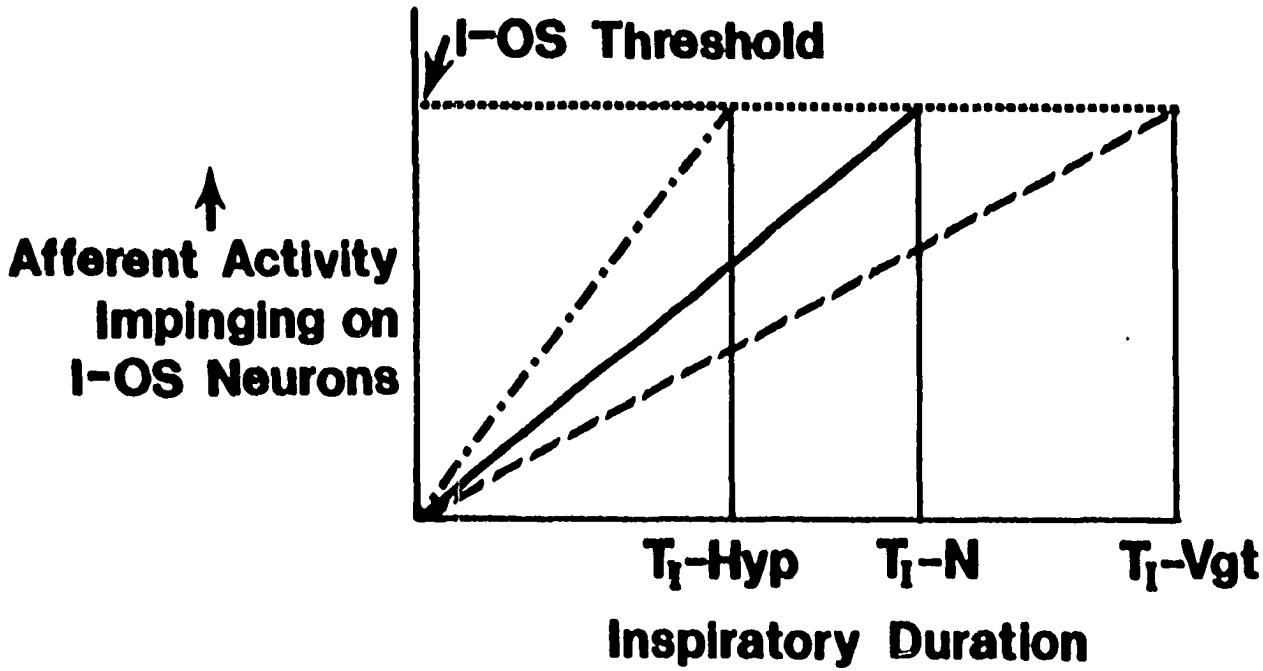
operational range of the bulbopontine pacemaker mechanism. Range II is thought to represent the Hering-Breuer reflex range where changes in inspiratory time depend on functional lung volume vagal feedback, particularly that arising from slow adapting pulmonary stretch receptors. The right end of the threshold curve, when no expansion of the lung occurs, is exactly the inspiratory time found in vagotomized or paralyzed animals, i.e., that set by the central inspiratory activity. This graphical approach for analyzing the control of breathing becomes very useful in understanding how humoral ventilatory drive and anesthetics interact with mechanical factors in pattern regulation.

The relative importance of vagal volume feedback in respiratory pattern regulation does appear to be species specific, although no comprehensive investigation has been undertaken. The threshold for phasic vagal regulation of the respiratory pattern (presumably due to PSR input) is in the eupneic range of ventilation for cats. In awake man the vagal effects manifested as changes in T_I only occur at tidal volumes of 1.5 to 2.0 times normal. However, PSR activity has been shown (Polacheck et al., 1978) to play an important role in the control of breathing in some humans anesthetized with enflurane.

In the absence of vagal feedback, inspiratory time is dictated solely by the intrinsic CIA pacemaker activity such that I-OS threshold takes longer to be reached and inspiratory time is lengthened (Figure 3). It follows that an increase in vagal afferent activity (hyperinflation) should terminate inspiration

Figure 3. Inspiratory duration depends upon the afferent neural input and threshold of the inspiratory off-switch.

Graph depicts rate of rise of afferent activity (e.g., Rß integration of central inspiratory activity plus vagal volume feedback) impinging on inspiratory-off switch (I-OS) neurons during hyperinflation (-·-·-), during normal breathing (——) and following bilateral vagotomy (----). Inspiratory durations in each situation are indicated on the horizontal as T_I-Hyp, T_I-N and T_I-Vgt, respectively.


I-OS Threshold
Afferent Activity
Impinging on
I-OS Neurons
T_I-Hyp
T_I-N
T_I-Vgt
Inspiratory Duration

earlier and that sustained vagal input (airway occlusion during inspiration) should theoretically delay the onset of another breathing effort by keeping input to the I-OS above threshold.

Such theory has been borne out in studies by D'Angelo and Agostoni (1975) in which they observed that the first breathing effort against airways occluded at peak inspiration had systematically shorter inspiratory times and longer expiratory times than efforts against airways occluded at end-expiration. Prolonged T_I of the first effort against occlusion at functional residual capacity (FRC) is most likely due to withdrawal of phasic inspiratory-inhibitory vagal influence (Widdicombe, 1961a; Richardson et al., 1973) resulting from failure of the lungs to expand. Airway occlusion at FRC subsequent to vagal cooling or vagotomy resulting in an unchanged or even a decreased T_I of the first effort in rabbits (Younes et al., 1975) and cats (Corda et al., 1965; Bradley, 1972) supports this contention.

In contrast, Sant'Ambrogio et al. (1972) observed that inspiratory time of the first occluded breath was longer when vagal conduction was blocked than when intact. This was attributed to the presence of high background residual or tonic PSR activity at FRC during occlusion of their vagally intact animals.

It should be evident that a central pattern generator produces the motor output of cyclic breathing without receiving any phasic sensory input. However, phasic sensory input is normally present which overrides the central pattern generator by reflexly

terminating phrenic output during eupneic breathing and during increased breathing driven by chemical and other stimuli.

Superficially it seems that the Hering-Breuer reflexes may compensate for occluded or overdistended airways. Actually, occluded airways result in slow and/or minimal lung filling and termination of inspiration by the CIA. In this regard, at least the vagal volume related portions of the Hering-Breuer reflex do not seem to contribute to determining T_I.

It has been proposed that mechanisms which determine inspiratory time indirectly determine total cycle duration and hence respiratory frequency by a time dependent relationship of expiratory time on inspiratory time. Clark and von Euler (1972) reported that within a single breath the duration of the expiratory phase was dependent on the preceding inspiratory phase while the T_I and T_E of each breath were completely independent of preceding breaths. In other words, expiratory duration of one breath had no influence on inspiratory time of the next breath. Similar observations have been reported by Knox (1973) and D'Angelo and Agostoni (1975).

Further evidence supporting the idea that both inspiratory and expiratory duration are controlled by similar mechanisms was reported by Nadel et al. (1973) in which differential cooling of the vagus nerves in dogs revealed a direct relationship between attenuation of the Hering-Breuer inspiratory-inhibiting reflex and a decrease in T_E. Further cooling of the vagi to temperatures which completely abolished the Hering-Breuer reflex was associated with an

increase in T_E. Therefore, it was suggested that impulses arising from receptors responsible for Hering-Breuer lung volume reflexes were also responsible for determining the expiratory period. These workers postulated that pulmonary stretch receptor activity arising from the lungs during inspiration may cause prolonged hyperpolarization of pontine and/or medullary inspiratory units, thus requiring a longer period for these cells to return to firing threshold, and thereby lengthening expiratory time.

In contrast to the studies described above, Bartoli et al. (1975) were unable to demonstrate consistent changes in T_E associated with specific changes in T_I. These conflicting reports may be due to species variations since Clark and von Euler (1972) used cats while Bartoli's group (1975) studied this relationship in anesthetized dogs. Regardless of these differences, the role of tonic PSR activity in regulation of T_E has become apparent from which a more clear understanding about the different mechanisms underlying the control of inspiratory versus expiratory duration has developed.

Central integration of phasic pulmonary stretch receptor information as stated before is known to be important in determining the rate and depth of breathing. In addition to phasic vagal control of respiratory frequency, Breuer (1868) postulated that the vagus might exert tonic control (lungs not subject to breathing movements) of respiratory frequency. This implies that changes in functional residual capacity could influence cycling frequency of

the respiratory controller. To confirm an effect of tonic vagal discharge on breathing rhythmicity requires the demonstration of pulmonary stretch receptor firing at FRC.

Although Grunstein et al. (1973) have reported that most PSR are silent at residual lung volume, the presence of tonic stretch receptor activity at FRC has been observed by others in dogs (Miserocchi and Sant'Ambrogio, 1974), cats (Paintal, 1966; Widdicombe, 1961b), and in rabbits and cats (Richardson et al., 1973). It has been suggested that pulmonary stretch receptor discharge during expiration prolongs the duration of expiration (Hering, 1868; Knox, 1973) by a mechanism analogous to that which terminates inspiration.

Increases in end-expiratory lung volume by continuous positive pressure ventilation have been shown to produce lengthening of T_E and inconsistent changes in T_I with an overall decrease in the T_I/T_E ratio. These observations led Martin et al. (1978) to conclude that changes in FRC significantly alter expiratory time which may be indicative of tonic vagal control of expiratory duration.

D'Angelo and Agostoni (1975) have also observed specific alterations in the ventilatory pattern of dogs breathing at volumes above and below FRC which they attributed to changes in tonic afferent vagal discharge since the effects were abolished by vagotomy. Furthermore, persistency of the altered breathing pattern during sustained changes in end-expired lung volume suggests that tonic PSR activity does not adapt, i.e., resume the firing level

present at normal end-expired lung volume. Such an idea had previously been suggested by Grunstein et al. (1973).

The predominant effect of tonic pulmonary stretch activity on expiratory time is inconsistent with the idea of a T_E-T_I dependency. However, the possibility that changes in functional residual capacity may influence breathing must be seriously evaluated when studying lung volume reflexes while breathing gas mixtures other than room air. Bouverot and Fitzgerald (1969) reported that FRC of normal awake dogs increased during hypoxia and decreased during hyperoxia, but was unchanged during hypercapnia.

Recent evidence has been presented (Eldridge, 1973; Tawadrous and Eldridge, 1974; Karczewski et al., 1976) for a phenomenon referred to as respiratory "habituation" whereby central mechanisms maintain breathing at levels different from control after the stimulus producing the initial change in breathing is removed. This kind of short-term memory is somewhat discordant with the postulate that each respiratory cycle is independent of one another.

Thus, the singular role of 'phasic' PSR activity in regulating rate and depth of breathing has been challenged. Evidence has been provided implicating irritant receptor activity in this control (Fishman et al., 1973; Phillipson et al., 1973; Phillipson, 1974). Pulmonary irritant receptors (PIR) whose afferents also course in the vagus have been shown to fire with rapidly adapting bursts, but only at the end of very large and rapid volume changes (Mills et al., 1970; Sellick and Widdicombe, 1971; Sampson and Vidruk, 1975)

such as might occur while breathing against restricted airways. Alterations in tidal volume, T_I and T_E during differential cooling of the cervical vagi led Nadel et al. (1973) to suggest that slowly adapting PSR and PIR actually play opposing roles in the normal control of respiration in awake dogs.

It is also tenable that c-fiber endings with non-myelinated vagal afferents are involved in respiratory pattern control. Indeed J-receptors (one type of c-fiber ending) are markedly stimulated by hyperventilation at elevated intratracheal pressures of 10-20 cm H_2O in cats (Armstrong and Luck, 1974) and dogs (Coleridge and Coleridge, 1977). However, Armstrong and Luck (1974) further reported that excitation of J-receptors was only present in cats with pneumothorax; increased tidal volume did not excite these nerve endings in closed-chested animals.

Guz and Trenchard (1971b) reported that activity in non-myelinated afferents arising from J-receptors played little or no part in the control of normal breathing but that the tachypnea associated with certain lung pathologies such as collapsed lung, hemorrhage, edema and microemboli was dependent upon the integrity of these fibers. Trenchard et al. (1972) extended these findings to the rapid shallow breathing associated with lung inflammation during experimental pneumonia. Such observations may explain some of the variation in the Hering-Breuer inspiratory-inhibitory reflex between open and closed-chest preparations and in animals with lung fluid accumulation and alveolar collapse.

As summarized by von Euler and Trippenbach (1976), three main factors may be considered to control expiratory duration: 1) the initial peak level of inhibitory activity present when inspiration is terminated; 2) the amount and timing of inhibitory and/or excitatory vagal and extravagal afferent activity that combines with the initial inhibitory activity; and 3) the rate of decay of inhibition.

Extravagal mechanisms

The complex interactions among mechanisms involved in inhibition of inspiration are still not completely understood. It is known that forebrain control is effected via descending pathways which bypass those associated with the automatic metabolic bulbopontine mechanisms (Plum, 1970; Newsom amd Plum, 1972). Furthermore, since breathing employs skeletal muscle for its performance; it is not surprising that myotatic-like reflexes also contribute to rate and depth control.

Airway occlusion at end-expiration (Remmers, 1970) or during inspiration (Sant'Ambrogio and Widdicombe, 1965) is capable of inhibiting phrenic discharge in vagotomized preparations. The mechanism of this inhibition has not been clearly defined. Corda et al. (1965) and Bland et al. (1967) have suggested that this inhibition is due to enhanced afferent discharge arising from diaphragmatic and intercostal muscle spindles in response to the large elastic load and that such termination of inspiration

represents autogenic regulation. In contrast, Shannon (1975) concluded that the increased respiratory frequency observed during external elastic loading in vagotomized cats and dogs was due only to increased chemical drive accompanying the hypoventilation. Shannon (1975) did demonstrate that extravagal mechanisms involving chest wall mechanoreceptors were involved in the reflex increase in breathing frequency following chest compression.

It is known that afferent signals from intercostal muscle spindles and tendon organs are altered during mechanical loading. Muscle spindles facilitate and tendon organs inhibit intercostal alpha-motorneuron activity via short spinal reflexes (Sears, 1964; Corda et al., 1965; Newsom and Sears, 1970). Furthermore, pathways from chest wall mechanoreceptors to the central respiratory centers have been proposed (Remmers, 1973); Remmers et al., 1973) since electrical stimulation of spindle afferents arising from external intercostal muscles have been observed to inhibit central inspiratory activity.

More recently, Shannon (1980) reported that proprioceptor afferents from all intercostal and abdominal muscles and perhaps cutaneous receptors do have an inhibitory effect on dorsal respiratory group Type α and Type β neurons which drive phrenic spinal motorneurons. However, their precise contribution to frequency control during spontaneus breathing still remains unclear.

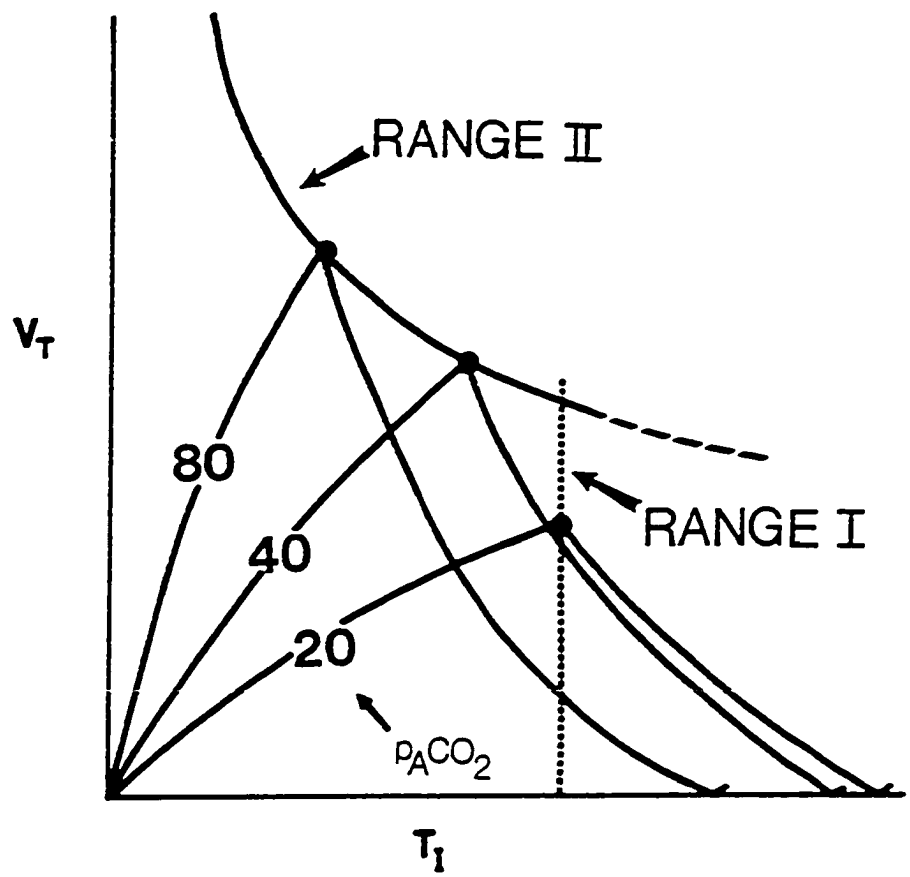
Phrenic activity

Phrenic output pattern is characterized by a rather linearly rising discharge with an abrupt cessation followed by a silent period. Phrenic patterns may be changed with respect to duration or intensity of discharge. In general, chemical drives affect the intensity (rate of rise and/or peak amplitude) of the integrated phrenic output while mechanical stimuli such as lung volume feedback affect the duration of discharge.

In the course of a normal breath lung volume rises until volume related afferent activity, together with CIA, reaches the I-OS threshold as described earlier. Inspiration is then terminated and expiration ensues. Figure 4 is the same volume threshold curve as shown in Figure 2 with the phrenic output of several breaths at different levels of inspired carbon dioxide superimposed. It can be seen that during a normal breath (p_ACO_2 = 40 mm Hg) the Hering-Breuer reflex overides timing of the central pattern generator. As the rate of rise of inspiratory activity increases during hypercapnea (p_ACO_2 = 80 mm Hg) the breath will reach the Hering-Breuer threshold earlier in inspiration at a greater volume, and therefore will terminate that inspiration earlier. At very low chemical drives (p_ACO_2 = 20 mm Hg) when volume threshold may actually not be reached inspiration is terminated by the central pattern generator.

Figure 4. Phrenic output patterns at three levels of carbon dioxide inhalation superimposed on the tidal volume-inspiratory duration relationship.

At high chemical drives ($paCO_2$ = 80 mm Hg) with large breaths, T_I is terminated by the Hering-Breuer mechanisms of Range II while at low chemical drives ($paCO_2$ = 20 mm Hg) with shallow breaths, T_I is dictated by CIA Range I mechanisms. Adapted from Clark and von Euler (1970).


RANGE II
RANGE I
80
40
20
P_ACO_2
V_T
T_I

Quantitative Evaluation of Phasic Lung Volume Reflexes

Strength of the Hering-Breuer reflex (and by extrapolation of its contributions during spontaneous breathing) has traditionally been assessed by measuring the duration of apnea following a 'threshold' lung inflation, i.e., time from lung inflation to the first inspiratory effort. Under any given experimental condition, a longer apnea was interpreted as a stronger reflex and vice versa. However, the duration of the Hering-Breuer apnea depends upon many factors. These include volume dependent afferent inhibitory input from stretch receptors, the humoral ventilatory drive, and the functional state of the respiratory center(s).

Younes et al. (1975) have suggested that it is inappropriate to use the duration of apnea as an index of phasic inspiratory-inhibitory vagal influence on the control of ventilatory parameters during spontaneous breathing. These workers provided an alternate approach for assessing phasic vagal influence on tidal volume. Their method involved comparing the maximum tracheal pressure during the first inspiratory effort against airways occluded at FRC with the pressure of this effort which is present at the inspiratory time of the preceding control breath.

Although the method of Younes et al. (1975) is appropriate for anesthetized subjects; it is probably not a reliable indicator in awake subjects since perception of an added load may influence the response and hence the development of maximal tracheal pressure (Margaria et al., 1973; Freedman, 1974). Whitelaw and coworkers

(1975) subsequently reported that load detection is not apparent during the first 100 msec of an inspiratory effort against the restricted airways. Based on this finding, these workers have suggested using the value of tracheal pressure developed against an occluded airway which is present just before conscious detection occurs. The $P_{0.1}$ value which is defined as the airway pressure at 100 msec after the start of a loaded inspiration is thought to reflect the force of approximately isometric contraction of inspiratory muscles and to represent neural output to these muscles in awake subjects. As such, it eliminates increased neuronal discharge from intercostals, diaphragm and larynx (autogenic reflexes) or from higher centers (conscious voluntary efforts) from biasing the measured Hering-Breuer reflex strength.

For $P_{0.1}$ to be a valid index of respiratory center output during unobstructed breathing, it must be verified that 1) occlusion itself does not produce a change in neuronal discharge to respiratory muscles and 2) $P_{0.1}$ bears a constant relation to neuronal discharge (Whitelaw et al., 1975). However, the presumption of a greater occlusion pressure ($P_{0.1}$) reflecting a greater neural output to the inspiratory muscles is not justified if end-tidal lung volume changes. This argument is especially valid when phasic lung volume reflexes are studied while breathing gas mixtures other than room air since changes in inspired oxygen can result in alterations of FRC.

Although tracheal pressure and timing measurements have inherent limitations they are better indices of respiratory center output than simple measurements of changes in minute volume or inspiratory muscle activity (diaphragm or intercostal electromyograms). At least tracheal pressure measurements during occlusion breathing are nearly independent of lung mechanics, particularly compliance and resistance which are known to alter the respiratory pattern. When either compliance or lung resistance is abnormal, i.e., the mechanical effector mechanisms are impaired; both the afferent and efferent neural limbs of the Hering-Breuer reflex may still remain completely normal. The error in correctly quantifying mechanical lung reflexes by using minute volume indices is most apparent in reports which suggest that carbon dioxide attenuates the respiratory response to mechanical loading. Actually, hypercapnea induces increased airway resistance and decreased lung elasticity such that the neurally driven ventilatory drive is just prevented from being fully expressed.

The Humoral Ventilatory Drive

The interaction of peripheral and central chemoreceptor activation with phasic lung volume reflexes and the eupneic breathing pattern has also received attention. Adrian (1933) was the first to introduce this concept reporting that neither CO_2 or low O_2 alter the discharge of pulmonary stretch receptors. More recently, Miserocchi (1976) reported no difference in the peak

firing frequency of PSR in cats during hypoxia as compared to normoxia at constant levels of CO_2 ($paCO_2$ = 27 - 30 mm Hg). From these two reports it might be surmised that increasing the humoral ventilatory drive by hypoxia or hypercapnia does not directly change the vagal discharge for a given lung volume and hence does not alter the strength of the Hering-Breuer apnea by this mechanism.

However, Clark and von Euler (1972) proposed an indirect mechanism such that the increased depth of breathing resulting from hypercapneic stimulation of peripheral and central chemoreceptors increases the amount of pulmonary stretch receptor discharge; thus terminating inspiration earlier with each deeper breath.

Shortly thereafter, Mustafa and Purves (1972) reported that inhalation of 3 - 9% CO_2 in oxygen with subsequent elevation of arterial pCO_2 reduced end-expiratory as well as the average and peak frequency during inspiration of PSR firing in rabbits ventilated at constant volume; a response similar to that found for avian intrapulmonary receptors (Fedde and Peterson, 1970). Similarly, PSR discharge is inhibited in dogs breathing 8% of CO_2 (intact pulmonary circulation); the hypercapnia being more effective in reducing tonic PSR activity during expiration than in reducing phasic inspiratory PSR activity (Sant' Ambrogio et al., 1974). This latter report is consistent with the observations that hypercapneic induced tachypnea is brought about primarily by changes in expiratory duration. However, discordant reports that inspiratory activity is much less, if at all, dependent upon CO_2 and is evoked by inflation of the

lungs only (Woldring, 1965) leaves the impression that only the expiratory part of the respiratory cycle is CO_2 sensitive.

Bartoli et al. (1974) have actually detected a vagal reflex originating from the lungs which produces tachypnea (predominantly due to a decrease in T_E) during CO_2 inhalation in dogs on cardiopulmonary bypass, i.e., arterial pO_2 and pCO_2 held constant. Mechanisms of this reflex have been studied in more detail by Banzett et al. (1978) using a differentially ventilated dog preparation. These workers observed an increase in phrenic activity when carbon dioxide was allowed to accumulate in a vascularly isolated lung excluded from ventilation. Restoration of normal ventilation to this test lung with subsequent reduction in alveolar CO_2 resulted in a significant attenuation of phrenic activity. Both responses were abolished by vagotomy. From these results Banzett and coworkers (1978) proposed that the physiological significance of a pulmonary-CO_2 ventilatory reflex may be to provide an inhibitory feedback to the respiratory center when lung pCO_2 falls below normal levels, rather than to drive ventilation when mixed venous carbon dioxide levels rise. Bradley et al. (1976) using cardiopulmonary bypass in dogs have verified that hypercapnic inhibition of PSR activity is due to changes in alveolar CO_2 with changes in arterial CO_2 (at constant alveolar CO_2) producing insignificant and inconsistent alterations in PSR activity.

Studies concerned with the CO_2-pulmonary reflex have all been done under hyperoxic conditions. No recent information about the effects of oxygen on specific PSR firing patterns and coincident phase relationships within the respiratory cycle is available.

The integrity of vagus nerves has long been considered a prerequisite for the increase in respiratory frequency which normally occurs both in man and animals in response to increased chemical drive of respiration (Scott, 1908; Cohen, 1964; Nesland et al., 1966; Guz et al., 1966b; Tang, 1967; Richardson and Widdicombe, 1969; Phillipson et al., 1970). However, Shannon (1975) has observed an increased frequency response during CO_2 breathing in some vagotomized cats and all vagotomized dogs indicating involvement of extravagal mechanisms as well. Similarly, vagal block does not prevent the increased ventilatory response to 'transient' hypercapnia in anesthetized rabbits (Delpierre et al., 1979) or cats (Bradley, 1976).

Vagal block does reduce the long term minute volume response to both hypercapnia and hypoxemia which Mills and Sampson (1969) have attributed to the fact that cervical vagal block interrupts efferent sympathetic impulses to the carotid bodies. This prevents vasoconstriction and reduction in blood flow to the chemoreceptor elements which sympathetic discharge normally causes.

Since norepinephrine and epinephrine are known to inhibit central respiratory output, attenuation of hypercapneic hyperpnea could also involve the increased plasma catecholamine levels

associated with an arterial PCO_2 exceeding 50 mm Hg (Sechzer et al., 1960; Dejours, 1964).

Reduced ventilatory response to absolute levels of CO_2 and the narrowing range of CO_2 responsiveness after vagotomy are primarily due to the inability to increase frequency. This has been demonstrated in man (Guz et al., 1966b), cats (von Euler et al., 1970; Clark and von Euler, 1972; Grunstein et al., 1973), dogs (Phillipson et al., 1970) and rabbits (Richardson and Widdicombe, 1969; Weimer and Kiwull, 1972). In fact, the increase in tidal volume for a given increase in alveolar pCO_2 has been reported to be larger after vagotomy such that in the lower $pACO_2$ ranges the tidal volume changes effectively compensate for the lack of frequency response thus sustaining normal minute volume (von Euler et al., 1970).

It is important to differentiate central from peripheral chemoreceptor activation in affecting the depth and timing of the respiratory cycle. The responses of central respiratory neurons to hypercapnia and/or hypoxia have been described (Nesland et al., 1966; Cohen, 1968; St. John and Wang, 1977; Folgering and Smolders, 1979). Central chemoreception has been reported to alter the bulbopontine rhythm thereby influencing the output to the respiratory muscles and to increase the sensitivity of the respiratory centers to phasic vagal input, i.e., displace the V_T-T_I relationship to the left (Miserocchi and Milic-Emili, 1975; Miserocchi, 1976). However, conflicting evidence has been presented

(Clark and von Euler, 1972; Bradley et al., 1974) that the same V_T-T_I curve describes the termination of breaths taken under a variety of carbon dioxide concentrations implying that CO_2 has no effect on the central threshold.

Peripheral chemoreceptors only influence the output of the respiratory centers (Miserocchi, 1976) such that an increase in peripheral chemoreceptor afferent activity will generate a greater inspiratory flow (more forceful breath). This implies that the threshold for inhibition of inspiratory activity is reached sooner at larger tidal volume according to the slope of the V_T-T_I relationship (cf. Figure 4).

Afferent activity arising from carotid chemoreceptors and pulmonary stretch receptors has opposing central effects on breathing; one excitatory and the other inhibitory. Hypercapnia causes an increase in carotid chemoreceptor activity but a decrease in pulmonary stretch receptor activity. Although the activity from these two receptor groups produces opposite effects on breathing, the receptors function in a complementary manner in producing the ventilatory response to carbon dioxide. Bouverot et al. (1970) have reported that increased alveolar CO_2 provokes a humoral ventilatory drive in awake dogs which involves both a chemoreflex and central mechanisms. They felt such an idea could explain why hypercapneic dogs (whether intact or chemodenervated) had shorter inspiratory-inhibitory reflex apneas than normocapneic animals. The interaction of chemical and mechanical loading is most apparent in dogs which

have carotid sinus nerve sections (chronic denervation of peripheral chemoreceptors) in which the apnea elicited by clamping the airway at a given lung volume was more prolonged than the apnea of an intact dog (Bouverot and Fitzgerald, 1969).

Blood and alveolar gases may also affect phasic lung volume reflexes by altering airway smooth muscle tone and thereby changing either phasic and/or tonic PSR activity. Both hypocapnia (Ingram, 1975; Banzett et al., 1978) and hypercapnia (Green and Widdicombe, 1966) have been reported to cause airway constriction in dogs. Green and Widdicombe (1966) reported that hypercapneic bronchoconstriction was mediated via the vagus while Banzett et al. (1978) reported that increases in tracheal pressure during hypocapnia were not affected by vagotomy. These conflicting reports may be due to differences in resting tension of the bronchial smooth muscle. A direct dilator action of CO_2 on bronchial smooth muscle is apparent only when the tissue has been previously constricted by drugs (Nissell, 1950; Sterling et al., 1972) or following pulmonary artery occlusion (Severinghaus et al., 1961; Tisi et al., 1970). Vagal effects of CO_2 on airway smooth muscle may be related to the actions of alveolar gas on pulmonary stretch receptor activity since PSR stimulation produces reflex relaxation of bronchial smooth muscle (Widdicombe and Nadel, 1963).

As for the effects of oxygen on airway smooth muscle, Nadel and Widdicombe (1963) observed hypoxic induced bronchoconstriction. Acute exposure to low inspired oxygen concentrations also result in small, but significant, decreases in specific airway conductance with increases in both airway resistance and thoracic gas volume (Green and Widdicombe, 1966; Bouverot and Fitzgerald, 1969). Similar changes have been reported in humans (Sterling, 1968). However, *in vitro* experiments have shown hypoxia to be a bronchodilator (Nisseli, 1950) and to cause loss of active tension developed by bronchial smooth muscle (Stephens et al., 1968).

Changes in inspired oxygen and carbon dioxide can also affect phasic lung volume reflexes by altering afferent activity arising from the muscles of respiration. Inspiratory muscle spindles and fusimotor fibers show an increase in activity in response to hypoxia and hypercapnia even in the absence of any mechanical loading (Newsom, 1970). This muscle activity was implicated earlier by Campbell et al. (1961, 1962, 1964) in the respiratory responses to mechanical loading.

J-receptors may be partially involved in the Hering-Breuer inspiratory inhibitory reflex. Therefore, it is important to understand the effects of changes in blood or alveolar gas concentrations on these receptors which, being anatomically situated in the interstitial spaces of the alveolo-capillary wall, are accessible to both blood and gas phases. Paintal (1955) originally reported that hypoxia does not affect the J-receptors. However,

Ahluwalia (1979) has recently shown that hypoxia (alveolar pO_2 47-67 mm Hg) abolishes the visceromatic J-reflex; an effect most probably due to some pre-synaptic inhibition at higher levels. Such an idea is compatible with the report by Eccles et al. (1966) that motorneurones themselves are remarkably insensitive to hypoxia. It remains to be determined if the inhibition actually arises from the lungs rather than at the level of the central nervous system.

Effects of Anesthesia on Respiratory Control

A most important consideration in evaluating phasic lung volume reflexes is the depth and type of anesthesia used during the experiments. Moyer and Beecher (1942b) reported that anesthetics generally enhance the lung inflation apnea. Similarly, Nadel et al. (1973) have shown that general anesthesia with sodium pentobarbitone or halothane progressively increased the duration of Hering-Breuer apnea elicited by inflating to airway pressures from 5-25 cm H_2O during inspiration compared to the response of the same dogs in the conscious state. However, more recently halothane has been shown to actually abolish pulmonary stretch receptor activity and hence the reflex events associated with PSR stimulation, namely inflation apnea. Similarly, Bouverot and Fitzgerald (1969) have observed time related differences in the Hering-Breuer apnea during pentobarbital anesthesia with the reflex being maximal at 1-2 hours after induction, less intense at 30 minutes and even less intense at 3 hours post-induction.

The effects of specific anesthetic agents on the relationship between tidal volume and respiratory duration may underly these observations. Clark and von Euler (1972) reported that Range I of the V_T-T_I relationship was absent in vagally intact cats rebreathing air under pentobarbital anesthesia. However, in similar experiments under urethane anesthesia these cats did exhibit both Range I and Range II characteristics of the V_T-T_I relationship (cf. Figure 2).[1] Grunstein et al. (1973) also reported the absence of Range I in cats anesthetized with either sodium pentobarbital or Dial-urethane. Grunstein et al. (1973) further reported that the type of anesthesia used did not affect the slope or intercept of the frequency versus inspiratory time relationship. Thus, for a given breath the relationship between T_I and T_E was maintained in the presence of changes in the inspiratory-inhibitory effect of vagal feedback during anesthesia with different agents.

It is well-known that sodium pentobarbital depresses the central excitory state (Moyer and Beecher, 1942a; Florez and Borison, 1969) which alone could account for changes in phasic lung volume reflexes in these preparations. Anesthesia has been shown to abolish respiratory activity in the pontine reticular formation and to greatly reduce bulbar unit activity associated with respiration (Bertrand et al., 1976; Hugelin, 1977). It has been suggested

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[1]Range I of the V_T-T_I relationship includes the volume independent bulbopontine CIA determination of T_I while Range II represents the Hering-Breuer vagal volume related mechanisms controlling respiratory duration.

(Bianchi and Barillot, 1978) that the depressant effects of anesthesia on bulbopontine respiratory units results in a decreased rate of rise of central inspiratory activity without altering the inspiratory off-switch threshold. Such a mechanism could explain the slow shallow breathing pattern associated with deep anesthesia. Redgate (1963) has further shown that barbiturates selectively depress the hypothalamic areas to a greater degree than medullary centers, thereby impeding tonic nerve impulses descending from the hypothalamus to the medullary reticular formation which normally facilitate inspiration in cats. They proposed that reduction of the forebrain respiratory facilitating information allows the inhibitory vagal afferents to exert a larger effect such that the Hering-Breuer apnea is more pronounced during barbiturate anesthesia.

Anesthetics may also interfere with phasic lung volume reflexes by altering activity of the respiratory musculature. Tusiewicz et al. (1977) have shown that phasic intercostal muscle activity is more sensitive to anesthetic depression than diaphragmatic activity.

Since chemical and mechanical reflexes may interact it is important to consider the effects of anesthetic agents on chemoreflexes. Barbiturates and narcotics diminish the centrally mediated CO_2 response (Moyer and Beecher, 1942a). On the other hand, Comroe (1964) has proposed that peripheral chemoreceptor reflexes resist the depressive effects of anesthesia. Narcotics and barbiturates preserve and sometimes enhance peripherally mediated

responses to hypoxia (Moyer and Beecher, 1942a), hyperoxia (Marshall and Rosenfeld, 1936) and sodium cyanide (Dripps and Dumke, 1943). In direct contrast, parallel reduction in the ventilatory response to hypoxia and hypercapnia has been reported in humans anesthetized with thiopental (Knill et al., 1978) and morphine (Weil et al., 1975). Halothane has been shown to abolish the hypoxic response leaving the ventilation-CO_2 relationship essentially unchanged (Knill et al., 1978).

Effects of Cervical Vagotomy on Respiratory Control

Although the vagus nerves are the afferent pathway for the Hering-Breuer inspiratory-inhibitory and several other respiratory reflexes that affect the rate and depth of breathing; it is not known what influences specific reflexes exert on the control of normal breathing. Interruption of vagal conduction in experimental animals whether by application of local anesthetics (Phillipson et al., 1970; Nadel et al., 1973), reversible cooling (Fishman et al., 1973; Nadel et al., 1973) or severing of the nerves results in slow deep breathing and abolishes the Hering-Breuer lung volume reflexes. Both these observations are cited as evidence for the tonic influence of these reflexes in quiet breathing.

Along these lines it is interesting that the ability of humans to detect added elastic loads and the sensation associated with externally loaded breathing is not affected by lidocaine vagal block (Guz et al., 1966c). These results support the idea that humans are

functionally vagotomized with respect to the respiratory system showing negligible reliance on Hering-Breuer reflex control of respiration during eupneic breathing.

However, vagotomy has other important consequences which must be considered in conjunction with the respiratory reflex arc during normal or altered chemical drive. Vagal block in cats and dogs results in larger tidal volumes, higher levels of peak phrenic output and the associated increases in diaphragmatic activity which are achieved as a consequence of prolonged inspiratory time; the rate of increase in inspiratory activity of each breath remaining unchanged (Head, 1889; Hammouda and Wilson, 1932; Larrabee and Knowlton, 1946; von Euler et al., 1970; Bartoli et al., 1973; Bartoli et al., 1975; Feldman and Gautier, 1975). Irregularities in the instantaneous phrenic motorneuronal output expressed mechanically as deflections in the inspiratory flow trace are also typical of the vagotomized state (Bartoli et al., 1975).

Although tidal volume increases and respiratory frequency decreases, bilateral vagal block has no significant effect on arterial CO_2 tension or on the apneic threshold CO_2 tension in conscious dogs (Phillipson et al., 1970; Nadel et al., 1973) suggesting that the vagi do not normally inhibit the respiratory center. These findings differ from results in anesthetized dogs (Lim et al., 1958; Honda et al., 1962) in which vagotomy produced a decrease in arterial CO_2 and in the apneic threshold CO_2 tension.

The effect of vagotomy on expiratory time is variable (Bartoli et al., 1973). According to the T_E-T_I relationship proposed by von Euler et al. (1970) one would predict the vagotomized breathing pattern to have a characteristic lengthening of T_E which is proportional to the lengthening of inspiratory time. However, D'Angelo and Agostoni (1975) have reported that expiratory time increases from 3.19 sec before to 4.94 sec after bilateral vagotomy in dogs. This change in T_E was less than the lengthening of T_I which they observed (1.27 sec before to 4.11 sec after vagotomy). Expiratory time has also been observed to decrease following vagotomy such that frequency actually increased in 71% of the dogs studied by Bartoli et al. (1973).

METHODS

The experimental protocol of this investigation was directed at obtaining a preparation for comparing the influence of intra- and extrapulmonary chemoreflexes on: 1) steady state spontaneous breathing patterns and 2) respiratory responses to unilateral and bilateral airway occlusions set at functional residual capacity and at several volumes above the end-expiratory level.

Surgical Procedures

Experiments were performed on 38 adult dogs (20.9 to 45.4 kg) anesthetized with thiopental (22 mg/kg) followed by a mixture of alpha-chloralose (38 mg/kg) and urethane (300 mg/kg). Alpha-chloralose (2.5%) and urethane (20%) were solubilized in saline (52°C) and infused at a rate of 1.5 ml/kg.min. Supplementary doses of alpha-chloralose (10 mg/kg·hr) were administered as required. All studies were performed with the animal in dorsal recumbency. Rectal temperature was kept between 37-39°C with a thermal pad under the dog and external radiant heat.

Initial surgical procedures included catheterization of a carotid artery and jugular vein and isolation of both cervical vagi for later sectioning. A Kottmeier canine endobronchial tube (Rusch Inc.) was inserted through a tracheostomy just below the cricoid

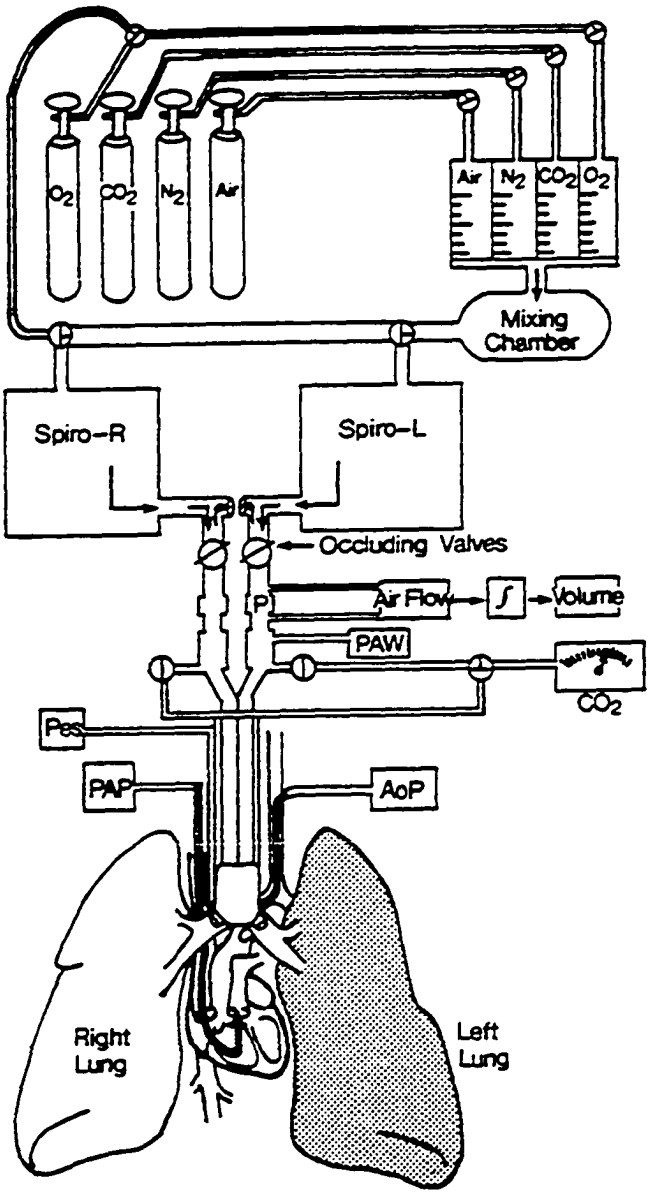
cartilage and positioned at the carina. A saline-filled cannula was placed in the lower third of the esophagus for estimating pleural pressure (P_{ES}) as detected by a Bell and Howell transducer.

Cardiopulmonary Measurements

The experimental situation is illustrated in Figure 5. Inspiratory and expiratory airflow rates ($\dot{F}_I$ and $\dot{F}_E$, respectively) were determined by Fleisch # 0 pneumotachometers (warmed to 37°C) connected to each side of the tracheal divider. Airflow signals were electronically integrated to give a continuous record of tidal volume (V_T). Pneumotachometers were calibrated with room air before every experiment over a range of constant airflows (1-45 L/min). Volume integration was calibrated with a 500 ml glass syringe. The relationship between differential pressure (Statham PM5E) recorded from the pneumotachometers and flow was linear over the range of 5-30 cm H_2O above atmospheric pressure. Previous calibration of the pneumotachometers with 100% nitrogen, 100% oxygen and 10% oxygen (balance nitrogen) revealed no measurable differences compared to the room air calibrations. Airway pressures (P_{AW}) were measured through side ports of the tracheal divider connected by means of polyethylene tubing to Statham (PM5E) differential pressure transducers. Airway pressures were referenced to atmospheric pressure. The pneumotachometers were in series with manually controlled occluding valves. These occluding valves were connected either to spirometers (Godart model 16000 Expirograph during

Figure 5. Schematic of apparatus used for measuring cardiopulmonary parameters in anesthetized dogs.

Note that each lumen of the endobronchial divider opens individually into one of the mainstem bronchi. System resistance is 0.4 cm $H_2O/L \cdot s$ at 10 L/min airflow and 1.2 cm $H_2O/L \cdot s$ at an airflow of 40 L/min. Dead space of the endobronchial divider and external apparatus to each lung was approximately 40 ml.


O2
CO2
N2
Air
Air
N2
CO2
O2
Mixing Chamber
Spiro-R
Spiro-L
Occluding Valves
P
Air Flow
∫
Volume
PAW
CO2
Pes
PAP
AoP
Right Lung
Left Lung

measurements of oxygen consumption ($\dot{V}O_2$) or through unidirectional valves (Rudolph #1400) to bags filled with the desired gas. The concentration of carbon dioxide in airway gas (ET-pCO_2) was monitored by an infrared CO_2 analyzer (Beckman LB-1 Medical Gas Analyzer) sampling at a rate of 500 ml/min from either the left or right port of the tracheal divider. Dead spaces was adjusted to maintain identical ET-pCO_2 for each lung.

Airflows, tidal volumes, airway pressures, and pulmonary arterial blood pressure were continually monitored in every experiment on an 8-channel pen recorder (Beckman R-611). Permanent records of esophageal pressure, arterial blood pressure and end-tidal pCO_2 were obtained intermittently.

End-tidal gas from each lung as well as arterial and mixed venous blood samples were collected from the same cannulas used for pressure recordings. Subsequent measurements of pO_2, pCO_2 and pH were made with a pH/Blood Gas Analyzer (Model 513, Instrumentation Laboratory). Oxygen consumption of each lung was calculated from the spirometric recording at the time of blood and airway gas sampling.

Airway Occlusion Procedures

It was of major importance to effectively separate the right and left lungs from each other and to insure that they remained separated during occlusion maneuvers. Three tests were used to verify that the two sides were completely separated.

The first of these is a modification of the procedure used by Seed and Sykes (1972). It involves connecting one side of the tracheal divider to an underwater seal of 1 cm H_2O pressure while the contralateral side is left open to room air. The submerged side is occluded for 5 consecutive inspiratory efforts. Absence of bubbling through the water seal during the expiratory phase of the third, fourth, and fifth breath indicates separation.

The second test was used for detecting leaks around the cuff and to insure that the external system of tubes and valves to each lung was completely airtight. Sustained positive pressure plateaus in the airways during the apneic period of bilateral occlusion at peak inspiration verified that the system was airtight (Figure 6). A typical example of recordings which indicate the presence of air leaking around the endobronchial divider cuff during the apneic period is shown in Figure 7.

The third test used to insure that the left and right lungs were separated involved monitoring airway CO_2 during unilateral occlusions at peak inspiration (Figure 8). Adequate separation was verified if: a) CO_2 progressively accumulated in the lung which was occluded, i.e., pCO_2 at peak inspiration was greater than zero, and b) the pCO_2 gradient from peak inspiration to end-expiration was less than 5 mm Hg.

A negative result for any of these tests was interpreted to mean less than adequate separation of the two lungs; the endobronchial divider was repositioned and the tests repeated. Once the

Figure 6. Test used to monitor external apparatus air leaks.

Records show airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung as well as pulmonary arterial blood pressure (PAP) and esophageal pressure (P_{ES}). Inspiration is indicated by a downward deflection in each of the respiratory parameter recordings. Four normal breaths appear at the left. Both airways are occluded at peak inspiration of the fifth breath (arrow) and remain occluded for three breaths (heavy black line). Note the sustained positive pressure plateaus (*) in both airways during the apneic and/or expiratory periods of occluded breathing. These plateaus indicate that the two lungs are completely separated and free of external apparatus air leaks.

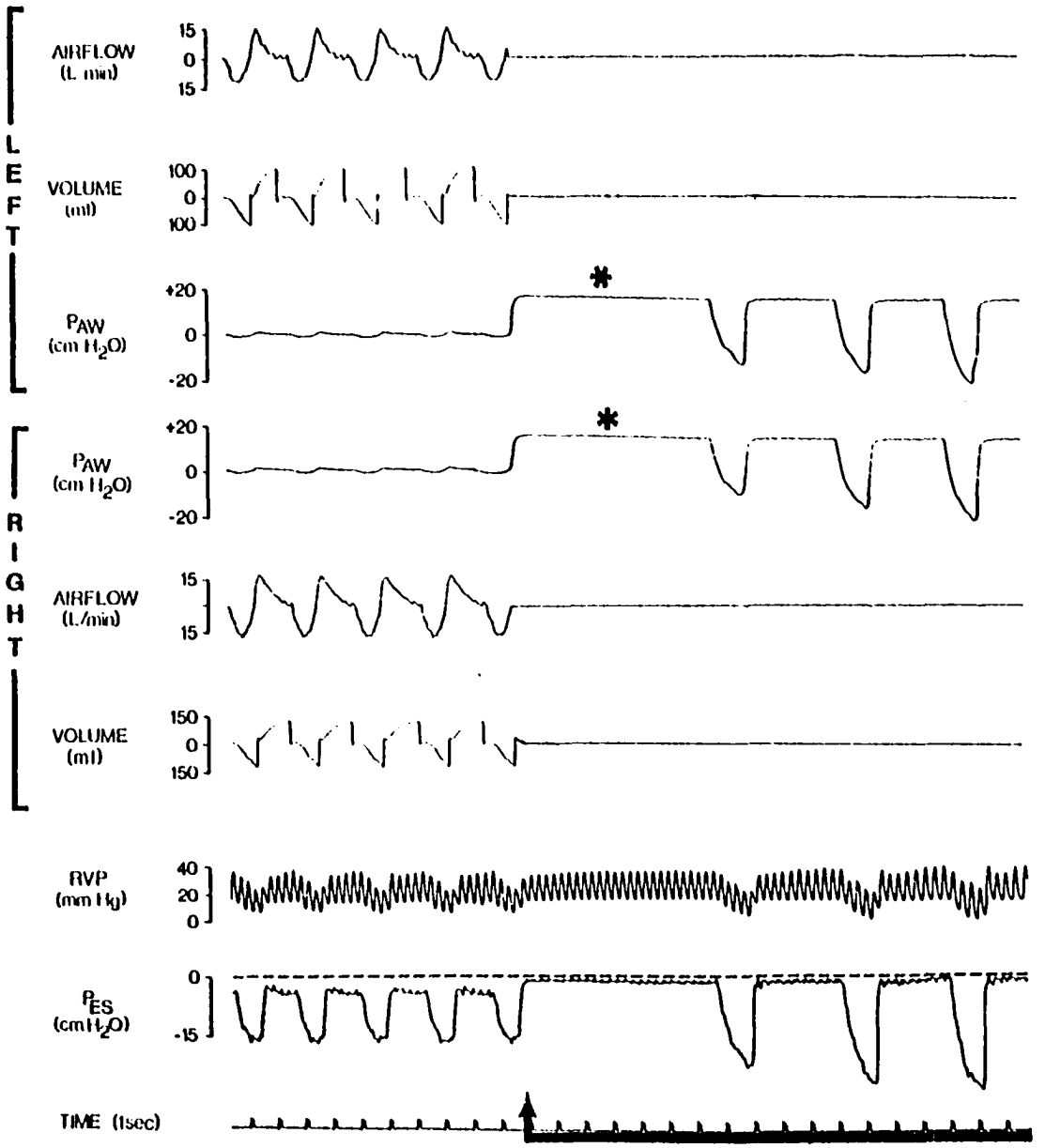

LEFT
AIRFLOW (L min)
15
0
15
VOLUME (ml)
100
0
100
PAW (cm H2O)
+20
0
-20
*
RIGHT
PAW (cm H2O)
+20
0
-20
*
AIRFLOW (L/min)
15
15
VOLUME (ml)
150
0
150
RVP (mm Hg)
40
20
0
PES (cmH2O)
0
-15
TIME (1sec)

Figure 7. Record showing decay of pressure in both airways during bilateral occlusion set at peak inspiration.

Airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung as well as aortic blood pressure (AoP) and pulmonary arterial blood pressure (PAP) are shown. Both airways are occluded at peak inspiration (downward deflection) of the fourth breath as indicated by the vertical arrow on the time trace. Absence of pressure plateaus (curved arrows) during subsequent expirations against the occlusion is indicative of external apparatus air leaks.

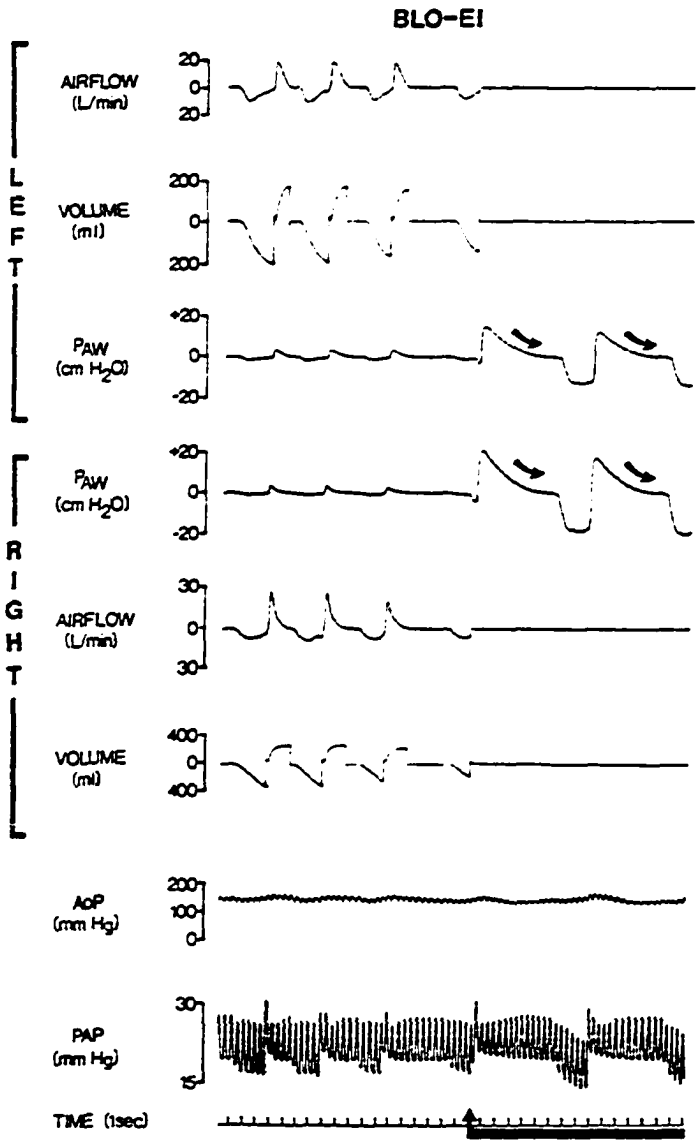
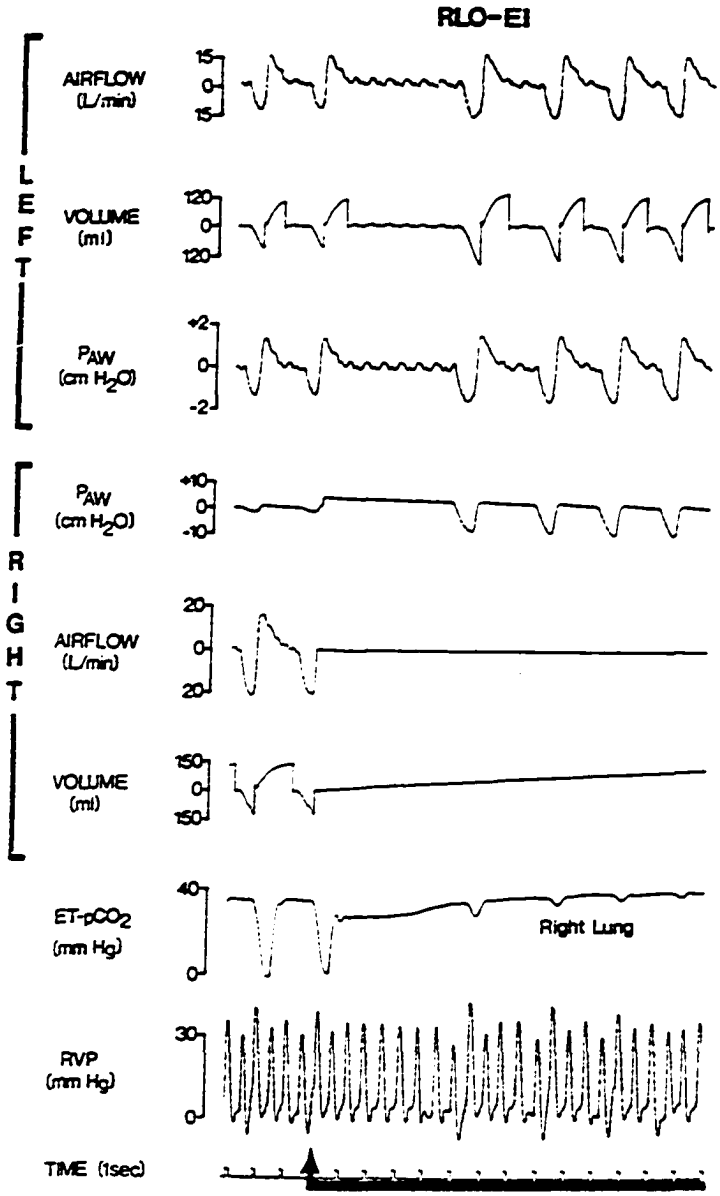

BLO-EI
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
PAW (cm H2O)
PAW (cm H2O)
AIRFLOW (L/min)
VOLUME (ml)
AoP (mm Hg)
PAP (mm Hg)
TIME (1sec)
20
0
20
200
0
200
+20
0
-20
+20
0
-20
30
0
30
400
0
400
200
100
0
30
15

Figure 8. Test used to insure complete separation of the left and right airways.

Traces show airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung as well as right lung carbon dioxide (ET-pCO_2) and right ventricular pressure (RVP). The right lung is occluded at peak inspiration (downward deflection) of the second breath and remains occluded for 4 subsequent efforts. The period of occlusion is indicated with the time trace at the bottom of the records. Note the accumulation of alveolar CO_2 and diminuation of tidal pCO_2 fluctuations during subsequent efforts against the occluded airway.


RLO-EI
LEFT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
120
0
120
PAW (cm H2O)
+2
0
-2
RIGHT
PAW (cm H2O)
+10
0
-10
AIRFLOW (L/min)
20
0
20
VOLUME (ml)
150
0
150
ET-pCO2 (mm Hg)
40
0
Right Lung
RVP (mm Hg)
30
0
TIME (1sec)

endobronchial divider was properly positioned, it was secured in place by two tight ligatures above and below the tracheostomy.

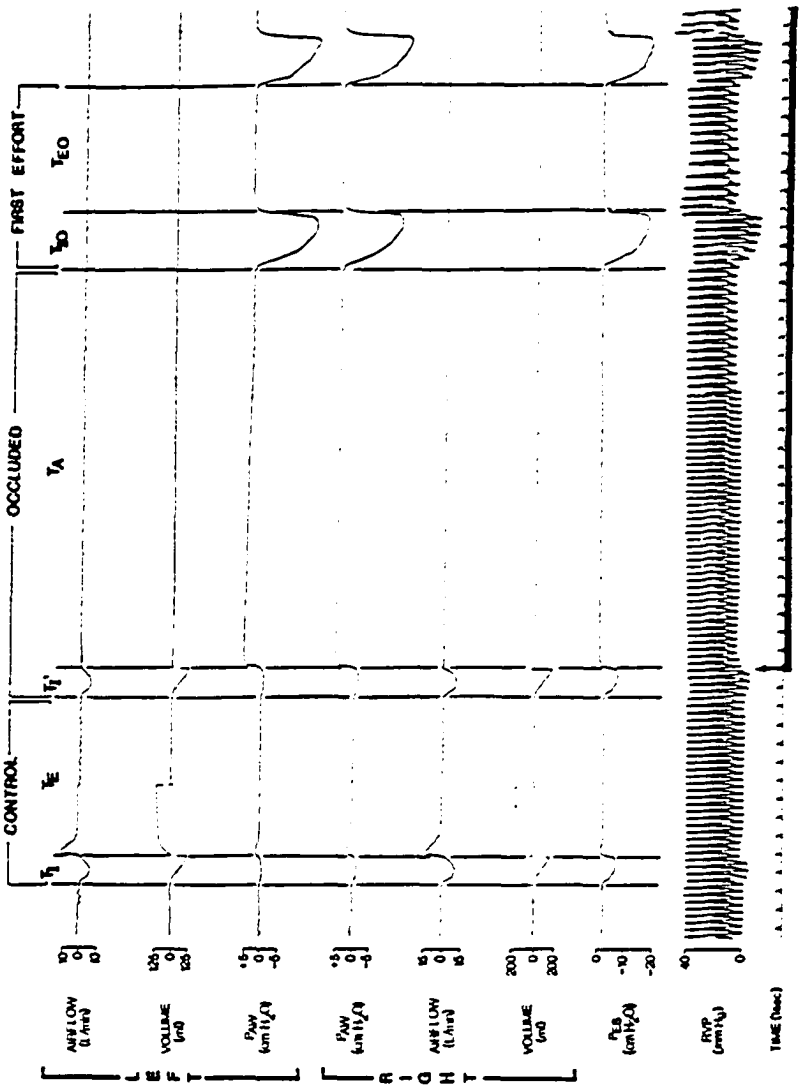
A pillow was placed under the dog's head and the pneumotachometers were set slightly above the plane of the dog's head to aid in dorsally directing the distal end of the tracheal divider. These procedures prevented the endobronchial divider from inadvertently compressing the right pulmonary artery which lies directly over the carinal bifurcation.

Unilateral and bilateral airway occlusions were set at end-inspiratory and end-expiratory lung volume during spontaneous breathing. Occlusions were applied randomly and always maintained for three breaths. Each maneuver was repeated at least twice. The animal was allowed to breath normally for 2 minutes between occlusions.

All maneuvers were analyzed with respect to three breaths: 1) the control breath immediately preceding occlusion; 2) the breath during which the occlusion was actually set, i.e., the occluded breath; and 3) the first effort breath following occlusion (Figure 9). Measurements of inspiratory duration and expiratory duration for all control breaths (T_I and T_E respectively) and for the first effort breaths (T_{IO} and T_{EO} respectively) during unilateral airway

Figure 9. Breath-by-breath recording used for analyzing reflex respiratory responses to airway occlusions.

Airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung are shown. Unless indicated otherwise, the upper six traces will be recordings of these same parameters in subsequent figures. The esophageal pressure (P_{ES}), right ventricular pressure (RVP) and time scale appear in the lower three traces of this figure. From left to right: control, occluded and first effort breaths. Onset and duration of occlusion are indicated with an arrow and heavy black line on the time trace. Inspiratory and expiratory periods of the control breath (T_I, T_E) and first effort breath (T_{IO}, T_{EO}) are designated. The expiratory period of the occluded breath is referred to as the apneic period and is abbreviated T_A. Refer to ABBREVIATIONS for more complete definitions of specific time intervals.


CONTROL
OCCLUDED
FIRST EFFORT
T_I
T_E
T_I'
T_A
T_{ED}
T_{EO}
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cmH$_2$O)
P_{AW} (cmH$_2$O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cmH$_2$O)
PVP (mmHg)
TIME (sec)

occlusions were taken from the flow or volume tracings.[1] However, since no flow or volume signals were generated during bilateral airway occlusions the first effort duration measurements were taken from the tracheal pressure tracings during these maneuvers.

The effect on breathing pattern of eliminating (partially or completely) phasic pulmonary stretch receptor activity was examined by occluding one or both airways at end-expiration (EE maneuvers). Except for slight expansion due to decompression of intrathoracic gas, there was effectively no volume change during subsequent inspirations in the lung(s) occluded at FRC.

As suggested by Grunstein et al. (1973), bulbopontine respiratory activity (phase-switching or rhythm) was described by the relationship between inspiratory and expiratory durations of first effort breaths during bilateral airway occlusion at end-expiratory lung volume. Phasic vagal activity is negligible during these maneuvers. However, tonic PSR vagal activity is still present during EE maneuvers in vagally intact dogs and is therefore included in these descriptions of bulbopontine rhythm. The tonic PSR component was evaluated by: a) comparing reflex responses to BLO-EE maneuvers in vagally intact dogs with the timing characteristics of unoccluded breathing in bilaterally vagotomized dogs, and b)

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[1]Duration of the inspiratory, expiratory and total respiratory cycle periods are expressed in units of time. As such, they have been abbreviated as T_I, T_E and T_{TOT}, respectively. These specific periods will be referred to in the text as inspiratory, expiratory and total cycle time. As such, the inverse of the total cycle duration or period ($1/T_{TOT}$) is properly defined as respiratory frequency.

comparing phase-switching parameters (T_I, T_E, T_E/T_I, and T_{TOT}) of first effort breaths against end-expiratory occlusions with those during end-inspiratory occlusions. Occlusions at end-inspiration (EI maneuvers) were used to selectively increase the tonic PSR vagal component while simultaneously eliminating phasic PSR activity.

Similar comparisons were made between EE and EI maneuvers for the rate of change of airway pressure ($I\text{-}P_{AW}/T_I$) and peak airway pressure ($I\text{-}P_{AW}$) during first effort inspirations. Values of these parameters have been used as estimates of central output to the respiratory muscles. To accurately use $I\text{-}P_{AW}/T_I$ and $I\text{-}P_{AW}$ as determinants of bulbopontine activity it was important to monitor respiratory mechanics, i.e. effector mechanisms. Dynamic elastance (E_{dyn}) was calculated for each lung as the change in airway pressure per unit inspired volume at points of zero airflow during spontaneous tidal breathing. This is in contrast to passive elastance measurements obtained by manual volume inflations over the vital capacity range in paralyzed animals. Measurements of quasi-static elastance (E_{qs}) were obtained during the apneic period of EI maneuvers. Airway pressure of the occluded lung during the apneic period was divided by the volume inspired by that lung at the time of occlusion. Quasi-state elastance for each lung was calculated from 3 maneuvers performed at different volumes in the tidal range.

Experimental Protocol

All 38 dogs were surgically prepared in the same manner. Steady-state baseline data (room air with intact vagi) were recorded and samples collected for evaluating blood-gas and acid-base status. Following the steady-state baseline period the entire series of airway occlusions was tested. Blood and end-expired gas samples and steady-state data were again collected. The same sequence was performed during hypoxic (both lungs, F_IO_2=0.1; n=12), and hyperoxic (both lungs, F_IO_2=1.0; n=14) and differential lung ventilation (left lung, F_IN_2=1.0, F_IO_2 = 0.0; right lung F_IO_2 = 1.0; n=18) of vagally intact dogs. Animals were allowed to breathe each mixture for at least 15 min or until tidal volume, frequency, blood and end-tidal gases remained steady for several minutes. New steady-state data were collected; occlusions performed, and a second set of post-occlusion steady state data collected. The dogs were returned to room air between exposures to the test gases. Baseline data and samples were collected during these room air recovery periods. Only those runs for which pre- and post-occlusion room air data were not significantly different were included for statistical analysis. Values for steady state breathing parameters were obtained by averaging the pre- and post-occlusion periods for the test gas responses and by averaging all of the room air baseline data.

Reflex responses to airway occlusions were also tested in unilaterally (left vagotomy, n=12; right vagotomy, n=8) and bilaterally vagotomized (n=12) dogs breathing room air. Bilaterally vagotomized dogs were also exposed to 10% O_2 (n=9), 100% O_2 (n=8) and differential ventilation (n=11) for examining both steady-state respiratory patterns and reflex responses to airway occlusions. Following vagotomy each animal was allowed time (25 - 40 min) to achieve a new steady-state breathing pattern before being subjected to mechanical and chemical loading.

Statistical Evaluation

Variables describing steady state breathing patterns during hyperoxic, hypoxic and differential lung ventilation were compared with normoxic values by one-way analysis of variance; each animal serving as his own control. Results reported as degree of change are expressed as a percent of the control value obtained during room air breathing of intact or vagotomized dogs where applicable. Paired analysis by the Student t-test was used to determine significant differences in the respiratory characteristics between unoccluded control breaths and occluded first effort breaths.

The null hypothesis was rejected for statistical tests if $P < 0.05$. Additional details of protocol and statistical approaches are included with RESULTS.

RESULTS

Data are presented which describe the respiratory responses to left, right and bilateral lung occlusions. Alterations in these responses during inhalation of each test gas (cf. below) and following partial and complete vagotomy have been analyzed. Quantitative evaluation of phasic lung volume reflexes was based on changes in steady-state respiratory patterns in a given experimental situation (i.e., gas breathed, vagal integrity). Therefore, values obtained from blood and end-tidal gas analysis and descriptive respiratory parameters are detailed for all steady-state conditions.

The four test gas experimental conditions include: 1) normoxia (room air) - both lungs F_IO_2 = 0.2, 2) hypoxia - both lungs F_IO_2 = 0.1, balance nitrogen plus < 1% CO_2, 3) hyperoxia - both lungs F_IO_2 = 1.0, and 4) differential ventilation or unilateral hypoxia - left lung F_IN_2 = 1.0, F_IO_2 = 0.0; right lung F_IO_2 = 0.9 to 1.0.

Quantitative evaluation of the respiratory responses to occlusion of one or both airway(s) at specific times during the respiratory cycle has been separated into 'occluded breath' and 'first effort breath' characteristics. Special emphasis is placed on inspiratory and expiratory durations of these breaths. The importance of the vagi in mediating these reflexes was ascertained by severing one or both vagus nerves and comparing pre- and post-vagotomy responses to occlusions and to test gas breathing.

Anesthesia

Variation in the depth of anesthesia was minimized by slowly administering small doses of the alpha-chloralose/urethane mixture approximately every hour. The depth of anesthesia was gauged by respiratory rate, end-tidal CO_2, deep lumbar stretch reflexes and systemic blood pressure oscillations in phase with the respiratory cycle, i.e., Traube-Hering waves. Sympathetically mediated sinus arrhythmia and Traube-Hering waves were least apparent when the respiratory rate was held at about 12 breaths per minute; indicative of a moderate plane of anesthesia. This was also the level of anesthesia found most desirable for consistently demonstrating phasic lung volume reflexes.

Preliminary studies revealed that rapid administration of chloralose resulted in a transient (2-3 min) ventilatory depression and/or apnea (Figure 10). Furthermore, slow administration of too large a dose of chloralose, although avoiding the transient response, consistently produced a Biot-type respiratory pattern which was sustained for several hours. These effects of the anesthesia were not abolished by vagotomy or by increasing the chemical drive to breath, e.g., during hypoxic hyperventilation.

Blood and End-Tidal Gas Analyses

Both the blood-gas and acid-base status (Table 1) during steady state normoxia are within the physiologic ranges reported for normal dogs spontaneously breathing room air (Pickrell and Schluter,

Figure 10. Respiratory effects of alpha-chloralose/urethane anesthesia.

Records show the transient (Panel A and B) and sustained (Panel C) ventilatory depression resulting from rapid injection or overdose of alpha-chloralose/urethane. The duration of injection is indicated with the time trace at the top of each panel. Note differences in the time scale for each panel. Although not shown, restoration of normal breathing patterns in panel A and C occurred at 6 min and 118 min, respectively following injection. This anesthetic combination has minimal effects on aortic (AoP) and right ventricular blood pressure (RVP) as shown in Panel A.

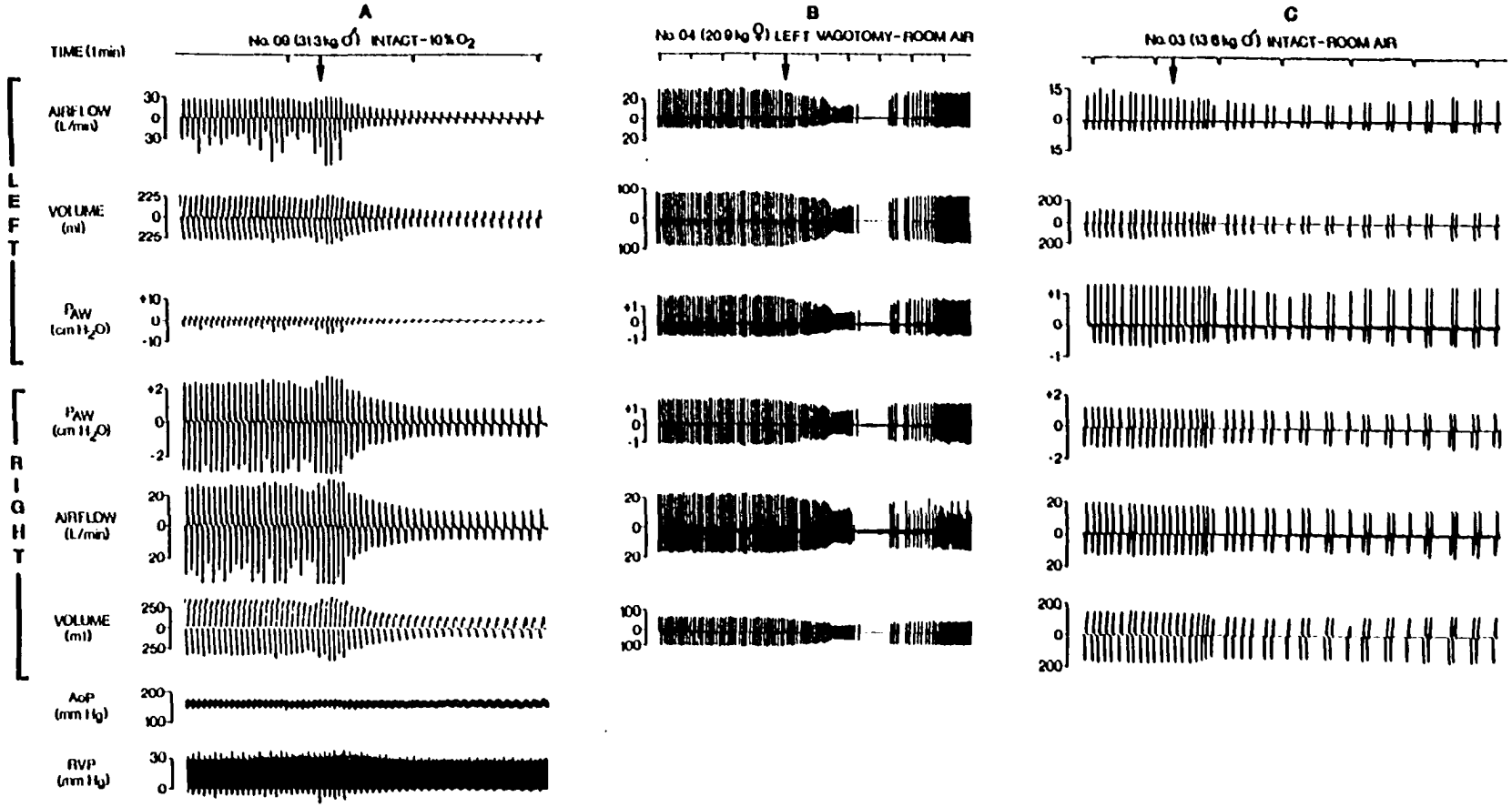

A
No. 09 (31.3 kg ♂) INTACT - 10% O_2
B
No. 04 (20.9 kg ♀) LEFT VAGOTOMY - ROOM AIR
C
No. 03 (13.6 kg ♂) INTACT - ROOM AIR
TIME (1 min)
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
AoP (mm Hg)
RVP (mm Hg)

Table 1. Summary of blood-gas analyses and acid-base status of 38 vagally intact anesthetized dogs breathing room air

	Mean ± SD	Range
ARTERIAL		
pH (units)	7.28 ± 0.06	7.20 - 7.38
pCO_2 (mm Hg)	56.4 ± 7.4	44.3 - 62.6
pO_2 (mm Hg)	73.6 ± 6.2	62.1 - 99.4
BE (mEq/L)	-1.9 ± 4.2	-7.9 - +8.3
HCO_3^- (mEq/L)	25.5 ± 4.1	20.4 - 34.9
MIXED VENOUS		
pH (units)	7.25 ± 0.07	7.00 - 7.34
pCO_2 (mm Hg)	62.7 ± 7.3	52.2 - 79.9
pO_2 (mm Hg)	51.1 ± 9.3	40.8 - 77.2
BE (mEq/L)	-1.7 ± 5.0	-11.2 - +8.9
HCO_3 (mEq/L)	26.5 ± 4.5	18.7 - 37.5
END-TIDAL		
Left pCO_2 (mm Hg)	35.5 ± 10.6[a]	16.9 - 50.4
Left pO_2 (mm Hg)	102.5 ± 14.9[a]	69.1 - 114.3
Right pCO_2 (mm Hg)	38.9 ± 7.1	21.5 - 47.1
Right pO_2 (mm Hg)	98.7 ± 16.6	68.7 - 121.2

[a]Values include samples from 6 dogs after correcting left lung dead space.

1973). Although not statistically significant, the average $ETpCO_2$ was generally lower (35.5 ± 10.6 vs 38.9 ± 7.1 mm Hg) and $ET\text{-}pO_2$ higher (102.5 ± 14.9 vs 98.7 ± 16.6 mm Hg) in the left than the right lung. Left lung dead space was increased in six dogs to minimize differences in left and right end-tidal gases during the baseline period.

Preliminary studies revealed a significant decrease in $ETpCO_2$ (ca. - 12 mm Hg) of both lungs during hypoxic hyperventilation and of the nitrogen ventilated left lung($\Delta ET\text{-}pCO_2$ = -16 mm Hg) during differential ventilation. Thereafter, changes in pH, $paCO_2$ and $ET\text{-}pCO_2$'s were minimized by adding carbon dioxide to the hypoxic lung(s) during 10% O_2 and differential ventilation. Therefore, the effects of changing arterial and/or alveolar oxygen tensions were examined under isocapneic conditions ($paCO_2$ = 56.4 ± 7.4 mm Hg).

Arterial pO_2 was significantly higher during hyperoxia (388.4 ± 67.3 vs 74.1 ± 16.3 mm Hg, $P < 0.001$), significantly lower during hypoxia (33.8 ± 2.6 vs 79.1 ± 16.3 mm Hg, $P < 0.001$), and unchanged during differential ventilation (84.6 ± 27.3 vs 79.6 ± 14.6 mm Hg) with respect to values obtained during normoxia (Table 2, cf. Table A-1 for mixed venous values). End-tidal pO_2 values of the left and right lung were not significantly different from one another during bilateral hypoxia (44.0 ± 9.6 and 45.9 ± 8.3 mm Hg) or bilateral hyperoxia (422.9 ± 117.0 and 418.7 ± 116.5 mm Hg). During differential ventilation end tidal pO_2 values of the left hypoxic lung (34.5 ± 13.9 mm Hg) and right hyperoxic lung (381.6 ± 58.9 mm

Table 2. Blood-gas and acid-base status during steady state hypoxic, hyperoxic, and differential ventilation with vagi intact

		Hypoxia (n=12)	Hyperoxia (n=14)	Diff. Vent. (n=18)
ARTERIAL				
pH (units)	N	7.30 ± 0.05[a]	7.27 ± 0.04	7.25 ± 0.05
	SS	7.34 ± 0.05	7.26 ± 0.06	7.27 ± 0.07
pCO_2 (mm Hg)	N	54.2 ± 5.7	56.7 ± 7.2	52.5 ± 5.3
	SS	47.2 ± 2.9	56.5 ± 10.5	48.2 ± 2.9
pO_2 (mm Hg)	N	79.1 ± 16.3	74.1 ± 16.3	79.6 ± 14.6
	SS	33.8 ± 2.6***	388.4 ± 67.3***	84.6 ± 27.3
BE (MEq/L)	N	-1.1 ± 3.2	-2.1 ± 3.6	-4.9 ± 2.4
	SS	0.8 ± 3.3	-3.2 ± 2.6	-5.1 ± 2.8
HCO_3^- (mEq/L)	N	25.3 ± 3.2	25.5 ± 3.8	22.4 ± 2.1
	SS	22.0 ± 3.6	24.7 ± 3.1	21.5 ± 2.8
END-TIDAL[b]				
L-ETPCO_2 (mm Hg)	N	40.7 ± 6.5	38.1 ± 8.3	34.2 ± 10.0
	SS	43.9 ± 4.3	39.6 ± 9.7	31.1 ± 7.5

R-ETPCO_2 (mm Hg)	N	40.7 ± 6.2	41.6 ± 4.0	38.1 ± 5.1
	SS	36.1 ± 11.4	39.6 ± 11.4	34.7 ± 6.9
L-ETpO_2 (mm Hg)	N	100.2 ± 4.9	99.4 ± 14.2	107.3 ± 13.7
	SS	44.0 ± 9.6***	422.9 ± 177.0***	34.5 ± 13.9***
R-ETpO_2 (mm Hg)	N	100.4 ± 13.9	93.9 ± 14.2	103.4 ± 11.2
	SS	45.9 ± 8.3***	418.7 ± 116.5***	381.6 ± 58.9***

[a]Values represent Mean ± SD for data obtained during normoxia (N) preceding inhalation of the test gas and during steady state (SS) breathing of the test gas. Statistical comparisons between N and SS value represented by ***$P < 0.001$.

[b]End-tidal samples collected from the left (L) or right (R) lung as indicated.

Hg) were comparable to values measured in both lungs during bilateral hypoxia and hyperoxia respectively; all were significantly different ($P < 0.001$) from values measured during room air breathing.

Similar data were obtained from bilaterally vagotomized dogs during inhalation of the test gases (Table A-2). However, during room air breathing vagotomized dogs had slightly lower $paCO_2$ and slightly higher pH values due to the ventilatory pattern associated with vagotomy. Unilateral vagotomy did not significantly change either arterial or end-tidal PO_2. However, compared to intact dogs, right vagotomized dogs did have slightly lower arterial pCO_2 (42.3 ± 0.7 mm Hg) and $ETpCO_2$ values (left lung = 29.7 ± 4.5; right lung = 29.0 ± 5.7 mm Hg). As stated before, this was easily corrected prior to performing occlusions by adding CO_2 to the inhaled gas mixtures to maintain isocapnia.

The changes in arterial and alveolar oxygen tension while maintaining isocapnia and normal pH were necessary for comparing the effects of intrapulmonary versus peripheral chemoreflexes on steady state breathing patterns and reflex adjustments in these patterns during airway occlusions.

Oxygen Consumption

Oxygen consumption ($\dot{V}O_2$) by each lung was measured with closed-circuit spirometry in 10 normoxic, 5 hypoxic, 7 hyperoxic and 6 differentially ventilated dogs (vagi intact). Baseline $\dot{V}O_2$ averaged

7.7 ± 0.3 ml/kg with a left:right distribution of 38:62% (Table 3). The distribution of oxygen uptake between the left and right lungs remained relatively constant during 10% and 100% O_2 breathing, but for obvious reasons was significantly altered during differential ventilation. The minimal reduction in $\dot{V}O_2$ during differential ventilation is physiologically significant since under these conditions (left lung F_IO_2 = 0.0, F_IN_2 = 1.0; right lung, F_IO_2 = 1.0), oxygen uptake is effected solely by the right hyperoxic lung. In fact, the driving gradient for oxygen between mixed venous blood and end-tidal gas was reversed in 4/6 dogs during differential ventilation such that oxygen was actually eliminated from the left hypoxic lung. This consequence of differential ventilation was evidenced by a downward slope on the spirometric trace.

In all six dogs tested, a transient decrease (-31%) in $\dot{V}O_2$ was measured during the first 10 min of bilateral hypoxia. However, an unexpected reversal in oxygen consumption, returning toward and even slightly exceeding the baseline $\dot{V}O_2$ was observed within 20 min. This elevated oxygen consumption during hypoxia can probably be accounted for by the increased demand of the respiratory muscles during hypoxic hyperventilation. Hypoxia is usually accompanied by an increased cardiac output (Tucker and Reeves, 1975; Morgan et al., 1968) which explains how this increased oxygen demand can be met.

Within a given animal, hyperoxic exposure produced either an increase, decrease or no change in oxygen consumption compared to the levels measured during room air breathing. There did not appear

Table 3. Oxygen consumption in individual dogs during normoxia, hypoxia, hyperoxia and differential lung ventilation

Dog No.	Body Weight (kg)	Hemoglobin (g/100 ml)	L:R[a] (%)	Oxygen Consumption (ml/Kg)			
				Normoxia	Hypoxia	Hyperoxia	Diff. Vent.[b]
1	25.0	16.1	44:56[b]	8.7	9.7	--	7.2
2	25.9	13.5	37:63	9.5	8.7	8.2	--
3	34.1	17.4	41:59	9.3	9.0	--	8.4
4	20.4	15.8	45:55	6.5	--	7.9	6.3
5	30.9	17.4	33:67	8.2	--	8.0	--
6	36.4	16.1	29.71	5.9	6.8	--	--
7	32.7	16.4	47:53	8.9	9.6	--	6.8
8	22.7	18.2	34:66	8.5	8.8	--	7.3
9	36.4	17.6	34:66	5.0	--	5.4	--
10	31.8	15.5	36:64	6.3	--	6.2	5.6
Mean	29.6	16.4	38:62	7.7	8.8	7.1	6.9
SD	(±5.7)	(±1.3)		(±1.6)	(±1.0)	(±1.3)	(±1.0)

[a]Distribution of oxygen uptake between the left and right lung expressed as a percent of the total body oxygen consumption during room air breathing.

[b]These values have been corrected for oxygen elimination from the left hypoxic lung. There were no significant changes in $\dot{V}O_2$ during inhalation of the 4 test gases.

to be a relationship between $\dot{V}O_2$ during hyperoxia and the ventilatory response to 100% oxygen breathing.

Hemodynamics

Average mean pulmonary arterial pressure (PAP) was 17 ± 3 mm Hg (range 11 - 16 mm Hg), systemic blood pressure (AoP) was 159/124 mm Hg (systolic/diastolic), and heart rate averaged 144 ± 16 beats per minute (range 102 - 162) during room air steady state breathing. Bilateral vagotomy usually produced a marked transient increase in AoP, PAP and heart rate (Figure 11). Although heart rate and AoP remained slightly elevated, mean pulmonary arterial pressure was somewhat lower than that measured prior to severing the vagi.

In the 12 dogs tested during hypoxia mean PAP increased in 7 dogs (ΔPAP = 7 ± 2 mm Hg) and remained unchanged in the remaining 5 dogs. The PAP pulse contour changed in the dogs responding to 10% oxygen (Figure 12). Both systolic and diastolic pressures increased, the former more than the latter producing an elevation in pulmonary arterial pulse pressure. Systemic blood pressure showed a small transient increase (+12%) during the first 3 min of hypoxic exposure, but generally returned to baseline levels within 10 min. Changes in heart rate were inconsistent but most apparent during the first 5-10 min of hypoxia. The hypoxic pressor response was more marked in vagotomized dogs and was generally sustained throughout the period of exposure. Mean PAP increased from 19 ± 2 mm Hg during normoxia to 34 ± 6 mm Hg during hypoxia in vagotomized dogs.

Figure 11. Effects of bilateral vagotomy on pulmonary arterial and systemic blood pressure.

The traces shown include airflow and tidal volume of the left and right lung, esophageal pressure (P_{ES}), right lung tidal CO_2 (ET-pCO_2), aortic blood pressure (AoP) and mean pulmonary arterial blood pressure (PAP). Normal cardiopulmonary signals prior to vagotomy are shown to the left. Arrow indicates point at which the vagi were transected. Note the change in paper speed as indicated by the time trace at the bottom. Severing of both vagi caused an initial pulmonary and systemic hypotension (peak response at ca. 8 sec) followed by a more gradual increase in both AoP and PAP (peak responses at ca. 110 sec). The AoP subsided slightly but remained above the pre-vagotomy level. Conversely, PAP abruptly reversed and remained slightly below the pre-vagotomy value. Changes in AoP corresponded quite closely with changes in P_{ES}.

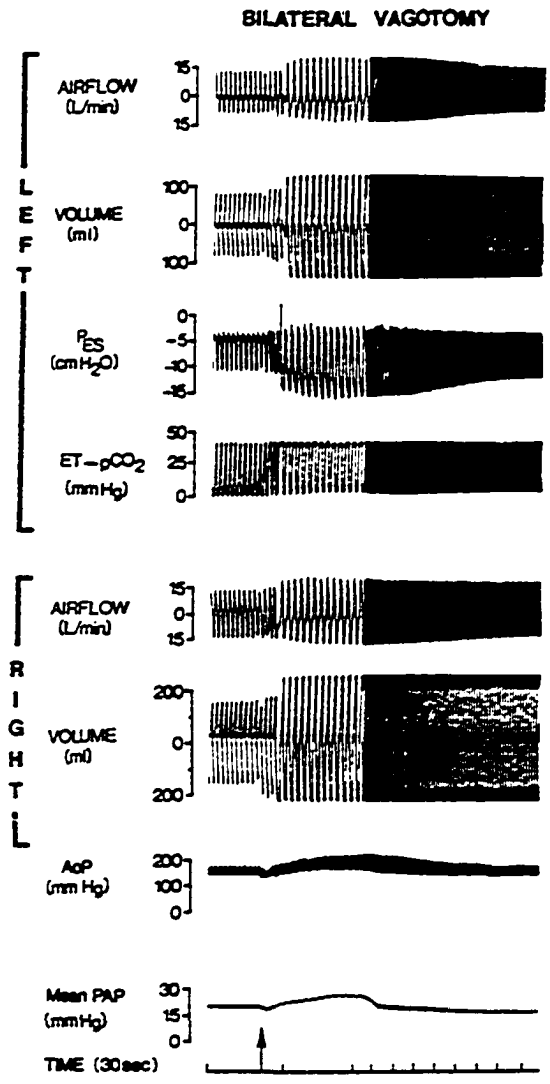
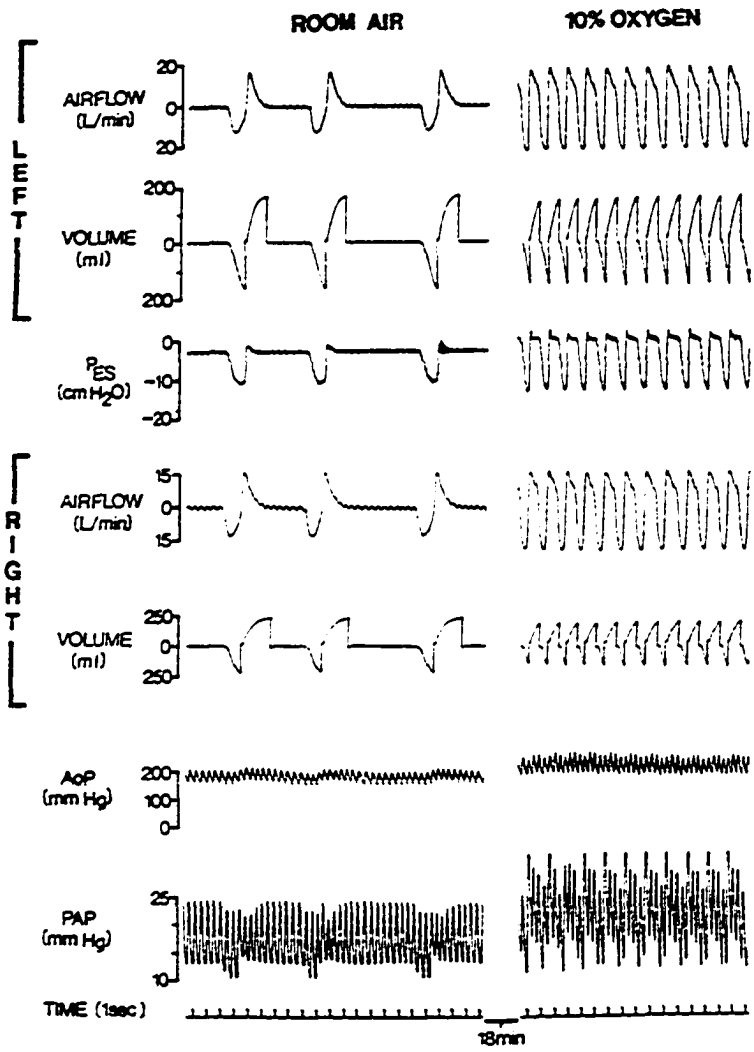

BILATERAL VAGOTOMY
LEFT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
100
0
100
P_{ES} (cmH_2O)
0
-5
-10
-15
ET-pCO_2 (mmHg)
50
25
0
RIGHT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
200
0
200
AoP (mmHg)
200
100
0
Mean PAP (mmHg)
30
15
0
TIME (30 sec)

Figure 12. Hypoxic pressor response and changes in steady state respiratory pattern.

From top to bottom: left lung airflow and tidal volume, esophageal pressure (P_{ES}), right lung airflow and tidal volume, aortic blood pressure (AoP), pulmonary arterial blood pressure (PAP) and time trace. The ventilatory response to inhalation of 10% O_2 is due to an increase in breathing frequency without a change in tidal volume. Increased esophageal pressure is indicative of more forceful breathing efforts during hypoxia. Hypoxia in this particular dog was associated with an elevated pulse pressure and mean pressure in both the systemic and pulmonary circulation.


ROOM AIR
10% OXYGEN
LEFT
AIRFLOW (L/min)
20
0
20
VOLUME (ml)
200
0
200
P_{ES} ($cm H_2O$)
0
-10
-20
RIGHT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
250
0
250
AoP (mm Hg)
200
100
0
PAP (mm Hg)
25
10
TIME (1sec)
18min

Vagotomy itself produced an increase in heart rate (+16%) which was further increased (+9%) during hypoxia in these dogs. The increase in AoP (+14 mm Hg) observed following vagotomy was not affected by hypoxia.

Mean PAP increased (8/14 dogs), decreased (4/14 dogs) or remained unchanged in (2/14 dogs) during inhalation of 100% O_2 by vagally intact dogs. Systemic blood pressure decreased (Mean ΔAoP= -14%) in all cases except one. A slight increase in heart rate associated with the reduced AoP indicates that the baroreflex was still operating during hyperoxia.

The pressor response during differential ventilation was slightly more delayed than during 10% and 100% O_2 breathing. Peak pulmonary arterial pressures (range 20 to 35 mm Hg) were attained at 20 ± 6 minutes. Systemic blood pressure either slightly increased or remained unchanged while heart rate averaged an increase (+14 beats per minute) in 70% of the dogs tested.

Steady State Breathing Patterns (SSBP)

SSBP: Baseline (room air, intact)

Average values of ventilatory parameters and lung mechanics for all 38 vagally intact dogs during normoxia are presented in Table 4. The respiratory cycle duration of 5.14 ± 0.12 sec (breathing frequency ca. 12 breaths per min) was phase-switched with an expiratory/inspiratory time ratio (T_E/T_I) of 3.26 ± 0.08. It is apparent from Figure 13 that the frequency distribution of minute

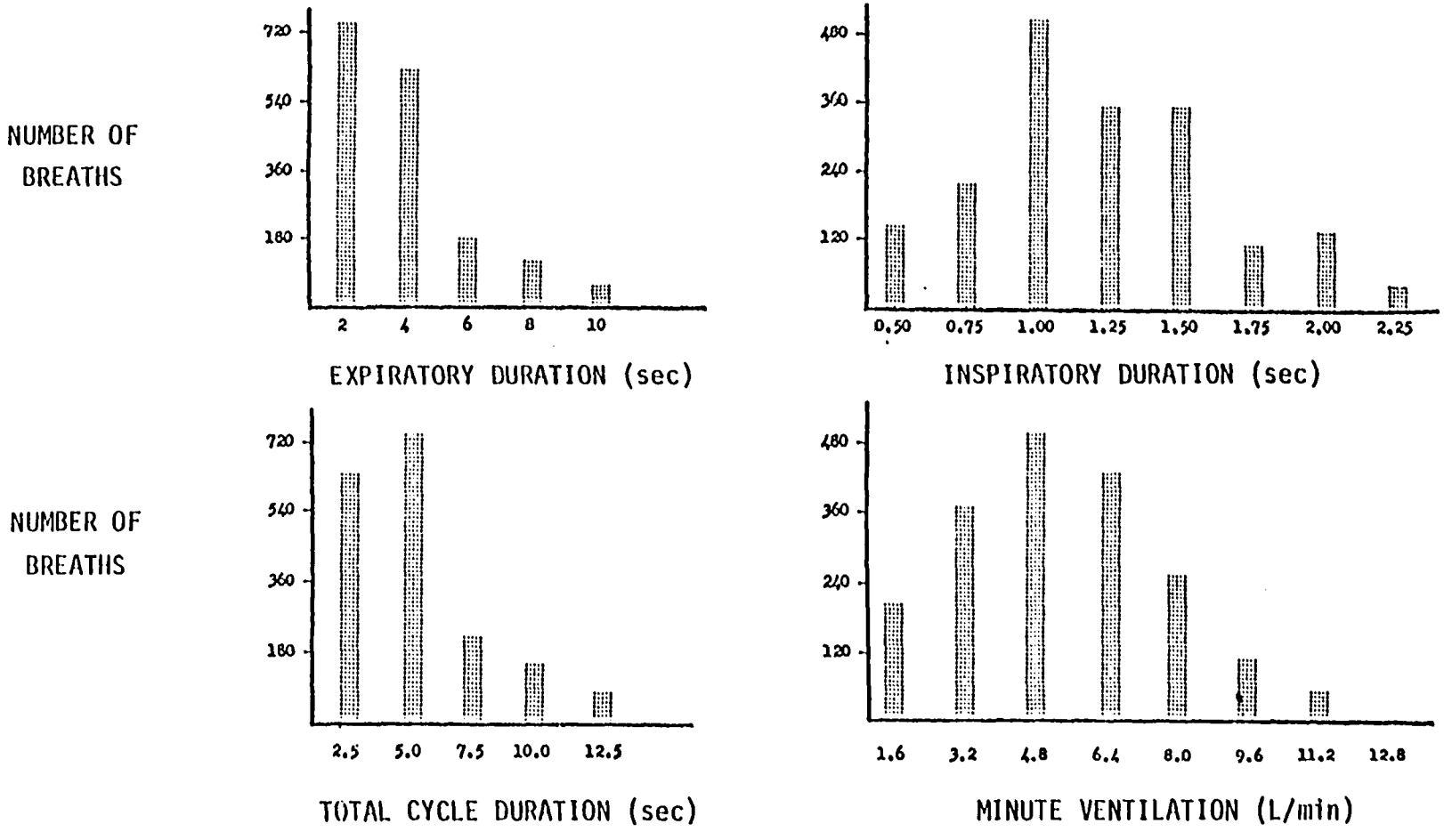
Table 4. Summary of respiratory data in 38 dogs during steady state room air breathing with vagi intact

Variable[a]	Mean ± SEM
T_I (sec)	1.20 ± 0.02
T_E (sec)	3.94 ± 0.11
T_{TOT} (sec)	5.14 ± 0.12
T_I/T_{TOT} (%)	26.9 ± 0.3
T_E/T_{TOT} (%)	73.1 ± 0.3
T_E/T_I	3.26 ± 0.08
V_T^L (ml)	162 ± 2
V_T^R (ml)	251 ± 2
V_T (ml)	413 ± 3
V_T^L/V_T (%)	39.2 ± 2.1
V_T^R/V_T (%)	60.8 ± 2.1
V_T^L/T_I (ml/sec)	142 ± 2
V_T^R/T_I (ml/sec)	187 ± 0.3
$\dot{V}_E$ (L/min)	5.30 ± 0.09
$I\text{-}P_{AW}^L$ (cm H_2O)	1.15 ± 0.02
$I\text{-}P_{AW}^R$ (cm H_2)	1.53 ± 0.03
$E\text{-}P_{AW}^L$ (cm H_2O)	1.41 ± 0.02
$E\text{-}P_{AW}^R$ (cm H_2O)	1.52 ± 0.02
$I\text{-}P_{AW}^L/T_I$ (cm H_2O/sec)	1.08 ± 0.03
$I\text{-}P_{AW}^R/T_I$ (cm H_2O/sec)	1.50 ± 1.06
P_{ES} (cm H_2O)	8.27 ± 0.14
$I\text{-}\dot{F}^L$ (L/min)	13.5 ± 0.1
$I\text{-}\dot{F}^R$ (L/min)	15.4 ± 0.2
$E\text{-}\dot{F}^L$ (L/min)	16.1 ± 0.1
$E\text{-}\dot{F}^R$ (L/min)	16.8 ± 0.2
E_{dyn}^L (cm H_2O/L)	7.3 ± 0.1
E_{dyn}^R (cm H_2O/L)	7.6 ± 0.1

[a]Refer to ABBREVIATIONS.

Figure 13. Frequency histograms of expiratory, inspiratory and total cycle duration as well as minute ventilation during spontaneous room air breathing in anesthetized dogs.

The skewed distributions of T_E and T_{TOT} correspond quite closely, e.g., slower breathing frequencies (longer T_{TOT}) are associated with longer expiratory durations. Inspiratory duration and minute volume were more normally distributed and inversely related. Bars are drawn over midpoint values of each interval.

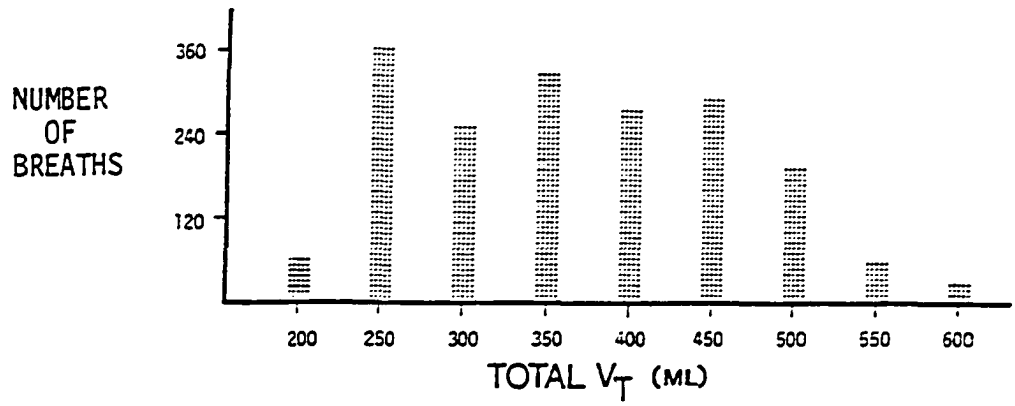

NUMBER OF BREATHS
720
540
360
180
2
4
6
8
10
EXPIRATORY DURATION (sec)
480
360
240
120
0.50
0.75
1.00
1.25
1.50
1.75
2.00
2.25
INSPIRATORY DURATION (sec)
NUMBER OF BREATHS
720
540
360
180
2.5
5.0
7.5
10.0
12.5
TOTAL CYCLE DURATION (sec)
480
360
240
120
1.6
3.2
4.8
6.4
8.0
9.6
11.2
12.8
MINUTE VENTILATION (L/min)

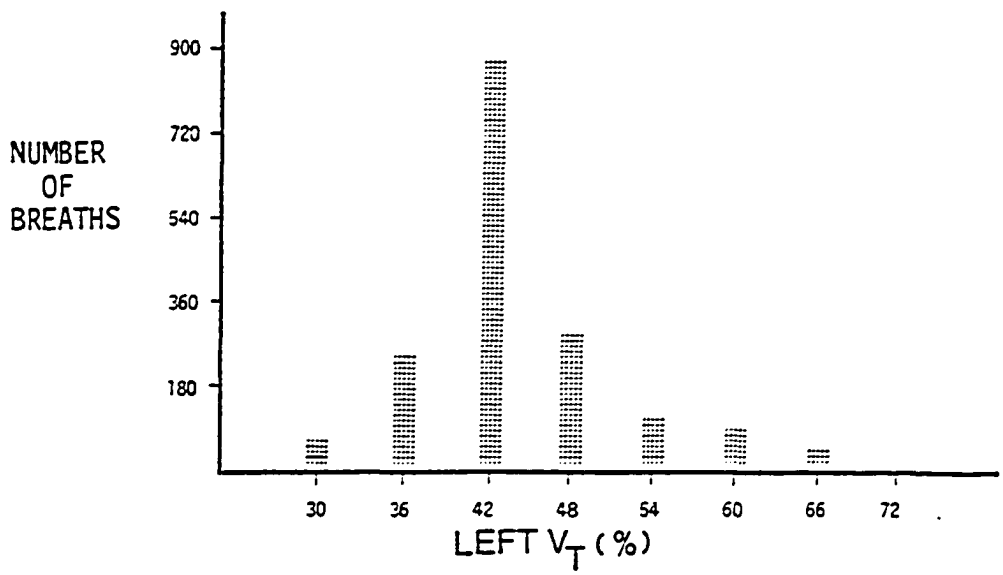
ventilation corresponds closely to that of T_I while the distribution of respiratory rate ($1/T_{TOT}$) parallels that of T_E. The physiological significance of these observations will become more apparent when the input-output relationships of the respiratory pattern generator(s) are altered by vagotomy and/or changes in inspired oxygen.

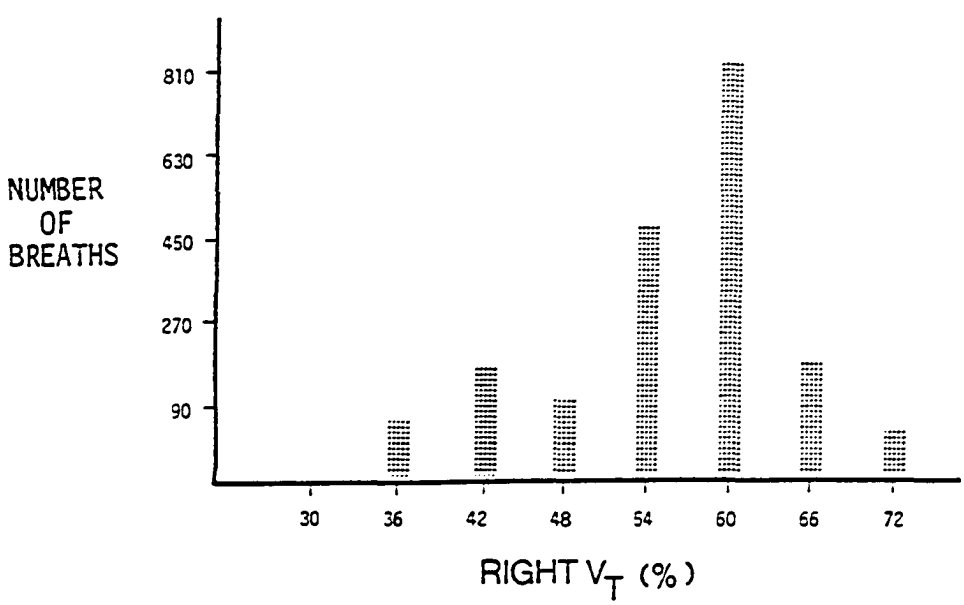
During spontaneous room air breathing there were significant differences ($P < 0.05$) between the right and left lungs for tidal volume (V_T), inspiratory airway pressure ($I\text{-}P_{AW}$, and inspiratory airflow ($I\text{-}\dot{F}$). Tidal volume averaged 413 ± 3 ml (ca. 13.6 ml/kg) with a left:right tidal volume ratio of 39.61%. This ratio remained quite consistent considering the wide range of volumes measured in these dogs (Figure 14). Right lung $I\text{-}P_{AW}$ was 33% higher than left lung inspiratory airway pressure. However, inspiratory airflow of the right lung was only approximately 14% greater than that measured in the left airway. These differences can be partially accounted for by the larger V_T and somewhat greater elastic recoil of the right lung. Upper airway resistance of both lungs was nearly identical.

Dynamic elastances of the right and left lung (7.6 ± 0.1 and 7.3 + 0.1 cm H_2O/L.s, respectively) were not significantly different. E_{dyn} remained relatively constant throughout the course of the experiments during all room air breathing periods in vagally intact dogs.

Figure 14. Frequency histogram of total lung tidal volume and the left and right lung volumes expressed as a percent of the total volume.


NUMBER OF BREATHS
360
240
120
200
250
300
350
400
450
500
550
600
TOTAL V_T (ML)


NUMBER OF BREATHS
900
720
540
360
180
30
36
42
48
54
60
66
72
LEFT V_T (%)


NUMBER OF BREATHS
810
630
450
270
90
30
36
42
48
54
60
66
72
RIGHT V_T (%)

SSBP: effects of vagotomy

Relative changes (Table 5) and absolute values (Table A3) for respiratory cycle characteristics obtained before and after right, left and bilateral vagotomy are presented. For statistical analysis the value of each respiratory parameter after vagotomy has been paired with the value obtained prior to vagotomy in each animal. Severing of either the right or left vagus nerve unexpectedly decreased T_{TOT}. The effect was more pronounced with right vagotomy (-33.9%, $P < 0.05$) than with left vagotomy (-9.4%). The increased breathing frequency (decreased T_{TOT}) produced by right vagotomy was due to disproportionate shortening of both T_E (-40.2%, $P < 0.05$) and T_I (-11.2%) such that the T_E/T_I ratio significantly decreased ($P < 0.05$) from 3.81 ± 0.26 before to 2.40 ± 0.22 after cutting the nerve. Expiratory duration was also slightly shortened (-13.9%) following left vagotomy. However, T_I was slightly prolonged from 1.34 ± 0.02 sec before to 1.45 ± 0.08 sec after left vagotomy. The changes in T_E and T_I, being in opposite directions (T_E decreased while T_I increased), resulted in a small decrease in the phase-switching T_E/T_I ratio.

The changes in tidal volume produced by unilateral vagotomy were very specific. Right vagotomy caused an increase (+15.9%, $P < 0.05$) in right lung V_T from 207 ± 12 ml to 240 ± 8 ml without altering left lung V_T. Similarly, left vagotomy produced a 13.8% increase ($P < 0.05$) in left lung V_T (152 ± 3 before to 173 ± 12 ml after) without affecting right lung volume. The combination of

Table 5. Relative changes in respiratory cycle characteristics during spontaneous room air ventilation following left, right and bilateral vagotomy

Variable[a]	Left Vagotomy (n=12)	Right Vagotomy (n=8)	Bilateral Vagotomy (n=12)
T_I	+ 7.7[b]	-11.2	+79.0*
T_E	-13.9	-40.2*	+14.4
T_{TOT}	- 9.4	-33.9*	+29.4*
T_E/T_I	-18.0	-37.0*	-41.2*
$V_T{}^L$	+13.8*	- 0.5	+66.1*
$V_T R$	- 1.0	+15.9*	+62.8*
V_T	+ 5.3	+ 8.6	+64.3*
$V_T{}^L/T_I$	+ 7.0	+ 8.1	- 4.9
$V_T{}^R/T_I$	-11.4	+23.5	-11.4
$\dot{V}_E$	+ 7.9	+63.8*	+26.6*
$I\text{-}P_{AW}{}^L$	+17.2	+10.9	+18.8
$I\text{-}P_{AW}{}^R$	+11.2	+20.1*	+14.9
$I\text{-}P_{AW}{}^L/T_I$	+10.3	+17.9	-30.6**
$I\text{-}P_{AW}{}^R/T_I$	+ 6.2	+28.5	-36.4*
P_{ES}	--	+12.6	+ 1.3
$I\text{-}\dot{F}^L$	+ 8.6	+ 6.0	+ 3.9
$I\text{-}\dot{F}^R$	- 0.7	+15.1*	+ 0.6
$E\text{-}\dot{F}^L$	+12.7	+ 5.4	+ 0.0
$E\text{-}\dot{F}^R$	+ 6.3	+ 7.7	+16.2
$E_{dyn}{}^L$	+ 4.3	+12.5	-27.8*
$E_{dyn}{}^R$	+10.7	+ 7.3	-29.0*

[a]Refer to ABBREVIATIONS.

[b]Values represent average percent change in treatment value from the value obtained in the intact animal. Significant differences represented as: *$P < 0.05$, **$P < 0.01$.

frequency and tidal volume changes were manifested as an unchanged minute ventilation following left vagotomy. However, a significant increase in $\dot{V}_E$ (+63.8%, $P < 0.05$) was associated with right vagotomy. This explains the decrease in $paCO_2$ and slight increase pH measured in the latter group.

The respiratory pattern observed following bilateral vagotomy was definitely not just a summation of the effects due to abolition of left and right vagal innervation taken separately. In the first instance and unlike the effect of either left or right vagotomy, bilateral vagotomy significantly prolonged T_{TOT} (+29.4%, $P < 0.05$). The change in T_{TOT} was due to lengthening of both T_I (1.13 ± 0.04 before to 2.02 ± 0.06 sec after, $P < 0.05$) and T_E (3.73 ± 0.08 before to 4.27 ± 0.11 sec after). The phase-switching index, (T_E/T_I) significantly ($P < 0.05$) decreased from 3.23 ± 0.12 before to 1.90 ± 0.09 after vagotomy. Secondly, increases in tidal volume of equal relative magnitude (left lung, +66.1%; right lung, +62.8%; both $P < 0.05$) were measured.

Both left and right unilateral vagotomies resulted in small increases in dynamic elastance of both lungs with a larger increase occurring in the lung contralateral to the vagotomy. Conversely, bilateral vagotomy resulted in a significant ($P < 0.05$) decrease in left lung E_{dyn} (-27.8%) and right lung E_{dyn} (-29.0%).

Indirect evidence that vagotomy disrupted the normal pattern of respiratory center output (phrenic efferent pattern) is suggested by

the extremely irregular flow patterns. Typical recordings are shown in Figures 15 and B1.

Analysis of steady state breathing patterns was necessary in these studies. It was these patterns upon which mechanical and chemical loads were superimposed. However, the purpose of this study was to describe phasic lung volume reflexes. Such reflexes represent the immediate respiratory compensation to an altered input (chemical or mechanical). Occlusions of one or both airways at different times in the respiratory cycle were used to alter sensory input to the respiratory center. Although overlooked in the early experiments, it became apparent that the first few breaths following unilateral and/or bilateral vagotomy also represent immediate respiratory compensation to an altered input.

The immediate ventilatory responses to left, right and bilateral vagotomy were unrelated to both the eupneic pattern prior to severing the nerve(s) and to the new steady state rhythmic cycles 25-40 minutes after vagotomy. This observation is particularly relevant in that the Hering-Breuer reflexes are generally used to extrapolate information concerning mechanisms of respiratory pattern control.

Unilateral vagotomy produced characteristic breathing patterns specific to left or right vagotomy. Severing the left vagus (Figure 16) usually produced an immediate increase in left lung tidal volume without affecting right lung V_T and without any interruption in breathing frequency. Left vagotomy produced gasping in several dogs

Figure 15. Irregular inspiratory airflow pattern following bilateral vagotomy indicates disruption in the phrenic motor output to the diaphragm.

Airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung as well as right ventricular pressure (RVP) traces are shown. Note different calibrations and time scale for recordings obtained 22 min after transecting both vagi. Vagotomy produced a significant decrease in frequency and increase in tidal volume, P_{AW} and airflow. Discontinuous phrenic output is evidenced by irregular inspiratory airflow signals and resetting of the volume integrator to zero (arrows) between inspiration and expiration. Heart rate increased from 120 to 180 beats/min and RVP remained unchanged following bilateral vagotomy.

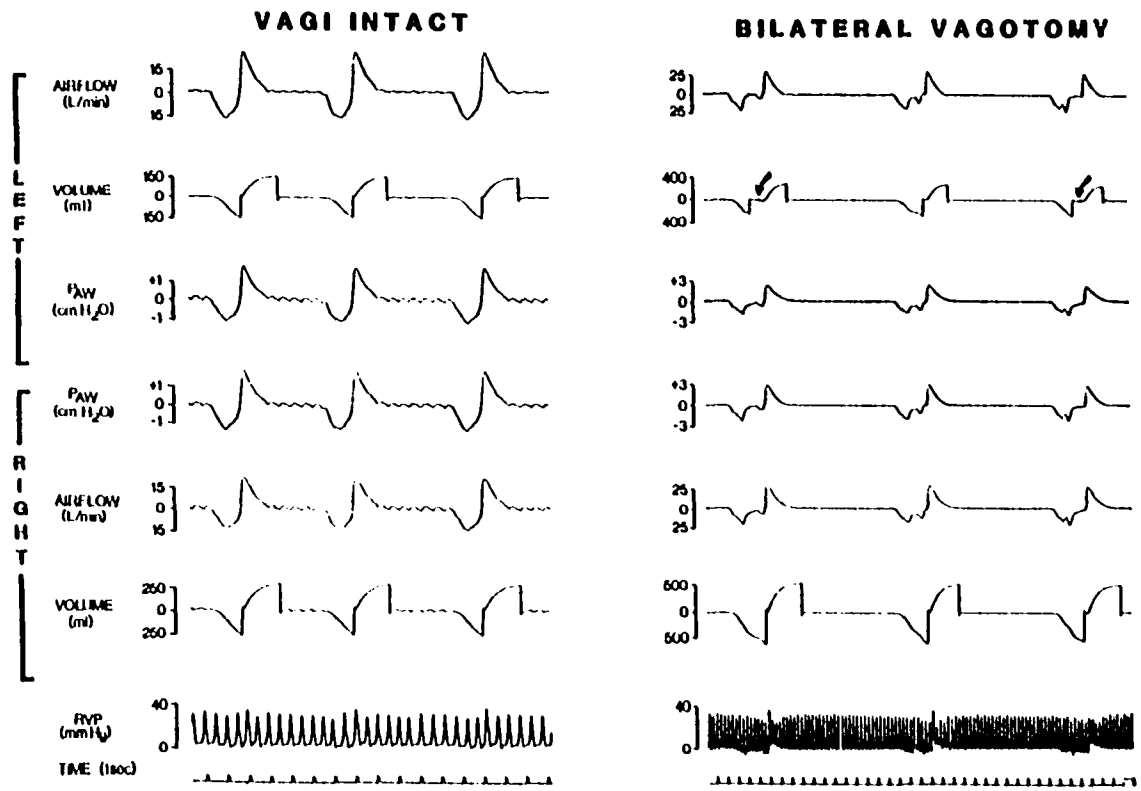
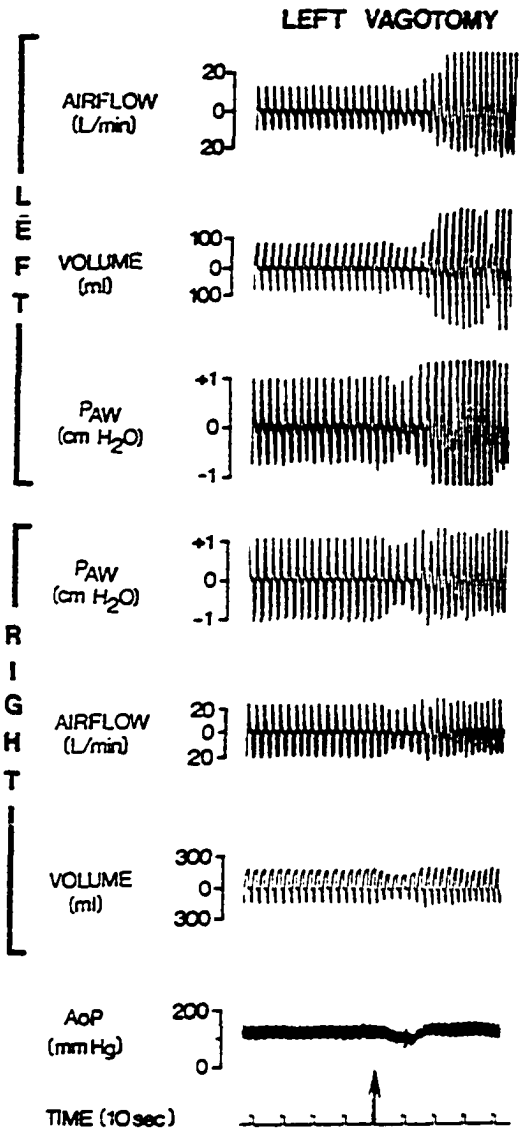

VAGI INTACT
BILATERAL VAGOTOMY
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
RVP (mm Hg)
TIME (1sec)
15
0
-15
150
0
-150
+1
0
-1
250
0
-250
40
0
+3
-3
25
-25
400
-400
500
-500

Figure 16. Immediate ventilatory response to left vagotomy.

Traces shown include airflow, tidal volume and airway pressure (P_{AW}) of the left and right lungs and aortic blood pressure (AoP). Arrow on time scale (10 sec) at the bottom indicates the point at which the left vagus was cut. Unilateral vagotomy produced a transient hypotension (peak response at 12 sec) followed by a rapid recovery to normal. These changes in AoP corresponded to the initial decrease and subsequent increase in respiratory parameters. Breathing frequency was slightly higher following left vagotomy.


LEFT VAGOTOMY
LEFT
AIRFLOW (L/min)
20
0
20
VOLUME (ml)
100
0
100
PAW (cm H2O)
+1
0
-1
RIGHT
PAW (cm H2O)
+1
0
-1
AIRFLOW (L/min)
20
0
20
VOLUME (ml)
300
0
300
AoP (mm Hg)
200
0
TIME (10 sec)

without causing tidal volume changes in either lung (Figure 17). Right vagotomy produced apnea or an immediate change in frequency with small increases in right lung V_T and/or left lung V_T (Figures 18, B2 and B3). Apnea of variable duration (2-18 sec) was the predominant response to bilateral vagotomy. This was followed by an abrupt increase in V_T of both lungs and regular, but slower rhythm (Figures 19, B2, B3, and B4). This pattern persisted with minimal changes throughout the remainder of the experimental period.

SSBP: Effects of changing inspired O_2 tension

The steady state breath profiles were noticeably different during hypoxia and hyperoxia (Figure 20). The immediate ventilatory response to bilateral hypoxia (both lungs F_IO_2 = 0.1, paO_2 = 33.8 ± 2.6 mm Hg) as shown in Figure 21 was similar to that observed during steady state hypoxia (Table 6, Table A4). A two-fold increase in minute ventilation from 5.11 ± 0.61 to 10.08 ± 1.22 L/min ($P < 0.001$ was due strictly to an increase in breathing frequency, i.e., decrease T_{TOT} from 5.71 ± 0.16 to 2.19 ± 0.09 sec ($P < 0.001$). Tidal volume remained relatively unchanged. The tachypnea was due to disproportionate decreases in T_I (-33%, $P < 0.001$) and and T_E (-69.6%, $P < 0.01$). The T_E/T_I ratio decreased ($P < 0.01$) from a value of 3.61 ± 0.42 during normoxia to 1.65 ± 0.11 during hypoxia.

Bilateral hyperoxia (both lungs F_IO_2 = 1.0, paO_2 > 350 mm Hg) did not significantly affect minute ventilation. However, the frequency of breathing was notably slower than that observed during

Figure 17. Transient ventilatory response to left vagotomy.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung and aortic (AoP) and pulmonary arterial (PAP) blood pressure. Note the changes in time scale. Left vagotomy (arrow) produced a gasping response of 8 sec duration. This was abruptly converted to a rhythmic respiratory pattern which was indistinguishable from that observed prior to vagal transection. The cardiovascular response consisted of a very short (< 2 sec) bradycardia and systemic hypotension followed by rapid recovery of both. PAP was not significantly affected by the procedure.

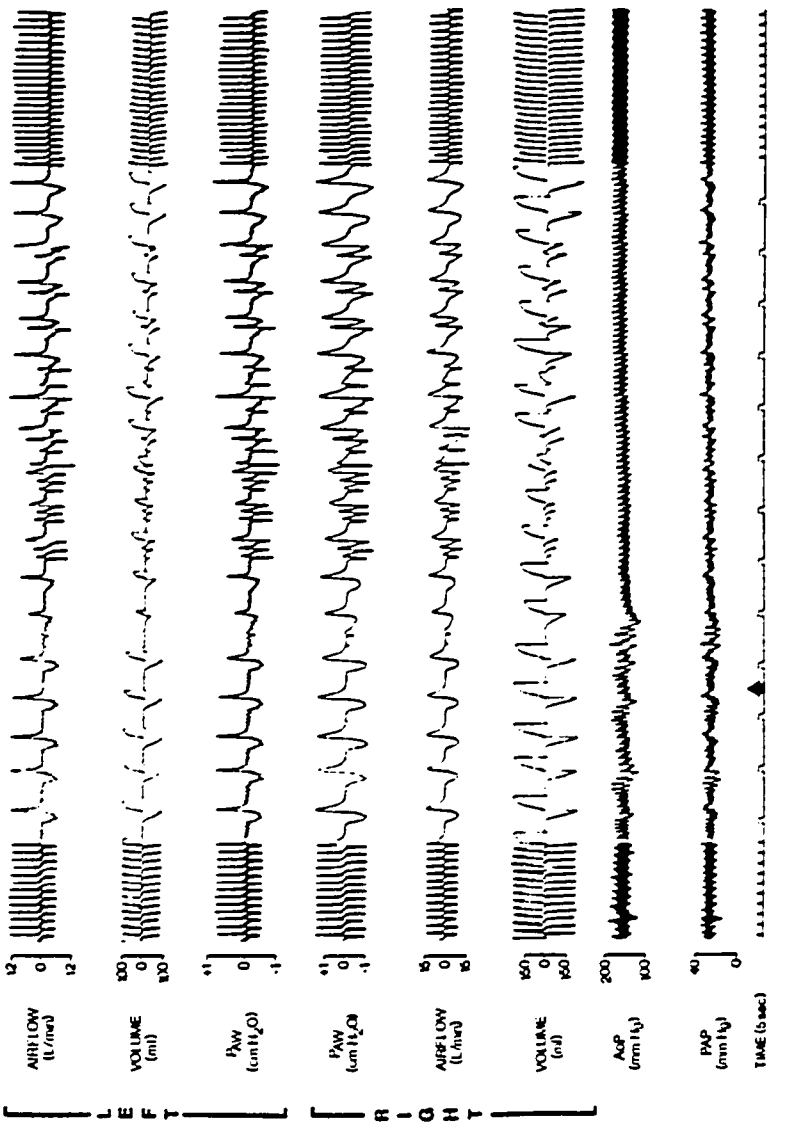

LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
AoP (mm Hg)
PAP (mm Hg)
TIME (5 sec)

Figure 18. Immediate ventilatory and cardiovascular responses to right vagotomy and bilateral vagotomy in the same animal.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung, esophageal pressure (P_{ES}) and right ventricular pressure (RVP). Time of nerve transection is indicated by the arrows on the time trace. Note that 43 min elapsed between cutting of the right and left vagi. Right vagotomy produced small increases in tidal volume of both lungs compared to the volume changes following bilateral vagotomy. Conversely, the initial frequency response was more marked after right vagotomy than bilateral vagotomy. Both procedures produced an increase in RVP.

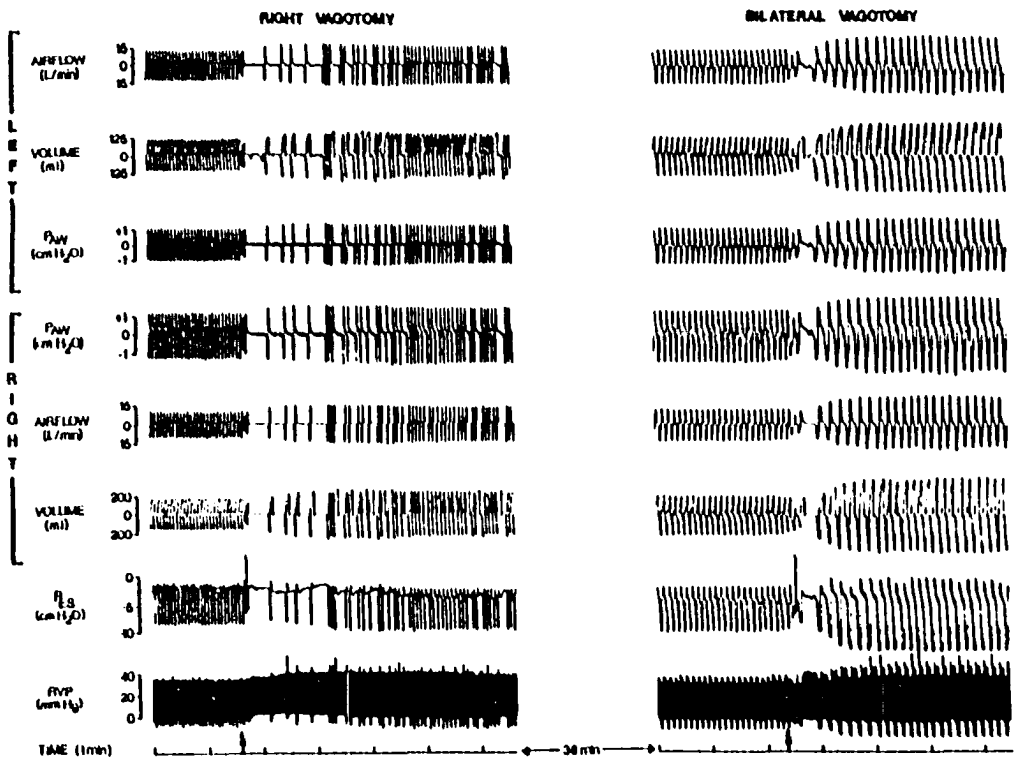

RIGHT VAGOTOMY
BILATERAL VAGOTOMY
LEFT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} ($cm H_2O$)
RIGHT
P_{AW} ($cm H_2O$)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} ($cm H_2O$)
RVP ($mm Hg$)
TIME (1min)
30 min

Figure 19. Immediate ventilatory response to bilateral vagotomy.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung and esophageal pressure (P_{ES}). Expanded time scales in panel A (pre-vagotomy) and C (post-vagotomy) show characteristic breath profiles in the two conditions. Note the change in volume calibration in panel C. Vagal transection (arrow) produced an initial decrease in tidal volume and slowing of frequency (panel B). These changes were followed by an abrupt increase in tidal volume and frequency within 20 sec after bilateral vagotomy.

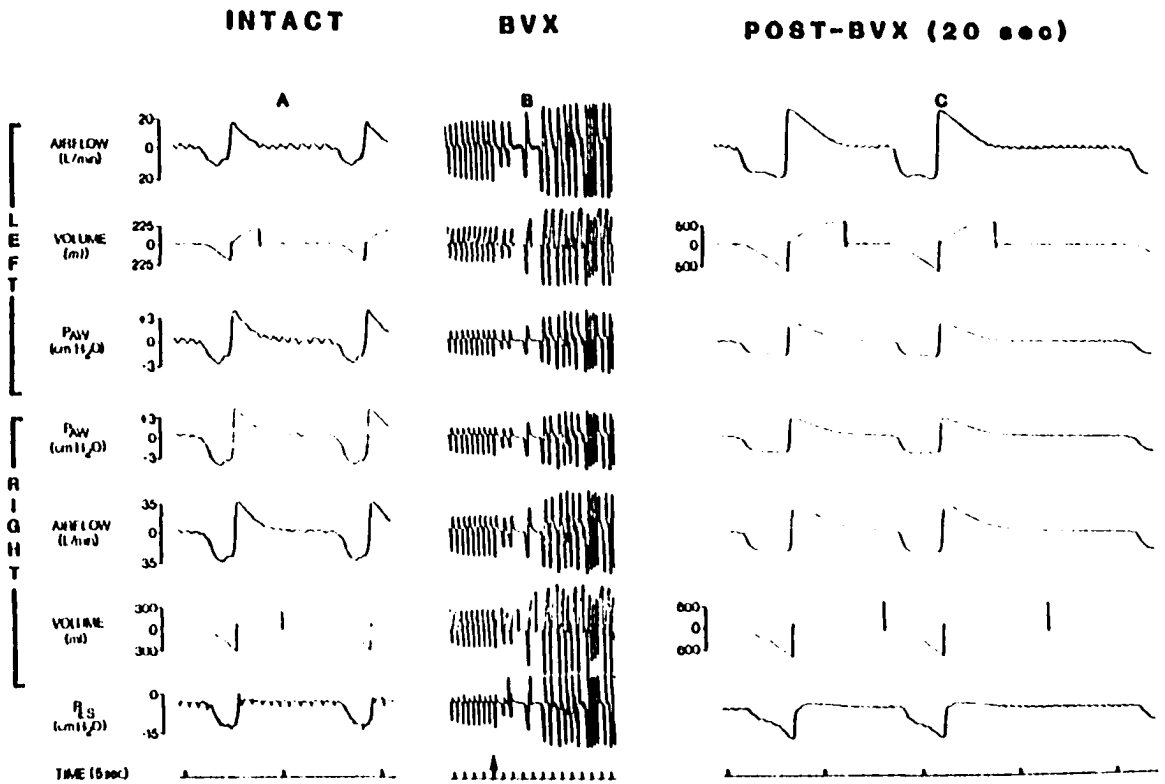

INTACT
BVX
POST-BVX (20 sec)
A
B
C
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cm H_2O)
TIME (5 sec)
20
0
-20
225
0
-225
+3
0
-3
+3
0
-3
35
0
-35
300
0
-300
0
-15
800
0
-800
800
0
-800

Figure 20. Characteristic breath profiles observed during normoxia, hyperoxia and hypoxia.

Airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung, esophageal pressure (P_{ES}) and pulmonary arterial pressure (PAP) traces are shown. Inspiration is represented by downward deflections. The decreased breathing frequency associated with inhalation of 100% O_2 and the increased frequency response during 10% O_2 breathing were predominantly due to changes in the duration of expiration. Pulmonary arterial pulse pressure was slightly elevated during hypoxia and hyperoxia although mean PAP remained unchanged.

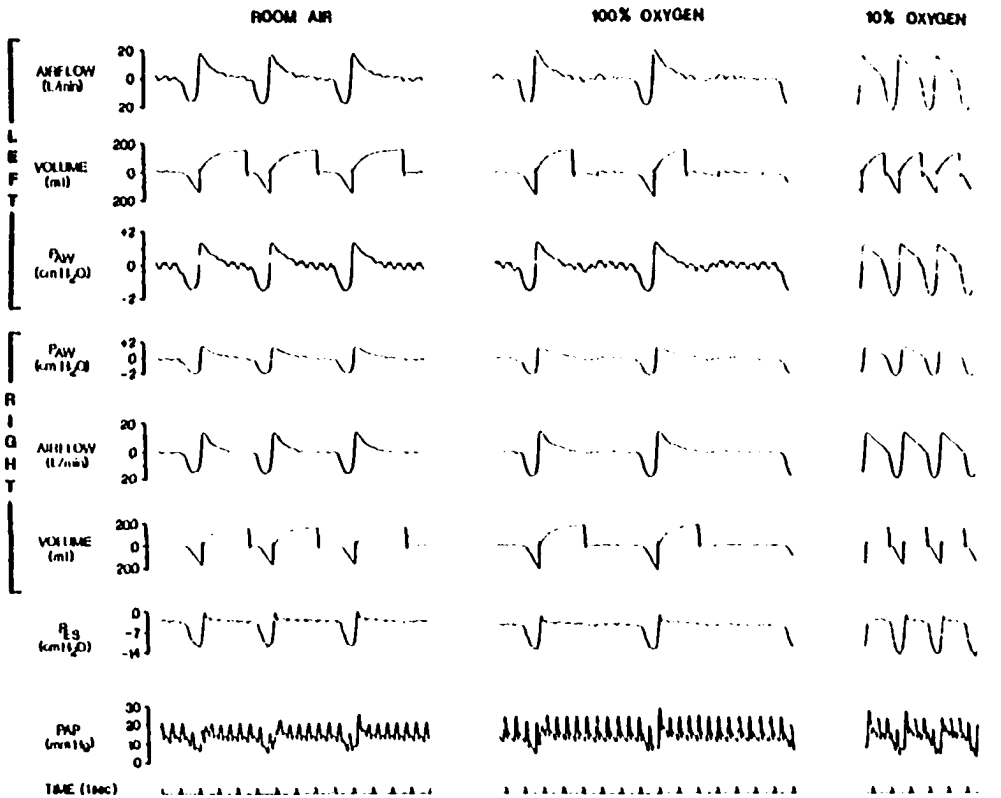

ROOM AIR
100% OXYGEN
10% OXYGEN
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cm H_2O)
PAP (mm Hg)
TIME (1sec)

Figure 21. Transient response and steady state breathing pattern observed during inhalation of 10% oxygen.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung and esophageal pressure (P_{ES}) recordings. The ventilatory response to hypoxia begins within the first few breaths of exposure (arrow). Tidal volume remains relatively constant. However, P_{AW}, P_{ES} and respiratory rate progressively increase. The change in breathing frequency during steady state hypoxia (far right panel) is due primarily to shortening of expiratory duration. Note the change in paper speed as indicated on time scale.

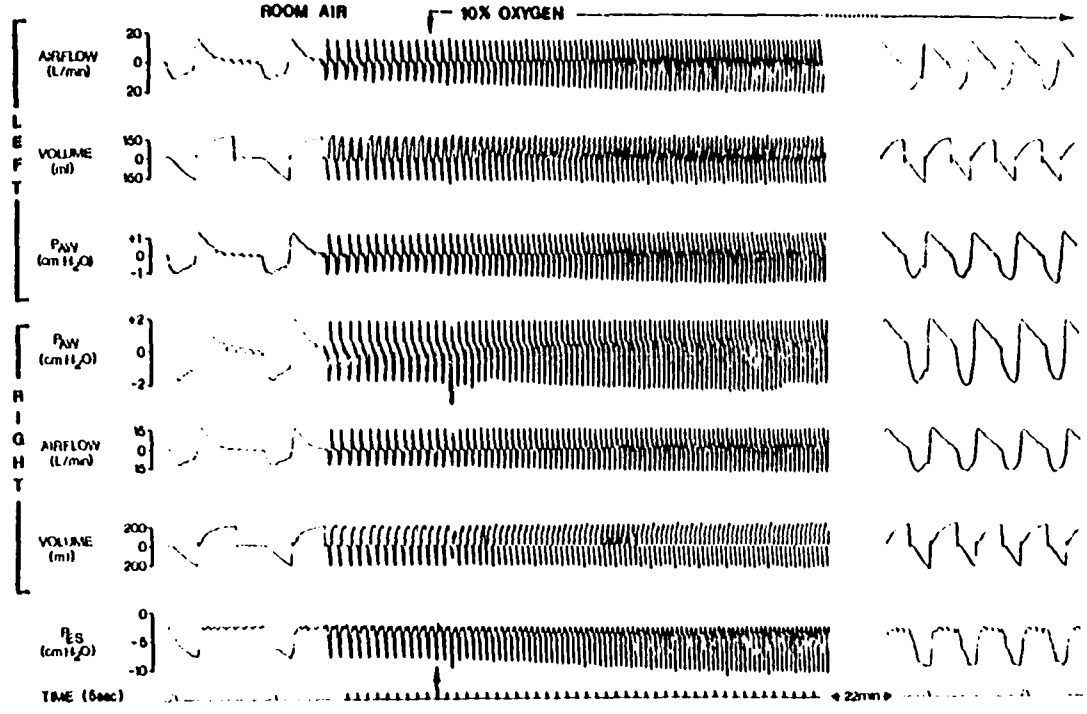

ROOM AIR
10% OXYGEN
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} ($cm H_2O$)
P_{AW} ($cm H_2O$)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} ($cm H_2O$)
TIME (5sec)
22mm

Table 6. Effects of hypoxic, hyperoxic and differential lung ventilation on steady state respiratory cycle parameters in vagally intact dogs

Variable[b]	Average Change from Normoxia (%)[a]		
	Hypoxia (n=12)	Hyperoxia (n=14)	Diff. Vent. (n=18)
T_I	-33.1***	+ 1.0	- 5.8
T_E	-69.6**	+25.0*	-18.8*
T_{TOT}	-61.6***	+19.2*	-15.4*
T_E/T_I	-54.3**	+22.2*	-16.9**
V_T^L	-10.1	+12.8*	- 1.4
V_T^R	-10.3	+18.2*	+ 4.9
V_T	-10.2	+15.7*	+ 2.0
V_T^L/T_I	+33.6*	+ 9.5*	+ 7.1
V_T^R/T_I	+28.8*	+12.7**	+10.6
$\dot{V}_E$	+97.1***	- 1.6	+22.6*
$1-P_{AW}^L$	+16.4**	+ 5.0	+ 5.0
$1-P_{AW}^R$	+19.7*	+13.9	+13.9

$1-P_{AW}^{L}/T_I$	+63.2***	+ 4.0	+22.6**
$1-P_{AW}^{R}/T_I$	+68.0*	+ 0.1	+32.1**
P_{ES}	+18.3	+ 8.9*	+22.8*
$1-\dot{F}^{L}$	+23.2**	+ 4.8*	+ 4.4
$1-\dot{F}^{R}$	+21.0**	+ 7.8*	+14.7*
$E-\dot{F}^{L}$	- 2.7	+ 5.5*	+ 0.5
$E-\dot{F}^{R}$	- 5.9	+ 4.9*	+ 0.5
E_{dyn}^{L}	+23.6	- 6.4	+ 4.5
E_{dyn}^{R}	+21.3*	- 6.3	+ 3.6

[a]Values represent mean change in parameter during test gas breathing when compared to that measured during normoxia. Significant differences indicated by: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

[b]Refer to ABBREVIATIONS.

room air breathing (Figure 20). Tidal volumes of the right and left lungs showed parallel increases (both $P < 0.05$) of +18% and +13% respectively. The frequency response (ΔT_{TOT} from 4.50 ± 0.10 during normoxia to 5.36 ± 0.06 sec during hyperoxia) was due to lengthening of T_E (+25%, $P < 0.05$); T_I remained unchanged.

The ventilatory response to differential ventilation (left lung $F_IN_2 = 1.0$; $F_IO_2 = 0.0$; right lung $F_IO_2 = 1.0$; $paO_2 = 84.6 \pm 27.3$ mm Hg) was unexpected since arterial oxygenation was comparable to that measured during room air breathing ($paO_2 = 79.6 \pm 14.6$ mm Hg). The increase in minute ventilation (+22.6%, $P < 0.05$) was due solely to an increase in breathing frequency (decrease in T_{TOT} from 4.54 ± 0.06 during normoxia to 3.84 ± 0.07 sec during differential ventilation) with negligible volume changes. The frequency response was due to decreases in both T_E (-18.8%, $P < 0.05$) and T_I (-5.8%) such that the phase switching T_E/T_I ratio decreased from a value of 2.74 ± 0.42 during normoxia to 2.27 ± 0.36 ($P < 0.01$) during differential ventilation.

Neither differential ventilation nor 100% oxygen breathing had any effect on dynamic passive elastance of the left or right lung. However, bilateral hypoxia did produce a significant increase ($P < 0.05$) in both left lung elastance (+24%) and right lung dynamic elastance (+21%).

SSBP: Effects of changing F_IO_2 in bilaterally vagotomized dogs

Bilateral vagotomy did not significantly alter the frequency response to acute hypoxia (Table 7, Table A5) which consisted of a decrease in T_{TOT}, T_E, T_I and the T_E/T_I phase-switching index. However, the V_T response to hypoxia in vagotomized dogs was opposite that which occurred in vagally intact dogs. The hypoxic ventilatory response of vagally intact dogs was associated with a small reduction in V_T. However, vagotomized dogs had a larger V_T (+15.5%, $P < 0.08$) during hypoxic ventilation compared to V_T during room air breathing (Figure 22). The increased breathing frequency and elevated tidal volume of bilaterally vagotomized dogs breathing 10% O_2 resulted in a 79% increase ($P < 0.05$) in minute ventilation.

Minute ventilation increased from 7.86 ± 0.88 to 10.01 ± 1.20 L/min ($P < 0.05$) during 100% O_2 breathing in vagotomized dogs. The ventilatory response was characterized by increases in left lung V_T (+33.2%, $P < 0.05$) and right lung V_T (+29.8%, $P < 0.05$) without a concomitant change in respiratory rate.

The ventilatory response to differential ventilation in BVX dogs was almost identical to the pattern observed during hyperoxia in BVX dogs. The minute volume response (+52.3%, $P < 0.01$) was characterized by increases in left V_T (+44.6%, $P < 0.05$) and right V_T (+50.7%, $P < 0.05$) without a change in respiratory rate. This pattern is exactly opposite that produced during differential ventilation of vagally intact dogs. Prior to vagotomy the increased

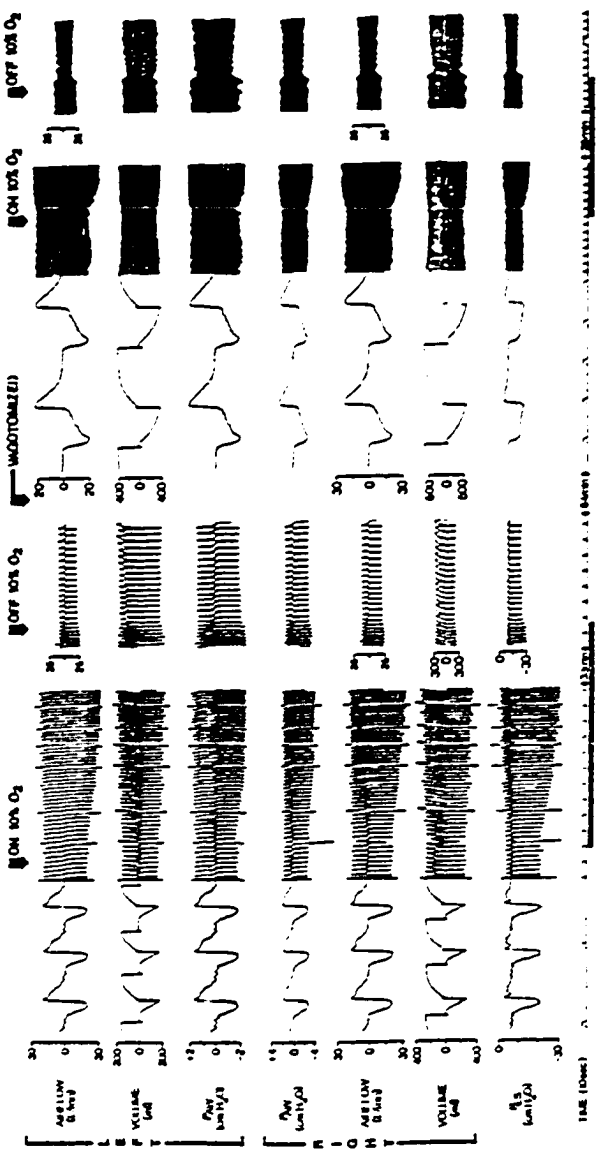
Table 7. Relative changes in steady-state respiratory cycle characteristics in bilaterally vagotomized dogs during hypoxic, hyperoxic and differential lung ventilation

Variable[a]	Hypoxia (n=9)	Hyperoxia (n=8)	Diff. Vent. (n=11)
T_I	-23.8[b]	-3.3	-14.5
T_E	-62.3*	-8.0	-7.9
T_{TOT}	-49.9	-6.5	-10.0
T_E/T_I	-45.3*	+6.3	+11.6
V_T^L	+17.0	+33.2*	+44.6*
V_T^R	+14.4	+29.8*	+50.7*
V_T	+15.5	+31.4*	+48.0*
V_T^L/T_I	+41.6*	+39.0	-63.6**
V_T^R/T_I	+40.6*	+38.0	+70.6**
$\dot{V}_E$	+78.6*	+27.4	+52.3**
$I\text{-}P_{AW}^L$	-3.0	+8.5	+37.2
$I\text{-}P_{AW}^R$	+7.4	+5.2	+4.3
$I\text{-}P_{AW}^L/T_I$	+10.8	+18.3	+55.9*
$I\text{-}P_{AW}^R/T_I$	+25.6	+10.9	+18.6
P_{ES}	+31.5	-5.9	+13.7
$I\text{-}\dot{F}^L$	+42.8	+16.3	+22.6
$I\text{-}\dot{F}^R$	+15.0	+26.6	+53.2
$E\text{-}\dot{F}^L$	+31.0	+32.3	+21.3
$E\text{-}\dot{F}^R$	+9.5	+14.9	+37.3
E_{dyn}^L	-15.8	-21.1	-3.5
E_{dyn}^R	-7.6	-16.7	-30.3*

[a]Refer to ABBREVIATIONS.
[b]Average percent difference from paired normoxic control values with statistical significance indicated by: *$P < 0.05$, **$P < 0.01$.

Figure 22. Immediate ventilatory responses to acute hypoxia with and without vagi intact.

Traces represent airflow, tidal volume, and airway pressure (P_{AW}) of the left and right lung and esophageal pressure (P_{ES}). Note the changes in calibrations and paper speed. The time which has elapsed between each panel is indicated on the time trace. Solid bars on time trace represent inhalation of 10% O_2. All other traces were obtained during room air breathing. The "on-off" frequency and tidal volume changes, when switching between room air and 10% O_2 breathing, are less apparent in the intact dog (Panel A and B) than in the vagotomized condition (Panel C and D). Expanded time traces in Panel A and C show more clearly the effects of vagotomy on T_I, T_E, frequency, and airflow pattern.



minute volume response to DV was due to frequency changes with tidal volume remaining constant.

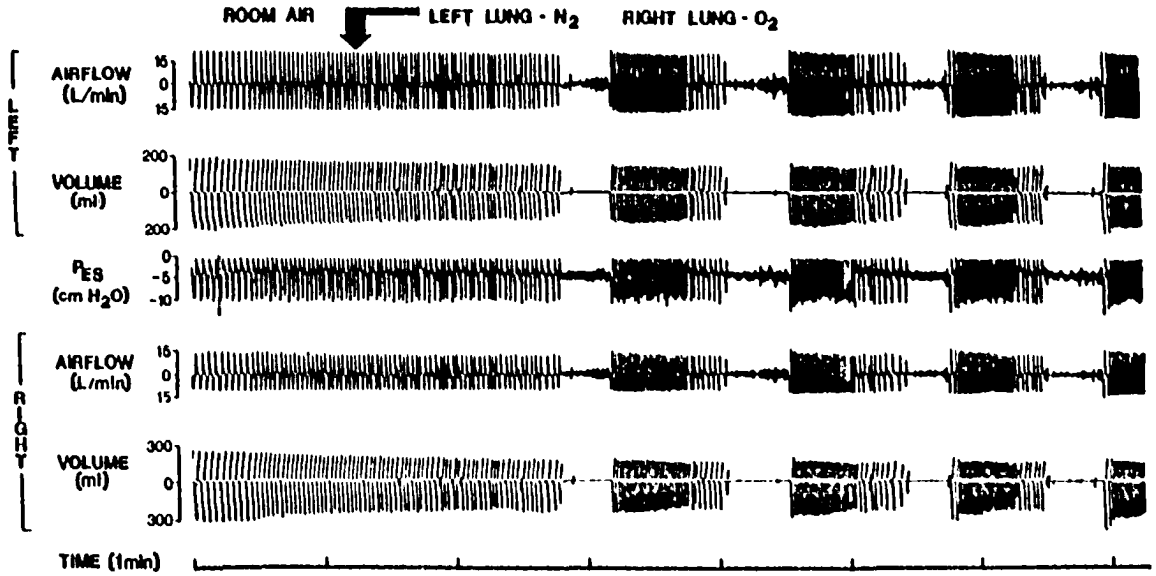
Vagally intact dogs maintained rather constant steady state patterns during inhalation of the test gases for 2-3 hours. However, three bilaterally vagotomized dogs became apneic at 12, 18 and 32 min of hypoxic exposure. One dog died because of ventricular fibrillation. The other two, when removed from the hypoxic stimulus and artificially ventilated, resumed spontaneously rhythmic breathing within 8 minutes. Four vagotomized dogs showed irregular breathing patterns within 2 minutes after initiating the differential ventilation (Figure 23). None of these dogs resumed normal rhythmic breathing when returned to room air. Data from these 7 vagotomized dogs with arrhythmic breathing responses were excluded from quantitative statistical evaluation. These apparently enhanced responses to chemical stimuli may represent increased sensitivity of central respiratory activity in the absence of vagal inhibition (Bartoli et al., 1973)

Reflex Respiratory Responses to Airway Occlusions

Reproducibility of reflex responses to the six types of airway occlusion maneuvers within a single animal was determined by analyzing the variance among three repetitions of the same maneuver under every experimental condition. Less than 10% error among the three repetitions was acceptable.

Figure 23. Arrhythmic respiratory pattern associated with differential ventilation in a bilaterally vagotomized dog.

Traces shown are airflow and tidal volume of the left and right lung, esophageal pressure (P_{ES}) and time scale. Differential ventilation was initiated at the arrow. An unusual breathing rhythm developed within 2 min. The cyclic pattern consisted of apneic periods (ca. 20 sec) interposed between periods of apparently normal breathing (ca. 40 sec). The respiratory rate during the 10-15 sec period preceding the apneic episodes showed progressive slowing.


ROOM AIR
LEFT LUNG - N_2
RIGHT LUNG - O_2
LEFT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
200
0
200
P_{ES} (cm H_2O)
0
-5
-10
RIGHT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
300
0
300
TIME (1min)

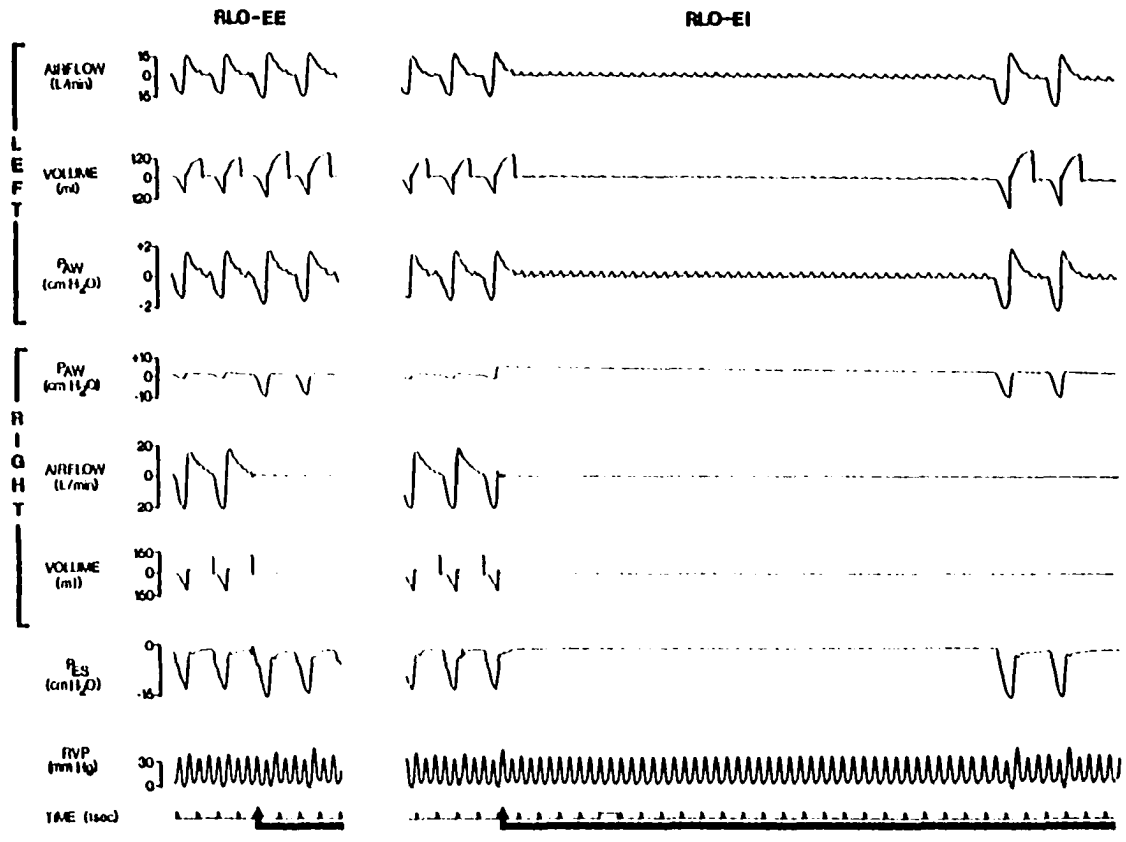
To be certain that repeated testing and/or duration of anesthesia were not responsible for altering the responses; preliminary studies were performed (four dogs) during which the entire sequence of occlusions was consecutively performed four times during a nine hour period. No consistent enhancement or attenuation of the responses was observed outside the limits of variation considered acceptable. Therefore, alterations in the reflex respiratory responses to airway occlusions could be attributed to changes in inspired oxygen and/or vagal integrity as described below.

Occluded breath

Occlusions set at end-expiration, whether unilateral or bilateral, did not affect the breath during which the airways were restricted for any of the gases tested (Figure 24). However, occluding one or both airway(s) at peak inspiration caused an abrupt termination of the inspiratory effort and an apneic period of variable duration (T_A). The apnea was held in the expiratory position as evidenced by a positive pressure plateau in the airway of the occluded lung(s). Receptive relaxation and gas absorption during the apneic period resulted in a small reduction in airway pressure of the occluded lung(s). Only those occlusions for which airway pressure fell by less than 10% during the apneic period were accepted for statistical analysis. As described in METHODS, a larger decrease (greater than 10%) in airway occlusion pressure was

Figure 24. Records comparing the effects of end-expiratory and end-inspiratory airway occlusion on the breath during which the airways were restricted.

Traces include airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung, esophageal pressure (P_{ES}) and right ventricular pressure (RVP). Onset (arrow) and duration (heavy black line) of occlusion are indicated on the time trace. Inspiration produces a downward deflection for respiratory parameter signals. Occlusion of the right lung at end expiration (RLO-EE) has no affect on the occluded breath as seen by the continuous respiratory cycling. Occlusion of the same lung at end-inspiration (RLO-EI) interrupts the normal respiratory pattern by prolonging the occluded breath, i.e., producing apnea.


RLO-EE
RLO-EI
LEFT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cmH_2O)
RIGHT
P_{AW} (cmH_2O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cmH_2O)
RVP (mmHg)
TIME (sec)

indicative of incomplete separations of the two lungs or of a leak in the external apparatus.

An increase in the apneic pressure plateau of the left hypoxic lung was often observed during differential lung ventilation. This may perhaps be accounted for by a reversed oxygen gradient ($P_{\bar{v}}O_2$ - $ETpO_2$ is positive) with subsequent oxygen elimination measured in the left hypoxic lung. During differential ventilation of intact dogs, end-tidal pO_2 of the hypoxic left lung averaged 34.5 ± 13.9 mm Hg with a simultaneously measured mixed venous pO_2 of 57.0 ± 5.7 mm Hg.

A progressive increase in the apneic pressure plateau was also apparent (Figure 25) in one dog which became hyperthermic (body temp. = 106°F). This might be explained by the effect of thermal gas expansion, i.e., Boyles' Law, or by activation of normally quiescent expiratory muscles. Although this dog had to be eliminated from study, observations were made which implicate a facilitory influence of body temperature in respiratory pattern control and mechanical lung reflexes.

Airway occlusion (left, right and bilateral) at peak inspiration of vagally intact dogs produced significant prolongation of the occluded cycle during inhalation of all four test gases (Table 8). With the exception of differentially ventilated dogs, the apneic period of BLO-EI was greater than RLO-EI which was greater than LLO-EI. Summation of the apneic prolongation produced by unilateral occlusions was very close to that produced by

Figure 25. Effects of elevated body temperature on the reflex respiratory response to bilateral airway occlusion set at peak inspiration.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung and esophageal pressure (P_{ES}). Inspiration produces a downward deflection on all traces. Onset (arrow) and duration (heavy black line) of occlusion are indicated on the time trace. Unlike in normal dogs (cf. Figure 27), the first breath is characterized by short gasping inspiratory efforts and very prolonged expiratory durations during which airway pressure progressively increases. Furthermore, hyperthermia appears to have an inspiratory facilitating effect and thereby eliminates the apneic response to these maneuvers.

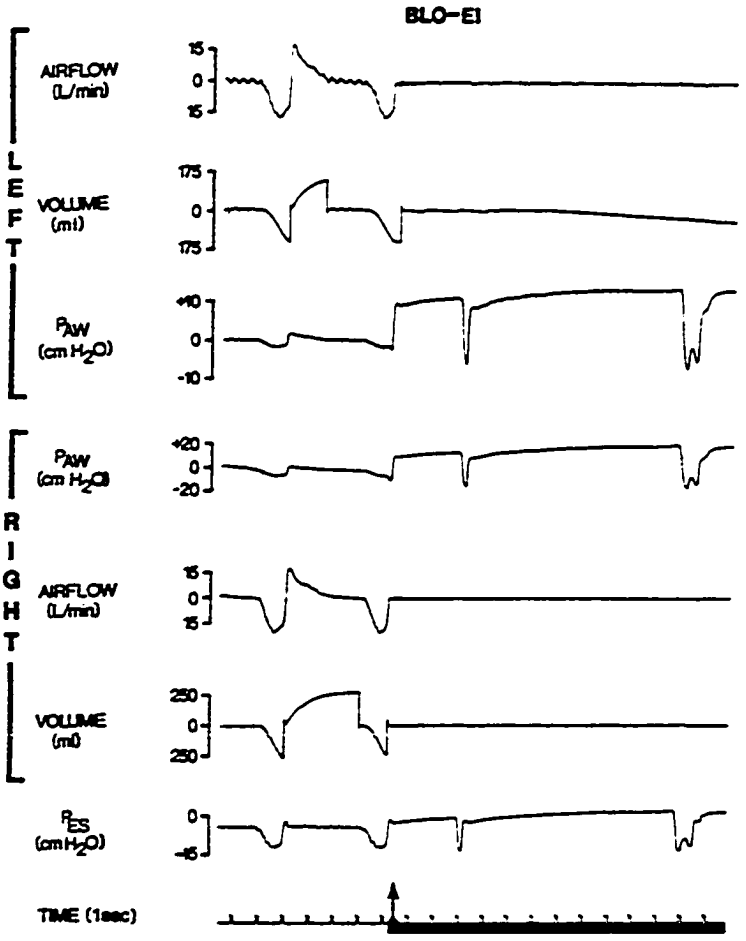

BLO-E1
LEFT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
175
0
175
P_{AW} ($cm H_2O$)
+10
0
-10
RIGHT
P_{AW} ($cm H_2O$)
+20
0
-20
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
250
0
250
P_{ES} ($cm H_2O$)
0
-15
TIME (1sec)

Table 8. Absolute prolongation of respiratory cycle duration caused by occluding the airway(s) at peak inspiration

	TOTAL CYCLE DURATION (sec)		
	RLO-EI	LLO-EI	BLO-EI
I-Room Air	5.09 ± 1.36***[a]	3.25 ± 0.69***	8.52 ± 1.36***
I-Hypoxia	3.93 ± 1.89*	0.99 ± 0.38*	5.37 ± 1.71**
I-Hyperoxia	9.30 ± 2.18***	6.69 ± 1.64***	19.17 ± 3.22***
I-Diff. Vent.	14.88 ± 8.49[b]	19.61 ± 9.94[c]	20.00 ± 6.55**
LVX-Room Air	0.59 ± 0.63	-0.89 ± 0.63	2.04 ± 0.60**
RVX-Room Air	-0.47 ± 0.64	8.66 ± 2.96*	9.52 ± 4.28
BVX-Room Air	0.21 ± 0.05	0.10 ± 0.04	-0.41 ± 0.18
BVX-Hypoxia	0.03 ± 0.09	0.04 ± 0.15	-0.12 ± 0.02*
BVX-Hyperoxia	-0.04 ± 0.06	0.10 ± 0.21	0.35 ± 0.29
BVX-Diff. Vent.	0.0 ± 0.12	-0.24 ± 0.18	-0.64 ± 0.57

[a]Values represent Mean ± SD and are given in units of time (sec). Significant prolongation of cycle duration due to occlusion is represented as: *P < 0.05, **P < 0.01, ***P < 0.001.

[b]P = 0.1052.

[c]P= 0.0742.

bilateral occlusion during normoxia, hypoxia and hyperoxia, but significantly less during differential ventilation.

There was considerable variation in the apneic durations produced by unilateral occlusions in DV dogs with intact vagi. As indicated in Table 8, T_{TOT} prolongation due to right lung occlusion (14.88 ± 8.49 sec, P = 0.1052) and left lung occlusion (19.61 ± 9.94 sec, P = 0.0742) did approach statistical significance.

When occlusion-induced apnea is expressed in units of time it appears as if the Hering-Breuer inspiratory-inhibiting reflex is stronger in hyperoxic dogs and weaker in hypoxic dogs when compared to normoxic control responses (Figures 26 and 27). In other words, T_{TOT} prolongation due to left, right or bilateral airway occlusion at end-inspiration can be expressed in order of increasing magnitude as: hypoxia < normoxia < hyperoxia < differential ventilation.

The apneic response, i.e., inspiratory-inhibition, was eliminated by bilateral vagotomy. In fact, BLO-EI actually shortened (-0.13 ± 0.02 sec, P < 0.05) the occluded cycle of vagotomized dogs during room air, hypoxic and differential ventilation. Severing one vagi not only eliminated the apneic response elicited by occlusion of the ipsilateral lung, but actually shortened the occluded cycle in many cases. Unilateral vagotomy did not eliminate the apneic response to EI occlusion of the contralateral lung.

These results are not entirely indicative of pulmonary stretch receptor adaptation and may be somewhat misleading. The present

Figure 26. Augmentation of inspiratory-inhibition elicited by right lung airway occlusion during inhalation of 100% oxygen.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung, esophageal pressure (P_{ES}) and right ventricular pressure (RVP). Inspiration produces a downward deflection for all respiratory signals. The right lung has been occluded at peak inspiration of the third breath in each panel. The apneic response to RLO-EI is much longer during 100% O_2 breathing (T_A = 24.5 sec) than during room air breathing (T_A = 8.5 sec).

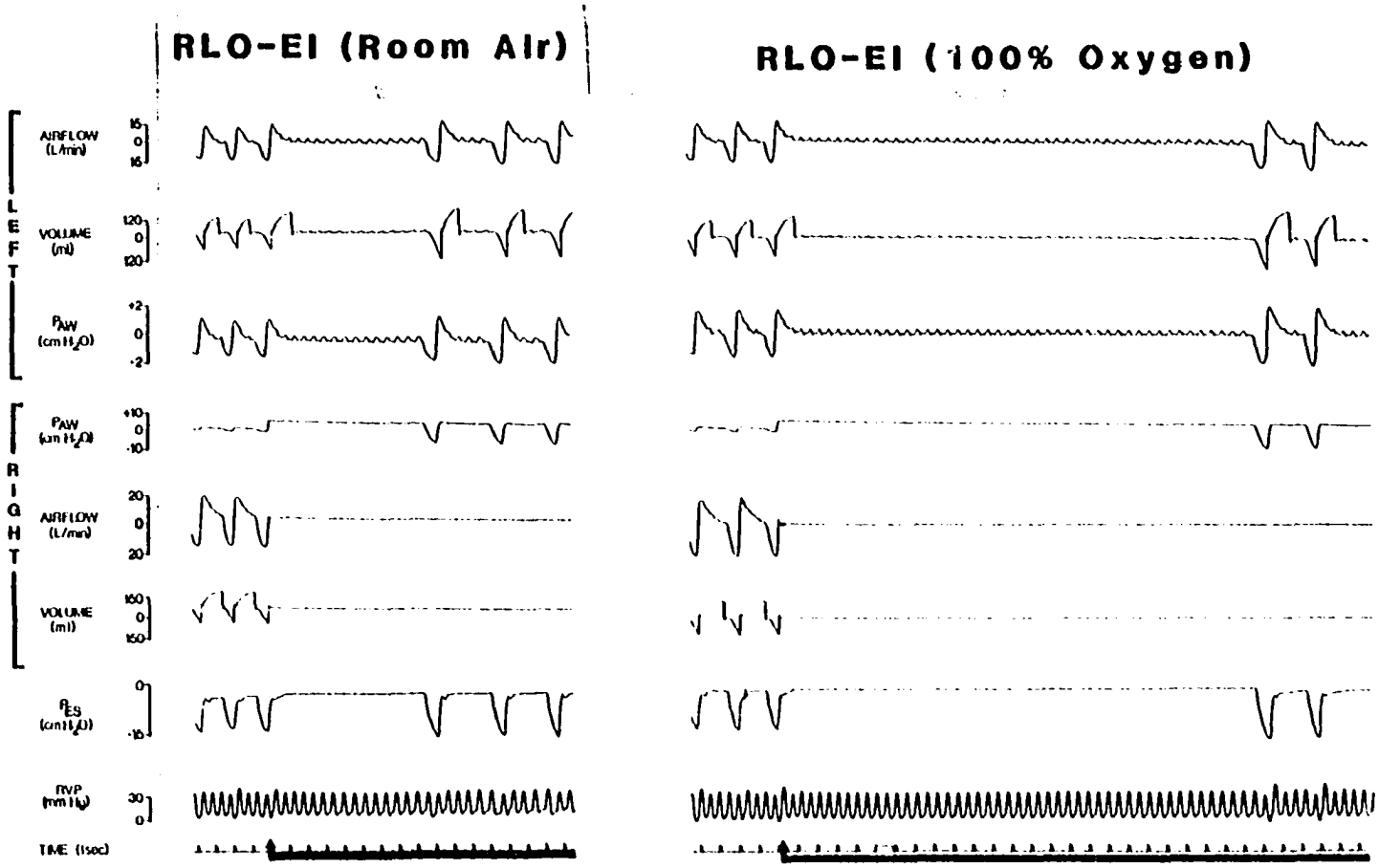
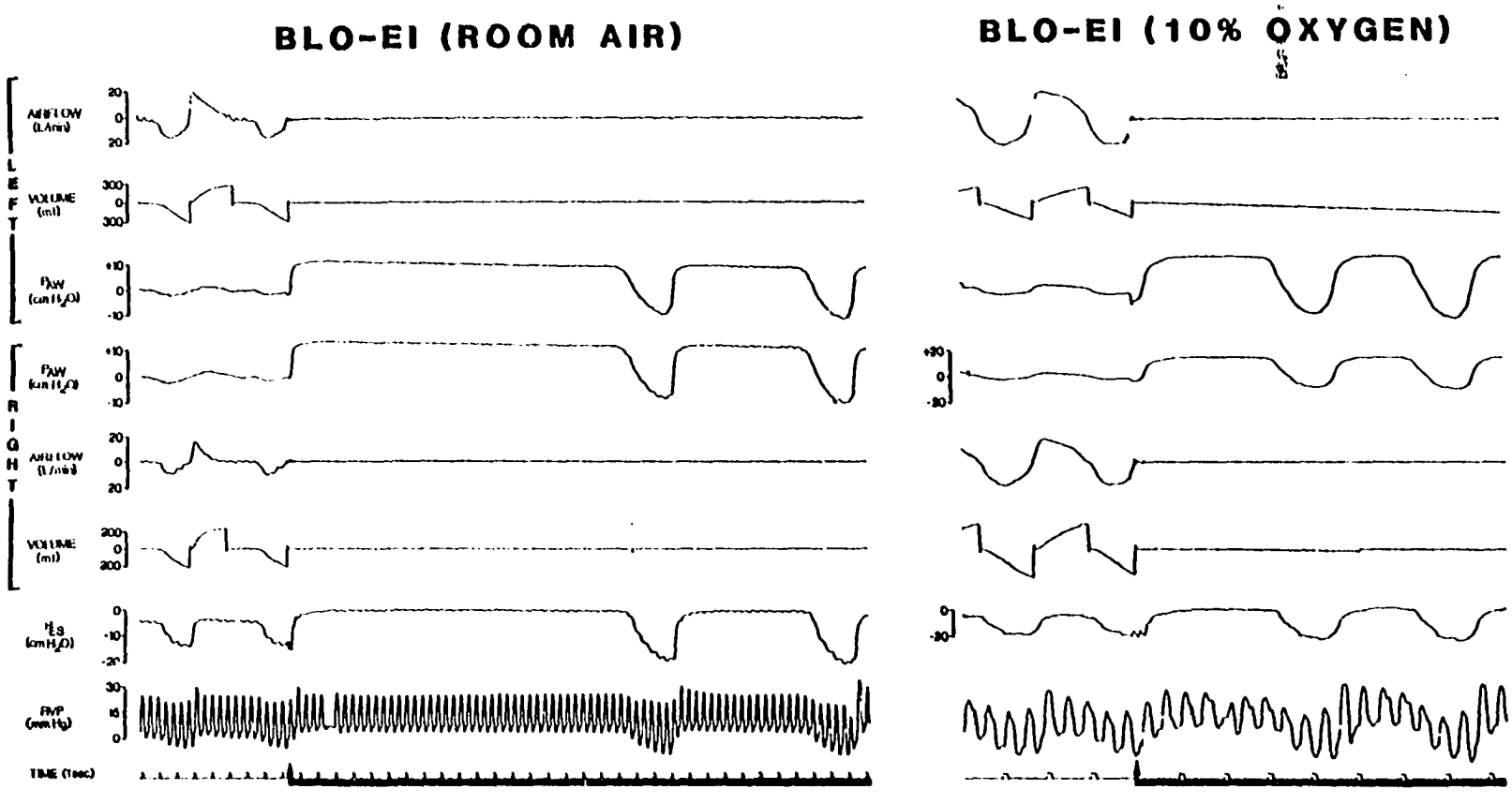

RLO-EI (Room Air)
RLO-EI (100% Oxygen)
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} ($cm H_2O$)
P_{AW} ($cm H_2O$)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} ($cm H_2O$)
RVP ($mm Hg$)
TIME (1sec)

Figure 27. Attenuation of the Hering-Breuer apneic response during 10% oxygen breathing.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung, esophageal pressure (P_{ES}) and right ventricular pressure (RVP). Inspiration produces a downward deflection for all respiratory signals. Onset (arrow) and duration of occlusion (heavy black line) are superimposed on the time trace. Note differences in P_{AW} and P_{ES} calibrations as well as time scale during hypoxia. Bilateral lung occlusion is set at end-inspiration of the second breath in both panels. The apneic response to BLO-EI is significantly longer during room air breathing (T_A = 19 sec) than 10% O_2 breathing (T_A = 3.2 sec).


BLO-EI (ROOM AIR)
BLO-EI (10% OXYGEN)
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cm H_2O)
RVP (mm Hg)
TIME (sec)

studies indicate that the apneic duration is 'partially' determined by humoral mechanisms, i.e., the chemical drive to breathe existing at the time of airway restriction. During room air, 10% O_2 and 100% O_2 breathing, the apneic duration appears to be related to the level of minute ventilation and steady state arterial oxygen tension present at the time of occlusion (Figure 28). Discordant results were obtained during differential ventilation. The apneic durations for all three EI maneuvers during DV were longer than those measured at comparable levels of paO_2 and $\dot{V}_E$ produced by room air breathing. Furthermore, the variation among right, left and bilateral EI responses during DV was markedly reduced.

In order to eliminate the dependency of apneic duration on ventilatory level the data were normalized. The reflex apneic response to airway occlusion at peak inspiration (RLO-EI, LLO-EI and BLO-EI) was quantitatively assessed as the ratio T_{TOT}^{O}/T_{TOT} where T_{TOT}^{O} is duration of the occluded breath and T_{TOT} is duration of the preceding control breath (Table 9). Prolongation of the occluded breath was more pronounced for right lung occlusion than left lung occlusion (Figure 29) and significantly ($P < 0.05$) greater for bilateral occlusion during normoxia, hypoxia and hyperoxia in dogs with vagi intact. However, during differential ventilation, occlusion of the hypoxic left lung resulted in a longer apneic period than occlusion of the hyperoxic right lung (T_{TOT}^{O}/T_{TOT} = 6.10 ± 1.20 and 4.87 ± 0.43, respectively). Furthermore, bilateral

Figure 28. Effects of minute ventilation and arterial oxygen tension on the apneic response to end-inspiratory occlusion of one or both airway(s).

Apneic duration is measured from the time of airway occlusion at end-inspiration to the beginning of the first inspiratory effort against occlusion. Solid lines are aproximations drawn through points which represent mean values obtained from 3 dogs exposed to all 4 test gases (symbols). Two relationships are apparent in these graphs. Firstly, the apneic duration generally lengthened as ventilation decreased with concomitant increases in F_IO_2 and thus paO_2. Secondly, at any level of arterial oxygen, the apnea was most prolonged for bilateral occlusions, less for right lung occlusions and least for left lung occlusions. Neither of these relationships apply during differential ventilation when F_IO_2 is changed without altering paO_2.

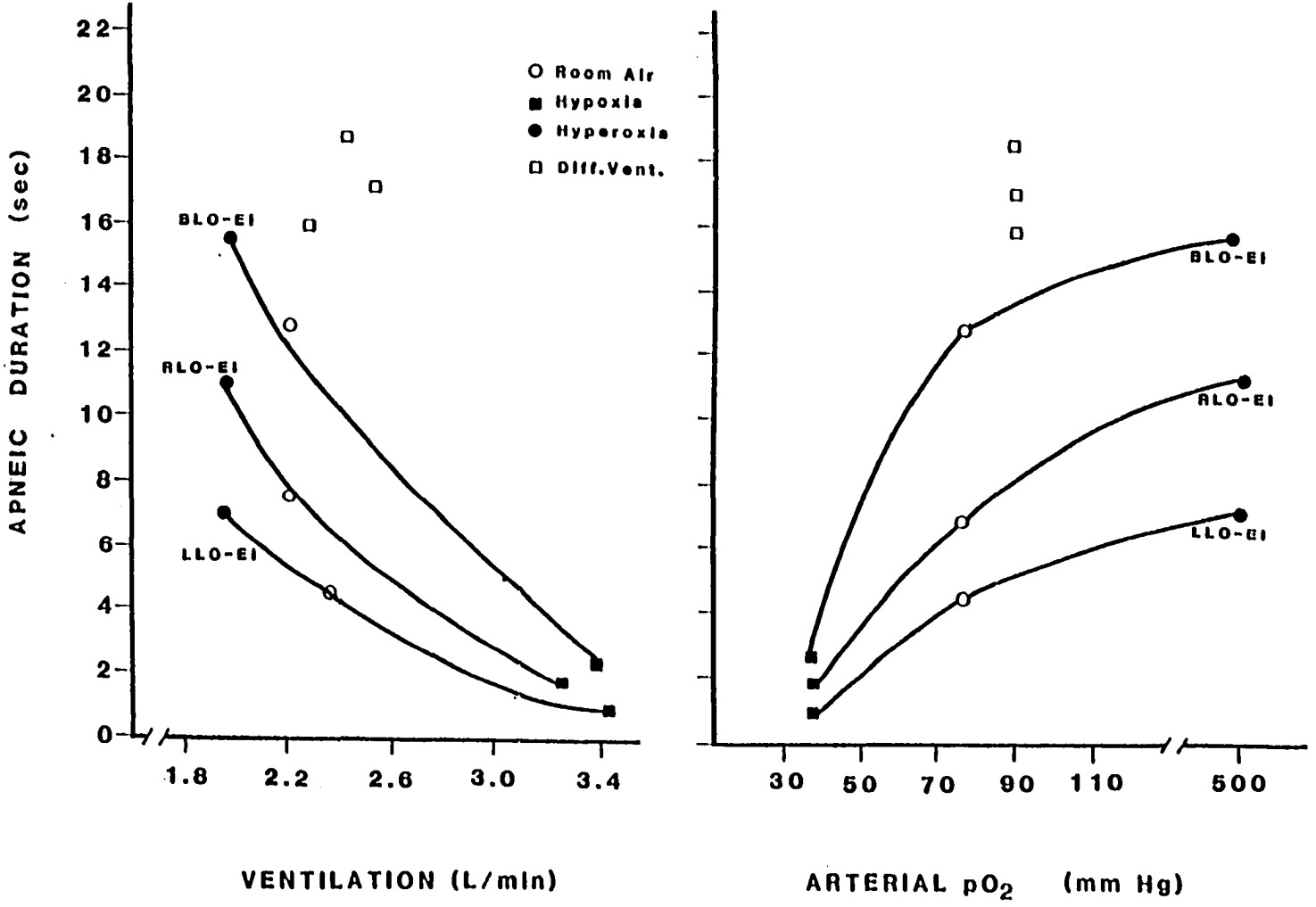

APNEIC DURATION (sec)
22
20
18
16
14
12
10
8
6
4
2
0
O Room Air
■ Hypoxia
● Hyperoxia
□ Diff.Vent.
BLO-EI
RLO-EI
LLO-EI
1.8
2.2
2.6
3.0
3.4
VENTILATION (L/min)
30
50
70
90
110
500
ARTERIAL pO_2 (mm Hg)

Table 9. Strength of inspiratory-inhibitory reflex expressed as a ratio between the duration of the occluded breath and the duration of the preceding control breath

	T_{TOT}^{o}/T_{TOT}^{a}		
	RLO-EI	LLO-EI	BLO-EI
INTACT			
Room Air	1.99 ± 0.07***	1.63 ± 0.08***	2.66 ± 0.60***
Hypoxia	2.79 ± 0.12*	1.42 ± 0.10*	3.45 ± 0 81**
Hyperoxia	2.74 ± 0.63***	2.25 ± 0.41***	4.58 ± 1.02***
Diff. Vent.	4.87 ± 0.43[b]	6.10 ± 1.20[c]	6.21 ± 1.22**
LEFT VAGOTOMY			
Room Air	1.10 ± 0.20	0.85 ± 0.17	1.35 ± 0.09**
RIGHT VAGOTOMY			
Room Air	0.87 ± 0.09	3.09 ± 0.12*	3.30 ± 0.92*
BILATERAL VAGOTOMY			
Room Air	1.03 ± 0.02	1.02 ± 0.03	0.93 ± 0.06
Hypoxia	1.01 ± 0.078	1.01 ± 0.11	0.96 ± 0.03*
Hyperoxia	0.99 ± 0.04	1.02 ± 0.16	1.06 ± 0.05
Diff. Vent.	1.01 ± 0.07	0.96 ± 0.09	0.89 ± 0.02

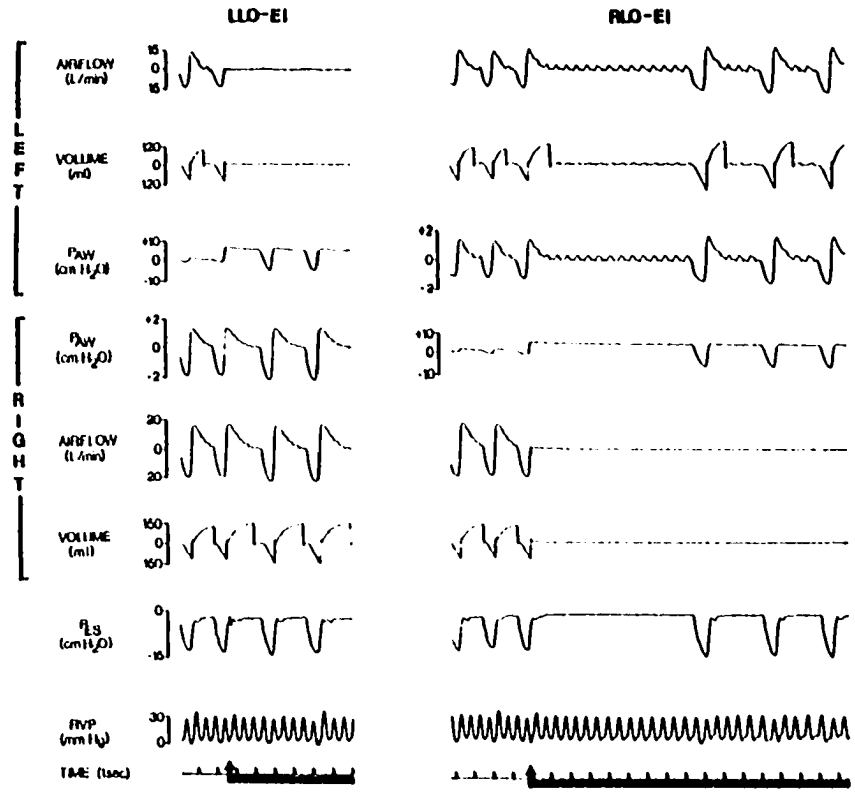
[a]Values represent Mean ± SD of the ratio T_{TOT}^{o}/T_{TOT} and indicate reflex strength of the Hering-Breuer inspiratory-inhibiting activity. Ratios which are significantly different from 1.0 are indicated by: *P < 0.05, **P < 0.01, ***P < 0.001. A significant ratio implies the presence of reflex alterations in respiratory pattern control.

[b]P = 0.1052.

[c]P = 0.0742.

Figure 29. Hering-Breuer inspiratory inhibition produced by unilateral airway occlusion at peak inspiration is more pronounced for right lung occlusion than for left lung maneuvers.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung, esophageal pressure (P_{ES}) and right ventricular pressure (RVP). Inspiration produces downward deflections on respiratory recordings. Onset (arrow) and duration of occlusion (heavy black line) are indicated on the time trace. One or two normal breaths precede occlusion at end-inspiration of the left lung (LLO-EI) and right lung (RLO-EI). Such maneuvers produce an apneic period of ca. 2 sec for LLO-EI and ca. 8 sec for RLO-EI. These values indicate strength of the reflex response to sustained vagal volume feedback.


LLO-EI
RLO-EI
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} ($cm H_2O$)
P_{AW} ($cm H_2O$)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} ($cm H_2O$)
FVP ($mm H_g$)
TIME (sec)

occlusion under these conditions was not significantly different from unilateral left lung occlusion at peak inspiration.

After correcting for minute ventilation dependency, the order of reflex strength generally remained as before: hypoxia < normoxia < hyperoxia with differential ventilation appearing to be strongest, although the variation among animals was considerable. It is noteworthy that the apneic response to RLO-EI was longer during hypoxic, hyperoxic and differential lung ventilation than that present during room air breathing.

The inspiratory-inhibitory reflexes whether induced by unilateral or bilateral occlusions and regardless of inspired oxygen tension were abolished by bilateral vagotomy, i.e. T_{TOT}^{o}/T_{TOT} was not significantly different from 1.0.

The results of unilateral vagotomy are somewhat consistent with the idea of ipsilateral vagal innervation. The reflex apneic responses to left lung occlusion with left vagotomy and right lung occlusion with right vagotomy were abolished. In fact, the occluded cycle was actually shorter (increased instantaneous breathing frequency) than the preceding control cycle when the lung ipsilateral to the vagotomy was restricted. This might be explained by afferent activity from the contralateral lung whose vagal innervation was still intact. Unilateral occlusion at peak inspiration of the lung contralateral to the vagotomy had a strength ratio greater than one. It should be noted that left lung occlusion apnea with the right vagus cut was significantly ($P < 0.05$) longer

than the apneic response to LLO-EI with vagi intact (T_{TOT}^{o}/T_{TOT} 3.09 ± 0.12 and 1.63 ± 0.08 respectively). For bilateral occlusions, reflex apnea was generally longer in the right vagotomized than the left vagotomized animals (T_{TOT}^{o}/T_{TOT} = 3.30 ± 0.92 and 1.35 ± 0.09 respectively).

First effort breaths

Unilateral and bilateral airway occlusions in 38 vagally intact dogs whether set at end-expiration or end-inspiration significantly ($P < 0.05$) prolonged T_I of the first effort (Figure 30, Table A-6), the effect being slightly more pronounced for occlusions set at peak inspiration. The change in T_I (+0.10 to +0.30 sec) was similar for left and right unilateral occlusions, but significantly ($P < 0.05$) less than T_I prolongation (+0.53 to +0.81 sec) of first effort breaths against bilateral occlusions. Quantitatively similar results were obtained during hypoxic, hyperoxic and differential lung ventilation. However, since T_I of control breaths during hypoxia (0.84 ± 0.06 sec) was significantly shorter than T_I of control breaths during room air ventilation (1.20 ± 0.11 sec), the relative prolongation of first inspiratory efforts was actually greatest during ventilation with 10% oxygen.

During left, right and bilateral airway occlusions, expiratory duration of the first effort was generally prolonged (Figure 31, Table A-7). The magnitude of prolongation varied considerably among the four gases tested. However, for a given gas, lengthening of T_E

Figure 30. Effects of inspired oxygen tension on reflex prolongation of inspiratory time during first effort breaths against specific airway occlusions.

The change in inspiratory time (T_I) plotted on the vertical axis represents the difference between T_I of the first respiratory effort against airway occlusion and T_I of the preceding control breathing. The specific type of airway occlusion maneuver is indicated on the horizontal axis (refer to ABBREVIATIONS). Each maneuver was evaluated during inhalation of 4 different test gases which are represented by the shaded bars. A significant change in T_I is indicated by: *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.

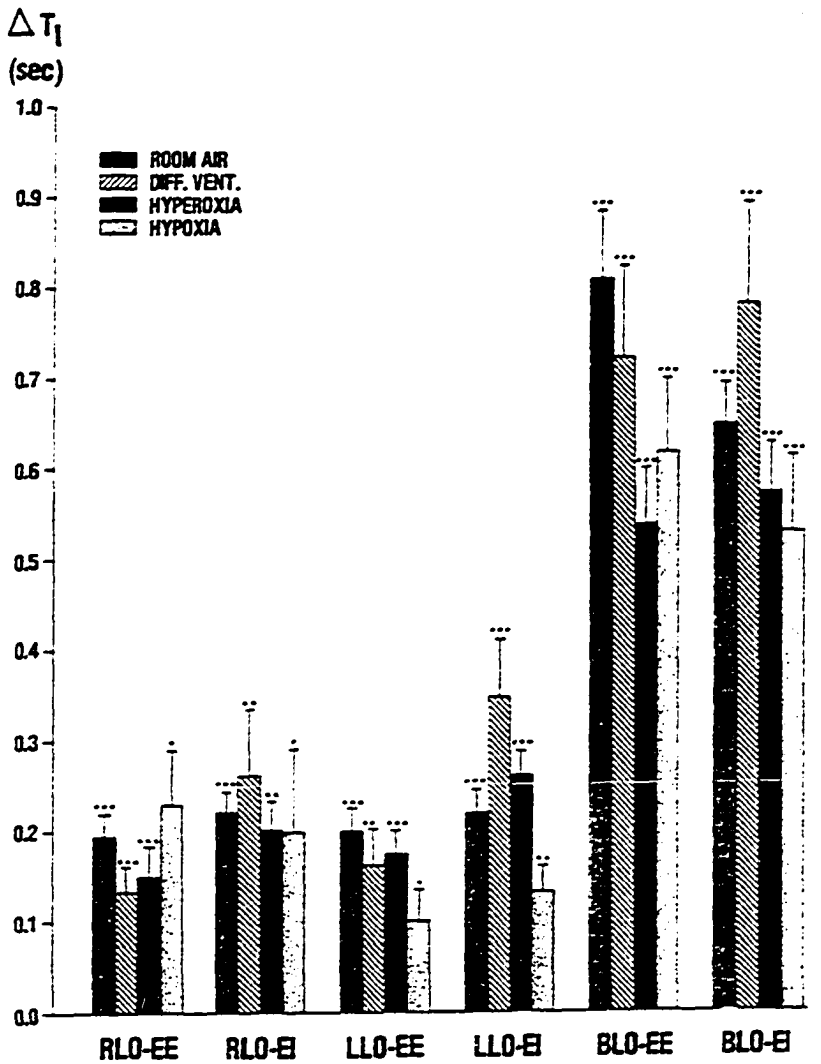
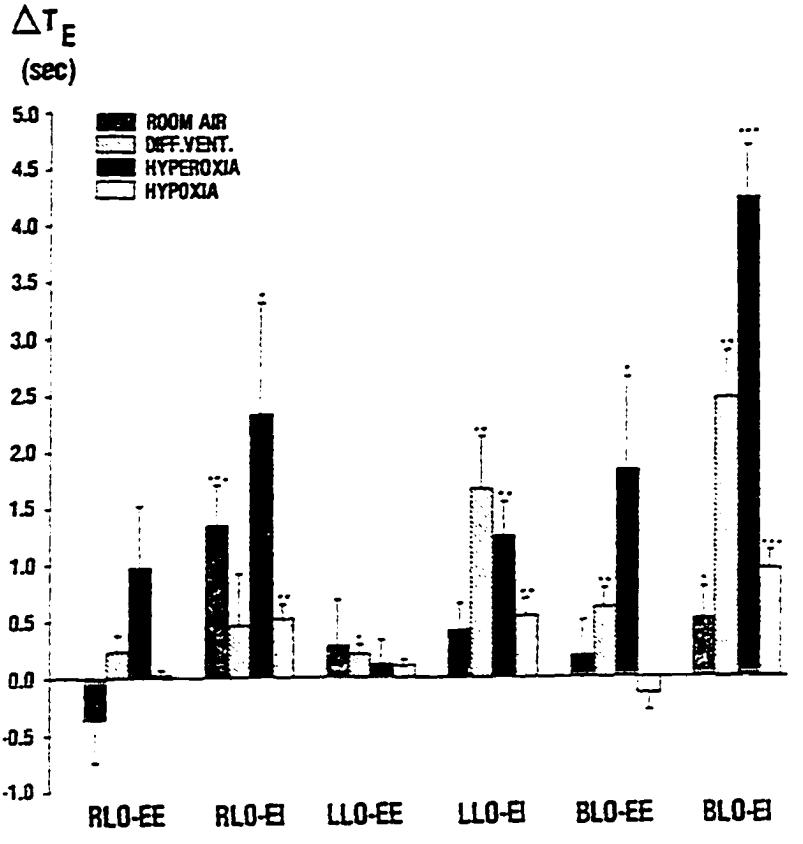

ΔTI
(sec)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
ROOM AIR
DIFF. VENT.
HYPEROXIA
HYPOXIA
RLO-EE
RLO-EI
LLO-EE
LLO-EI
BLO-EE
BLO-EI

Figure 31. Effects of inspired oxygen tension on reflex prolongation of expiratory time during first effort breaths against specific airway occlusions.

The difference between expiratory duration of the first respiratory effort against airway occlusion and expiratory duration of the preceding unloaded control breath is represented on the vertical axis as ΔT_E. The specific type of occlusion maneuver is shown along the horizontal axis (refer to ABBREVIATIONS). Shaded bars represent the test gas condition during occlusion maneuvers. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ designate a significant ΔT_E due to occlusion.


ΔT E
(sec)
ROOM AIR
DIFF.VENT.
HYPEROXIA
HYPOXIA
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
RLO-EE
RLO-EI
LLO-EE
LLO-EI
BLO-EE
BLO-EI

was significantly ($P < 0.05$) greater for occlusions set at EI as compared to first efforts against EE occlusions. This was true for right, left and bilateral occlusion maneuvers.

Inspiratory duration of first effort breaths against unilateral airway occlusion was not significantly different from T_I of the preceding control breath during room air breathing after bilateral vagotomy. However, BVX did not eliminate T_I prolongation of first efforts against bilateral airway occlusions. This was generally true of occlusions set during hypoxic, hyperoxic and differential ventilation in dogs with BVX (Figure 32, Table A6). Unilateral vagotomy abolished the change in T_I during first efforts against occlusion of the ipsilateral lung. However, bilateral airway occlusions still produced significant prolongation of T_I with only one vagi intact.

Bilateral vagotomy eliminated the reflex prolongation of T_E during first effort breaths against all six occlusion maneuvers during inhalation of room air, 10% O_2, 100% O_2 and the 100% O_2:100% N_2 supplied unilaterally (Figure 33, Appendix A7). Right lung occlusions produced significant lengthening of T_E while left lung maneuvers produced significant shortening of T_E in LVX dogs. First effort breaths in RVX dogs were significantly prolonged during LLO-EI and BLO-EI maneuvers.

The overall results of these changes in inspiratory and expiratory durations during specific airway occlusions are summarized in Table 10 (refer also to Table A8). Ratios of first

Figure 32. Effects of vagotomy on reflex prolongation of respiratory time during first effort breaths against specific airway occlusions.

Change in inspiratory time (ΔT_I) represents the difference between T_I of the first respiratory effort against occlusion and T_I of the preceding unloaded control breath. The type of airway occlusion maneuver is indicated on the horizontal axis (refer to ABBREVIATIONS). Maneuvers were performed in intact and vagotomized conditions as represented by the shaded bars.

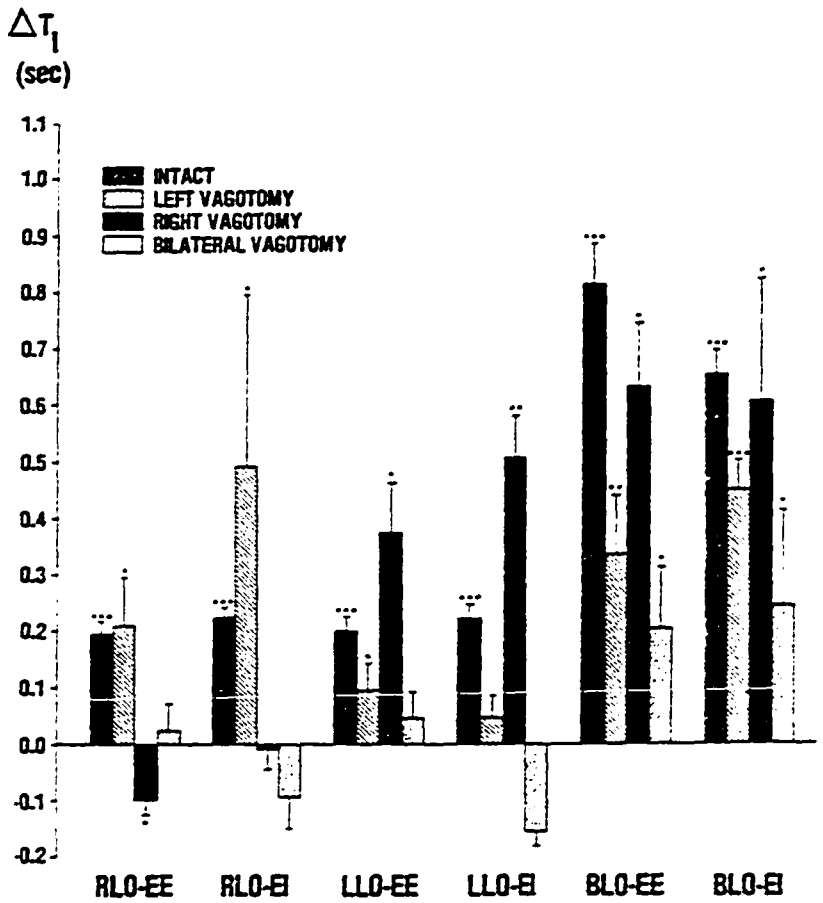

ΔT1
(sec)
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
INTACT
LEFT VAGOTOMY
RIGHT VAGOTOMY
BILATERAL VAGOTOMY
RLO-EE
RLO-EI
LLO-EE
LLO-EI
BLO-EE
BLO-EI

Figure 33. Effects of vagotomy on reflex prolongation of expiratory time during first effort breaths against specific airway occlusions.

Change in expiratory duration (ΔT_E) represents the difference between T_E of the first respiratory effort against airway occlusion and T_E of the preceding unloaded control breath. The type of airway occlusion is indicated on the horizontal axis (refer to ABBREVIATIONS). Maneuvers were performed in intact and vagotomized conditions as represented by the shaded bars.

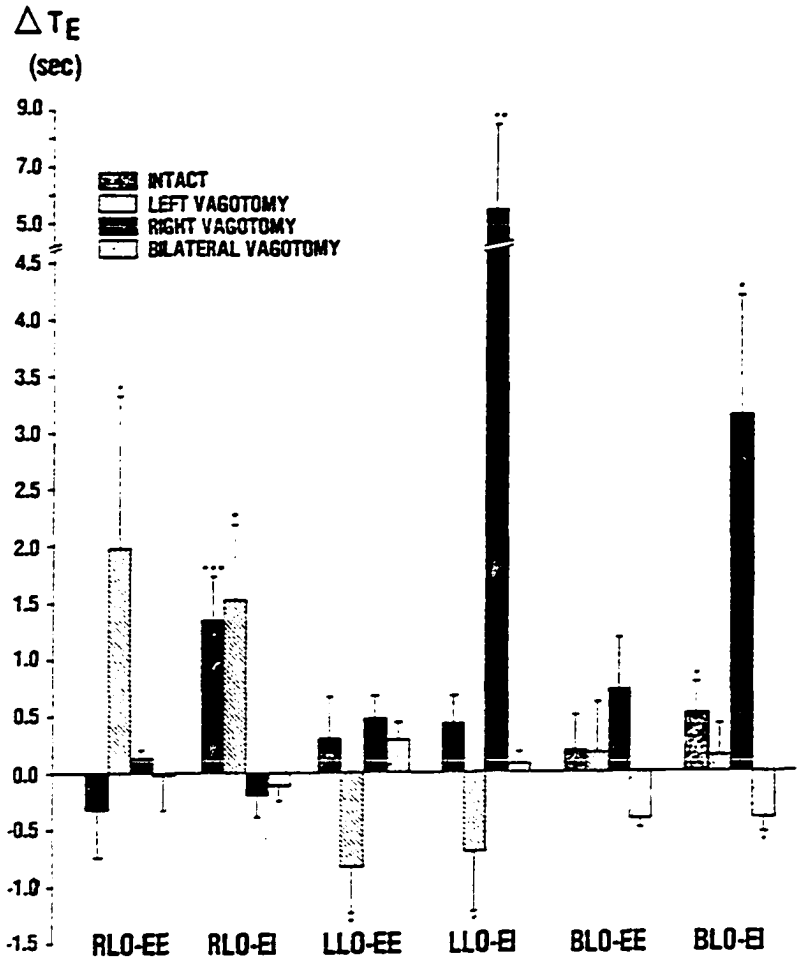

ΔTE
(sec)
9.0
7.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
INTACT
LEFT VAGOTOMY
RIGHT VAGOTOMY
BILATERAL VAGOTOMY
RLO-EE
RLO-⊟
LLO-EE
LLO-⊟
BLO-EE
BLO-⊟

Table 10. Occlusion induced changes in instantaneous breathing frequency and phase-switching index

Experimental Condition and Occlusion Type[a]	T_{TOT}^{-1}/T_{TOT}	T_E^{-1}/T_I^{-1}	T_E/T_I
Room Air-Intact			3.26 ± 0.08
RLO-EE	1.03 ± 0.09[b]	2.93 ± 0.19*	
RLO-EI	1.32 ± 0.03***	3.58 ± 0.21*	
LLO-EE	1.08 ± 0.06	3.25 ± 0.25*	
LLO-EI	1.12 ± 0.02**	3.02 ± 0.14*	
BLO-EE	1.21 ± 0.14	1.97 ± 0.11***	
BLO-EI	1.24 ± 0.11	2.40 ± 0.12**	
Hypoxia-Intact			1.65 ± 0.11
RLO-EE	1.10 ± 0.03*	1.28 ± 0.19**	
RLO-EI	1.35 ± 0.09*	1.90 ± 0.23*	
LLO-EE	1.08 ± 0.04**	1.59 ± 0.16	
LLO-EI	1.33 ± 0.16**	1.92 ± 0.22*	
BLO-EE	1.20 ± 0.03**	0.89 ± 0.14*	
BLO-EI	1.67 ± 0.20***	1.70 ± 0.23	
Hyperoxia-Intact			3.83 ± 0.28
RLO-EE	1.24 ± 0.06*	3.57 ± 0.55*	
RLO-EI	1.53 ± 0.99*	4.61 ± 0.69**	
LLO-EE	1.06 ± 0.10	3.07 ± 0.51*	
LLO-EI	1.32 ± 0.10***	3.44 ± 0.38*	
BLO-EE	1.58 ± 0.26*	2.78 ± 0.56**	
BLO-EI	2.13 ± 0.29***	4.76 ± 0.49***	
Diff. Vent.-Intact			2.27 ± 0.36
RLO-EE	1.11 ± 0.03*	1.96 ± 0.13**	
RLO-EI	1.20 ± 0.11	2.32 ± 0.18	
RLO-EE	1.20 ± 0.04*	1.92 ± 0.09**	

	LLO-EI	1.52 ± 0.13***	2.99 ± 0.19**	
	BLO-EE	1.38 ± 0.19***	1.54 ± 0.09***	
	BLO-EI	1.83 ± 0.31***	3.04 ± 0.36***	
Room Air-LVX				3.14 ± 0.34
	RLO-EE	1.44 ± 0.16*	3.71 ± 0.60*	
	RLO-EI	1.38 ± 0.09**	3.23 ± 0.49	
	LLO-EE	0.88 ± 0.21	2.54 ± 0.41***	
	LLO-EI	0.89 ± 0.10	2.62 ± 0.33**	
	BLO-EE	1.10 ± 0.05	2.43 ± 0.35***	
	BLO-EI	1.10 ± 0.01*	2.37 ± 0.23***	
Room Air-RVX				2.40 ± 0.22
	RLO-EE	1.01 ± 0.02	1.38 ± 0.03***	
	RLO-EI	0.94 ± 0.09	1.34 ± 0.03***	
	LLO-EE	1.27 ± 0.11*	1.32 ± 0.03***	
	LLO-EI	2.78 ± 0.42**	3.94 ± 1.43***	
	BLO-EE	1.36 ± 0.36	1.46 ± 0.15***	
	BLO-EI	2.04 ± 0.28*	2.63 ± 0.44*	
Room Air-BVX				1.90 ± 0.09
	RLO-EE	1.01 ± 0.04	1.73 ± 0.13*	
	RLO-EI	0.94 ± 0.01	1.68 ± 0.09**	
	LLO-EE	1.08 ± 0.02	1.73 ± 0.00*	
	LLO-EI	0.98 ± 0.08	1.95 ± 0.08	
	BLO-EE	0.95 ± 0.09	1.47 ± 0.04**	
	BLO-EI	0.96 ± 0.03	1.35 ± 0.11***	

[a]Refer to ABBREVIATIONS.

[b]Values represent Mean ± SD. Changes in the phase switching T_E/T_I index or in the ratio comparing total cycle duration of first effort breaths, when significantly different from 1.0 are indicated as: *P < 0.05, **P < 0.01 and ***P < 0.001.

effort total cycle duration versus total cycle duration of the preceding control breaths are used to correct for the range of ventilations measured during test gas and vagotomized conditions. The T_E/T_I ratios (phase-switching indices) represent central interpretation of vagal volume feedback and extravagal (chest and diaphragm distension) influences.

Bilateral vagotomy completely abolished the decrease in instantaneous breathing frequency ($1/T_{TOT}$) of first breaths, i.e., T_{TOT}^1/T_{TOT} is not significantly different from 1.0 for any maneuver. Unilateral vagotomy abolished the frequency response to ipsilateral occlusions (both EE and EI), but produced more marked slowing of respiratory rate during occlusion of the contralateral lung.

Changes in the T_E/T_I ratio suggest that extravagal afferent input is an integral part of respiratory control. No apparent relationship exists between the change in breathing frequency induced by airway occlusion and the change in the T_E/T_I phase-switching index. This disparity argues against the notion that mechanisms controlling T_I also mediate the duration of expiration.

The tendency for the respiratory system to withstand changes in tidal volume in the presence of changing respiratory loads is defined as ventilatory stability (Lynne-Davies et al., 1971; Mead, 1966). Ventilatory stability was analyzed in terms of instantaneous minute ventilation and tidal volume of first effort breaths during unilateral airway occlusion (Table 11). Obviously, bilateral

Table 11. Respiratory compensation to unilateral airway occlusions measured in terms of minute volume and tidal volume of first effort breaths.

Experimental Condition and Type of Occlusion[a]		$\dot{V}_E^1/\dot{V}_E$	V_T^1/V_T
Room Air-Intact			
	RLO-EE	0.65 ± 0.05[b]	0.62 ± 0.02
	RLO-EI	0.51 ± 0.02	0.64 ± 0.01
	LLO-EE	0.74 ± 0.04	0.77 ± 0.02
	LLO-EI	0.72 ± 0.03	0.81 ± 0.02
Hypoxia-Intact			
	RLO-EE	0.55 ± 0.03	0.59 ± 0.06
	RLO-EI	0.51 ± 0.04	0.66 ± 0.08
	LLO-EE	0.67 ± 0.02	0.73 ± 0.04
	LLO-EI	0.59 ± 0.05	0.78 ± 0.03
Hyperoxia-Intact			
	RLO-EE	0.50 ± 0.02	0.61 ± 0.05
	RLO-EI	0.44 ± 0.04	0.69 ± 0.03
	LLO-EE	0.71 ± 0.06	0.76 ± 0.06
	LLO-EI	0.61 ± 0.05	0.79 ± 0.09
Diff. Vent.-Intact			
	RLO-EE	0.52 ± 0.02	0.58 ± 0.02
	RLO-EI	0.53 ± 0.06	0.63 ± 0.04
	LLO-EE	0.68 ± 0.03	0.75 ± 0.03
	LLO-EI	0.59 ± 0.09	0.88 ± 0.06

Room Air-LVX			
	RLO-EE	0.61 ± 0.08	0.79 ± 0.05
	RLO-EI	0.62 ± 0.06	0.75 ± 0.04
	LLO-EE	0.95 ± 0.08	0.80 ± 0.03
	LLO-EI	0.80 ± 0.06	0.76 ± 0.05
Room Air-RVX		0.41 ± 0.14	0.40 ± 0.13
	RLO-EI	0.59 ± 0.01	0.56 ± 0.02
	LLO-EE	0.63 ± 0.00	0.80 ± 0.05
	LLO-EI	0.42 ± 0.08	0.98 ± 0.12
Room Air-BVX			
	RLO-EE	0.52 ± 0.03	0.52 ± 0.02
	RLO-EI	0.46 ± 0.04	0.43 ± 0.02
	LLO-EE	0.64 ± 0.00	0.69 ± 0.02
	LLO-EI	0.62 ± 0.01	0.60 ± 0.03

[a]Refer to ABBREVIATIONS.

[b]Values represent Mean ± SEM of minute ventilation and tidal volume of first effort breaths expressed in terms of the preceding values measured during the control breaths. Keep in mind that both values are obtained from the lung contralateral to the occlusion.

maneuvers are excluded from this type of evaluation since no volume changes occur. For the same reason, it should be apparent that ventilatory stability is accomplished by the lung contralateral to the occlusion.

During room air breathing in intact dogs first effort inspirations against RLO-EE and RLO-EI were terminated at volumes approximating 63% of the preceding control breaths. Corresponding left lung occlusions under these conditions were terminated at volumes of 77% and 81% for EE and EI occlusions respectively. Since left:right lung volume distribution was about 40:60 %, it can be seen that left lung volume expansion (from 40% to 63%) is approximately equal to right lung volume expansion (from 60% to ca. 79%). However, since the absolute volume inspired by the left lung is less than that inspired by the right lung, minute ventilation is better preserved during left lung occlusions. This latter observation argues against the idea that volume dependent phasic PSR activity is solely responsible for determining inspiratory duration since prolongation of T_I was comparable for left and right unilateral occlusions (Figure 30). These results further demonstrate that the relationship between mean ventilation and tidal volume (Hey et al., 1966) was less well-preserved during occluded efforts. This observation is particularly important since it could imply that mechanisms involved in reflex responses to airway occlusions are not necessarily identical to those which operate in normal pattern control of spontaneous unoccluded breathing.

Minute ventilation and tidal volume were less well-preserved in vagotomized dogs. First effort inspirations were terminated at lower lung volumes during EI occlusions than during the corresponding EE occlusions for both left and right lung responses. These results are exactly opposite those observed in intact dogs during inhalation of all four test gases.

The immediate ventilatory stability of the breathing pattern control mechanisms in the presence of airway occlusion is partially dependent upon the elastance of the respiratory system (Milic-Emili and Pengelly, 1971; Pengelly et al., 1971). Two different techniques were used to measure left and right lung elastance (Table 12). Dynamic elastance (E_{dyn}) was obtained from airway pressure and tidal volume traces during unoccluded control breaths at point of zero flow. Quasi-static measurements of elastance (E_{qs}) for both lungs were obtained by dividing the value of the apneic pressure plateau with the respective volume held in the lungs during EI occlusion maneuvers. Measurements of dynamic elastance were significantly lower than quasi-static estimates. Quasi-static measurements are very similar to values reported by Seed and Sykes (1972) although their mesurements were expressed as passive compliance, i.e., the inverse of elastance. The difference between E_{dyn} and E_{qs} is indicative of the increase in lung recoil developed by the distended or occluded lung. Dynamic elastance of the right lung was generally lower than that measured in the left lung. In contrast, quasi-static elastic recoil of the occluded left lung was

Table 12. Passive dynamic and quasi-static measurements of left and right lung elastance

Experimental Condition and Type of Occlusion[a]	Right Lung		Left Lung	
	E_{dyn}	E_{qs}	E_{dyn}	E_{qs}
Room Air-Intact				
RLO-EI	7.3 ± 0.5[b]	29.5 ± 4.1	--	--
LLO-EI	--	--	7.0 ± 0.4	54.3 ± 6.2
BLO-EI	6.6 ± 0.4	61.0 ± 8.2	7.0 ± 0.3	36.4 ± 3.8
Hypoxia-Intact				
RLO-EI	9.9 ± 0.8	33.0 ± 5.1	--	--
LLO-EI	--	--	8.4 ± 0.5	49.7 ± 6.2
BLO-EI	9.7 ± 0.8	54.0 ± 4.6	8.4 ± 0.4	41.5 ± 5.2
Hyperoxia-Intact				
RLO-EI	10.2 ± 0.1	25.3 ± 4.7	--	--
LLO-EI	--	--	8.3 ± 0.7	49.3 ± 3.3
BLO-EI	10.0 ± 0.1	47.6 ± 7.7	7.7 ± 0.7	28.2 ± 4.1
Diff. Vent.-Intact				
RLO-EI	10.0 ± 0.1	26.8 ± 2.3	--	--
LLO-EI	--	--	7.7 ± 0.8	46.7 ± 5.5
BLO-EI	9.1 ± 0.9	49.7 ± 3.9	7.0 ± 0.5	28.7 ± 3.8

Room Air-LVX				
RLO-EI	5.6 ± 0.4	34.2 ± 5.0	--	--
LLO-EI	--	--	6.3 ± 0.8	60.2 ± 8.9
BLO-EI	5.3 ± 0.4	74.0 ± 9.4	5.3 ± 0.3	50.0 ± 7.1
Room Air-RVX				
RLO-EI	8.2 ± 0.0	36.9 ± 6.6	--	--
LLO-EI	--	--	6.9 ± 0.0	40.6 ± 6.8
BLO-EI	7.5 ± 0.6	47.2 ± 3.7	6.9 ± 0.0	42.9 ± 5.3
Room Air-BVX				
RLO-EI	5.2 ± 0.0	22.8 ± 2.1	--	--
LLO-EI	--	--	5.6 ± 0.1	35.8 ± 3.9
BLO-EI	5.4 ± 0.6	33.9 ± 4.0	6.5 ± 0.6	23.8 ± 4.1

[a]Refer to ABBREVIATIONS.

[b]Values represent mean ± SD for passive dynamic elastance (E_{dyn}) and quasi-static elastance (E_{qs}) expressed as cm H_2O/L.

always greater than the recoil of the occluded right lung during unilateral maneuvers. These differences may reflect the fact that dogs have an incomplete separation of the left and right thoracic cavity such that compression of one lung by the other is common. However, during bilateral maneuvers, right lung quasi-static recoil was much greater than left lung quasi-static recoil. Unilateral predominance is evidenced by the reduced E_{dyn} after left and bilateral vagotomy and elevated E_{dyn} after right vagotomy. Changes in passive elastance following vagotomy probably reflect elimination of tonic vagally mediated bronchomotor tone.

Effect of F_IO_2 and Vagotomy on Respiratory Center Output

Average values for rate of change in airway pressure and peak airway pressure during first effort inspirations of BLO-EE maneuvers are presented in Table 13. Since there is negligible change in lung volume, rate of change of inspiratory airway pressure during BLO-EE maneuvers in intact dogs breathing room air represents the intensity of phrenic motor output in the absence of phasic PSR activity. These values averaged 7.61 ± 0.96 and 7.45 ± 0.89 cm H_2O/sec for the right and left lung respectively. It follows that peak inspiratory airway pressures were also similar in the right (12.48 ± 0.05 cm H_2O) and left lungs (12.12 ± 0.51 cm H_2O).

Hypoxia increased both the rate of rise and peak inspiratory airway pressure (P_{AW}). The effects were significantly more pronounced for the right lung. Even more discordant values between

Table 13. Indirect assessment of respiratory center output obtained from airway pressure measurements during first effort inspirations of end-expiratory lung occlusion.

Experimental Condition[a]		Right Lung		Left Lung	
		P_{AW}^{1}	P_{AW}^{1}/T^{1}	P_{AW}^{1}	P_{AW}^{1}/T_{I}^{1}
Intact					
	Room Air	12.48 ± 0.05[b]	7.61 ± 0.96	12.12 ± 0.51	7.45 ± 0.89
	Hypoxia	15.67 ± 2.00	9.50 ± 0.02	12.68 ± 1.19	7.66 ± 0.91
	Hyperoxia	13.83 ± 1.41	9.11 ± 1.24	10.19 ± 0.96	7.13 ± 1.39
	Diff. Vent.	13.44 ± 0.62	7.76 ± 1.03	9.99 ± 1.10	5.91 ± 1.08
LVX					
	Room Air	11.20 ± 0.31	6.85 ± 0.53	12.37 ± 0.72	7.54 ± 0.69
RVX					
	Room Air	14.65 ± 2.04	7.07 ± 0.62	10.35 ± 2.41	6.46 ± 1.12
BVX					
	Room Air	13.27 ± 0.07	7.88 ± 0.42	9.92 ± 0.06	5.47 ± 0.29

[a]Refer to ABBREVIATIONS.

[b]Values represent Mean ± SD of peak airway pressure (P_{AW}) and rate of change of airway pressure (P_{AW}/T_{I}) during first effort inspirations against bilateral occlusion at end-expiration as indicated by the prime superscript.

the right and left lung were obtained during bilateral hyperoxia when end-tidal gases of the two sides were nearly identical. Inhalation of 100% oxygen produced an increase in peak pressure and rate of change of pressure in the right lung (+11% P_{AW} and +20% rate of rise P_{AW}) compared to simultaneously measured decreases in left lung values (-16% P_{AW} and -4% rate of rise P_{AW}).

DISCUSSION

Several lines of evidence in the present study support the hypothesis that elements which 'sense' changes in the concentration of alveolar oxygen participate in breathing pattern control. The first of these was the observation that dogs responded to differential ventilation (DV: left lung hypoxic, right lung hyperoxic) with a significant increase in minute volume. Characteristics of the ventilatory response to DV were similar to those associated with hypoxic hypoxemia. However, normoxemia was established during DV by adjusting F_IO_2 of the right lung. As such, the ventilatory drive during DV could not be accounted for by peripheral chemoreceptor input. Furthermore, since special efforts were made to maintain end-tidal CO_2 of each lung isocapneic throughout the course of these experiments, the ventilatory response to DV could not be attributed to stimulation of central CO_2 chemoreceptors or to the CO_2-pulmonary reflex (Mustafa and Purves, 1972; Bartoli et al., 1974; Banzett et al., 1978).

Several possible mechanisms could account for alterations in the breathing pattern during differential ventilation. Among these are included: 1) an effect of alveolar oxygen on pulmonary stretch receptor (PSR) discharge or on other pulmonary vagal endings, 2) widening of the $A\text{-}aDO_2$ gradient with subsequent mismatch of peripheral chemoreceptor and intrapulmonary afferent activity coursing to the brainstem, 3) hypoxic or hyperoxic-induced release

of humoral factors which act on the bulbopontine respiratory mechansisms, 4) the cardiopulmonary baroreflex, and 5) other unknown mechanisms.

Qualitative aspects of the Hering-Breuer reflexes mediated by airway stretch receptors with vagal afferent projections to the bulbopontine respiratory center(s) are quite well-known. Stimulation of the whole vagal bundle has been used to investigate the mechanisms of central respiratory integration (Stanley et al., 1975; Bradley, 1976; Trenchard, 1977). However, since a number of afferents which produce quite different respiratory patterns are carried in the vagus, results of these studies may be misleading. Many of the ambiguities encountered in studying respiratory reflexes can be minimized by using more physiologic stimulation of vagal afferents such as is produced by changes in lung volume.

The effect of selectively eliminating (partially or completely) phasic PSR activity on the breathing pattern was examined in the present study by occluding one or both airways at end-expiration (EE). During the first breathing effort against these occlusions there is no change in lung volume of the occluded side(s) and thus no phasic PSR activity (Richardson et al., 1973) Occlusions set at peak inspiration (EI) were used to examine the effect of increased lung volume and thus increased tonic PSR activity on the respiratory pattern. As with EE maneuvers, respiratory efforts against airways occluded at EI were not associated with volume changes and thus phasic PSR activity was negligible. Changes in pressures, airflows,

volumes and timing of the occluded breaths were used to assess the contribution of phasic and tonic PSR input to respiratory pattern control.

The approach used to determine whether it was the alveolar hyperoxia or the alveolar hypoxia which was responsible for the ventilatory response to DV was to compare reflex respiratory responses to specific airway occlusions over a range of inspired oxygen tensions. To examine the role of arterial versus alveolar oxygen tension on lung volume reflexes and the drive to breathe, the dogs were fitted with an endobronchial divider. The double-lumen endobronchial divider enabled the left lung to breathe 100% nitrogen (i.e., an alveolar hypoxic stimulus) while the right lung breathed 90-100% oxygen (i.e., an alveolar hyperoxic stimulus). Differential ventilation was used as a non-invasive means of establishing systemic normoxemia and thereby prevent loading and unloading of peripheral chemoreceptors. Such loading was present when dogs were exposed to bilateral hypoxia (F_IO_2 = 0.1) and bilateral hyperoxia (F_IO_2 = 1.0). Hypoxia and hyperoxia, together with bilateral normoxia (F_IO_2 = 0.2) were used to produce parallel changes in arterial and alveolar oxygen tensions with a range of $AaDO_2$ gradients. Reflex respiratory responses to airway occlusion maneuvers and the steady breathing patterns in these situations are determined by interactions among bronchopulmonary mechanoreceptors and intra- and extrapulmonary oxygen chemoreceptors. By looking specifically at the right and left lung contributions to total lung

reflex reponses to airway occlusions during these interventions, evidence was obtained for the presence of intrapulmonary chemoreceptor mechanisms.

A prerequisite for this approach was to define the relationships among respiratory responses to left, right and bilateral lung occlusions. Systematic analysis of the interaction between left and right lungs during the well-known respiratory responses to tracheal occlusions had not been previously undertaken. These experiments have provided important data regarding the present assumptions concerning phasic and tonic PSR influence on control of respiratory cycle timing.

Application of a positive pressure at the mouth either by forced inflation or by occluding the airways at peak inspiration (these experiments) results in a period of apnea. The duration of the apnea has traditionally been attributed to phasic PSR activity and been used as an index of the strength of the vagal inspiratory inhibitory reflex. This Hering-Breuer reflex is thought to be responsible for, or at least contribute to, control of respiratory frequency and tidal volume during spontaneous breathing.

During room air, breathing, the reflex apnea following RLO-EI was always longer than that produced by LLO-EI. Furthermore, the apneic response to BLO-EI was always longer than the summation of apneic responses produced by unilateral occlusions. Identical results were obtained during hypoxia (10% O_2) and hyperoxia (100% O_2), although the differences between apneic responses were greatly

magnified. These results are consistent with the idea that volume-dependent PSR activity underlies this Hering-Breuer apnea. However, the data for apneic durations also suggest that central integration of vagal activity is not additive and that pulmonary vagal innervation may not be completely ipsilateral. Evidence for the latter is provided by the exaggerated apneic response to BLO-EI maneuvers in unilaterally vagotomized animals.

The disparity between these results obtained during normoxia, hypoxia and hyperoxia with those obtained during DV offers strong evidence for the hypothesis that alveolar O_2 tension participates in breathing pattern control. EI occlusion of the left hypoxic lung (smaller V_T) produced a significantly longer apneic response than EI occlusion of the right hyperoxic lung (larger V_T). Furthermore, the apneic duration of BLO-EI maneuvers during differential ventilation was significantly shorter than would be predicted from summation of the apneic durations produced by RLO-EI and LLO-EI. These results suggest that alveolar hypoxia sensitizes PSR's such that receptor discharge per unit change in lung volume is increased. In other words, PSR discharge at the time of LLO-EI would be greater during DV than during room air breathing. However, a direct effect of hypoxia in altering the gain of PSR discharge does not explain why the apneic response to RLO-EI during DV was so much longer than that produced by the same maneuver during normoxia.

It is now recognized that factors other than PSR activity participate in the inhibition and recovery of phrenic activity

during these maneuvers. The relationship between apneic duration and arterial oxygen tension in the present study is in accord with previous studies (Younes, 1974). These results suggest that phrenic output represents central interpretation of the chemical excitatory drive to breath and vagal inhibitory influence on this drive. However, chemical excitation alone cannot account for recovery of phrenic activity. Timing of the second and third efforts during occlusion was not significantly different from that measured during the first effort, although the chemical drive to breathe was continually increasing as evidenced by values of end-tidal pCO_2. However, it should be recognized that mechanisms which determine the apneic duration may not be identical to those which dictate respiratory cycle characteristics of subsequent efforts against occluded airways. Other factors thought to be involved in determining the duration of apnea include PSR adaptation and proprioceptive afferent activity arising from the chest wall and diaphragm. A hyperoxic induced decrease in the rate of PSR adaptation duration a sustained increase in lung volume could explain the long apnea produced by RLO-EI in differentially ventilated dogs.

Reflex respiratory respones to total airway occlusion at functional residual capacity (FRC) in the present study (BLO-EE maneuvers) were similar to those reported for conscious dogs (Phillipson, 1974). First effort breaths against such occlusions are characterized by prolongation of T_I, T_E, and T_{TOT}. With the

exception of a decrease in T_E for BLO-EE during hypoxia, qualitatively similar responses were obtained for all four gases tested. These changes theoretically represent the immediate reaction of the respiratory center(s) to withdrawal of phasic PSR activity (Head, 1889). Conventional theory states that a change in lung volume stimulates PSR's and that phasic PSR discharge, together with central inspiratory activity (CIA), determines T_I (Breuer, 1868; Hering, 1868, Adrian, 1933; Clark and von Euler, 1972). As stated, the effect of BLO-EE is to eliminate the normal rate of rise of phasic vagal discharge from PSR's in the occluded lung(s). This prolongs inspiration by delaying the time required to reach the inhibitory-off switch (I-OS) threshold. Prolongation of T_I during BLO-EE maneuvers in the present study was not related to paO_2. However, since T_I of the control breath preceding occlusion was shortest during hypoxia and longest during DV, reflex prolongation of T_I was relatively greatest during hypoxic hypoxemia and least during DV normoxemia. These results suggest that hypoxemia sensitizes pulmonary stretch receptors. An increase in the gain of PSR discharge would explain the short T_I of unoccluded breaths and the relatively long T_I of occluded breaths in the hypoxic dogs. Sensitization of PSR by hypoxia and conversely, desensitization by hyperoxia, does not fully explain the respiratory response to BLO-EE during differential ventilation.

Changes in T_E of first effort breaths against BLO-EE were associated with paO_2 during hypoxia, normoxia and hyperoxia. These

results are consistent with the report by Koepchen et al. (1973) that stimulation of peripheral chemoreceptor afferents excite expiratory neurons independently of their action on inspiratory neurons. However, BLO-EE maneuvers during DV produced T_E prolongation which was much greater than that observed during normoxia. These results support the hypothesis that F_IO_2 contributes to control of respiration by an effect on intrapulmonary chemoreceptors. This effect, being manifested primarily as changes in T_E, further suggests that intrapulmonary oxygen 'sensing' mechanisms may involve tonic PSR discharge.

Alterations in tonic PSR activity, and thus T_E, may be secondary to changes in functional residual capacity reported to occur during hypoxia and hyperoxia (Bouverot and Fitzgerald, 1969). The increased FRC during hypoxia would tend to increase tonic PSR firing while the decrease in FRC during hyperoxia would reduce the level of PSR firing. The decrease in T_E during hypoxic BLO-EE maneuvers and the increase in T_E during hyperoxic BLO-EE maneuvers are exactly opposite those which would be predicted if the FRC changes had occurred. Furthermore, repeated breathing efforts against closed airways during test gas breathing in the present experiments would tend to minimize alveolar collapse and/or increases in closing volume of the recumbent anesthetized dogs.

It has been proposed that mechanisms which determine T_I indirectly determine T_{TOT} and thus respiratory frequency by a time-dependent relationship of T_E on T_I (Clark and von Euler, 1972; Nadel

et al., 1973). Stated in other words, changes in T_E will parallel changes in T_I (i.e., constant T_E/T_I ratio) over a wide range of breathing frequencies. These conclusions are primarily based on data obtained from anesthetized, paralyzed cats rebreathing CO_2. Results of the present study are inconsistent with the postulate that T_E is dependent upon T_I. Conflicting results may relate to species differences or the use of CO_2 (discussion to follow). In the first instance, the distribution of respiratory frequencies in the present study during room air breathing for 38 vagally intact dogs was more closely associated with T_E than with T_I. Secondly, the frequency changes associated with hypoxic, hyperoxic and differential lung ventilation were accompanied by significant changes in the T_E/T_I ratio. More specifically, changes in respiratory rate were generally due to changes in expiratory duration; inspiratory duration remaining quite constant over a large range of frequencies. Thirdly, disproportionate changes in T_E and T_I, as well as assymetric alterations (changes in the opposite directions) in these variables were particularly apparent during respiratory responses to specific airway occlusions.

Respiratory responses to airway occlusions set at peak inspiration (EI maneuvers) were used to assess the contribution of tonic PSR input on control of the breathing pattern. Theoretically, the increased volume in the lungs during EI maneuvers should present a higher tonic component of PSR vagal volume feedback to the I-OS. As such, inspirations should be shorter and expirations longer than

first efforts against EE maneuvers. Central interpretation of afferent information coursing to the CNS during breathing efforts against EI occlusion should be analogous to the pattern which ensues when FRC is increased for some other reason. It has been shown that breathing patterns at lung volumes above and below normal FRC are characteristically altered with respect to the steady state spontaneous breathing pattern at normal end-expiratory lung volume (Martin et al., 1978; D'Angelo and Agostoni, 1975). Bartoli et al. (1973) used anesthetized paralyzed dogs on closed-chest cardiopulmonary by-pass to change the tonic level of PSR activity by inflating and deflating the lungs in the absence of phasic activity (i.e., the animals were not making inspiratory movements). They demonstrated large changes in T_E, but minimum changes in T_I. Similar results were obtained in the present study. Compared to EE occlusions, prolongation of expiratory duration was greater during EI maneuvers (i.e., increased end-expired lung volume → increased tonic PSR discharge → longer T_E). However, prolongation of first effort T_I for a given lung occlusion (left, right, bilateral) was nearly identical whether the airways were restricted at end-expiratory or peak-inspiratory lung volume. Consequently, the T_E/T_I ratios for first effort breaths were consistently higher for EI maneuvers. These experiments demonstrate that an increase in tonic PSR discharge (assumed during EI maneuvers) is capable of independently altering expiratory duration.

It is difficult to explain why the increase in tonic PSR activity has negligible effects on inspiratory duration during mechanically loaded breathing. Perhaps tonic PSR activity does facilitate inspiration, but that this effect is masked or counterbalanced by another inhibitory (i.e., T_I prolonging) input. Inhibitory signals arising from diaphragmatic and intercostal muscle spindles in response to large elastic loads (Corda et al., 1965; Bland et al., 1967) have been demonstrated to course directly (Remmers, 1973; Remmers et al., 1973) and indirectly (Shannon, 1980) to central respiratory neurons. The contribution of 'chest wall' mechanoreceptors to respiratory control has recently received a great deal of attention.

The contribution by extravagal mechanoreceptors to breathing pattern control was evaluated in the present study by comparing EE to EI maneuvers as well as to steady state breathing patterns in vagotomized and intact dogs. T_I prolongation due to vagotomy averaged 79% while that due to BLO-EE averaged 17%. Similar values have been reported by Phillipson (1974) for conscious dogs breathing room air. By comparing T_I prolongation during first effort breaths of BLO-EE maneuvers with prolongation of T_I produced by bilateral vagotomy, it appears as if tonic PSR discharge does contribute to determining T_I during unoccluded breathing. The significance of this comparison is limited by the lack of information concerning the effect of the occlusion maneuver itself on central respiratory mechanisms.

Respiratory center output was assessed in the present study by measuring peak inspiratory airway pressure and rate of change of inspiratory airway pressure during first effort breaths of BLO-EE maneuvers. Rate of change of inspiratory airway pressure relates to central inspiratory activity and thus, phrenic output. Peak inspiratory airway pressure changes indicate alterations in the I-OS threshold. The degree of mismatch between directional changes in CIA and/or I-OS threshold determine whether T_I will increase, decrease or remain unchanged for a given PSR input.

Bilateral vagotomy produced an increase in peak pressure and rate of change of inspiratory airway pressure during first effort breaths against BLO-EE. These changes most likely reflect the elimination of an inhibitory input to central respiratory mechanisms (Phillipson, 1974). If this is so, it follows that these same measurements taken during first effort breaths against BLO-EI maneuvers (i.e.,increased vagal feedback inhibition) in intact dogs should produce lower values compared to values obtained during BLO-EE maneuvers. However, if peak pressure and rate of change of inspiratory pressure are affected by changes in chest wall configuration, the predicted responses would not occur. Data obtained in the present experiments indicate that respiratory center output is markedly higher during EI maneuvers than EE maneuvers even in bilaterally vagotomized dog. These results suggest that extravagal afferents alter respiratory center output. These afferents relay information concerning chest wall distension

associated with EI occlusions. Changes in respiratory output, together with the probability that chest wall impedance was higher during EI maneuvers (Mead, 1979), may explain why tidal volume was better preserved during EI than EE maneuvers.

Until more is known about how the bulbopontine apparatus integrates afferent information and until all of the afferents to the respiratory center(s) are adequately evaluated, it is difficult to fully explain the significance or validity of pressure measurements as indicative of respiratory center motorneuronal output.

Several lines of evidence in the present study suggest that output of the respiratory center(s) is not a result of simple summation of bilateral vagal input. Firstly, unilateral vagotomy (both left and right) decreased T_I and T_E while bilateral vagotomy prolonged T_I and T_E. Secondly, bilateral vagotomy generally increased respiratory motor output as measured by peak pressure and rate of rise of inspiratory airway pressure during first effort breaths of BLO-EE maneuvers. In contrast, left vagotomy produced a decrease in respiratory output estimated from these parameters while RVX generally increased output measurements. In conjunction with this data, summation of the apneic responses to RLO-EI and LLO-EI was approximately equal to that present during BLO-EI after RVX. However, after LVX, the apneic summation was significantly less than that produced by bilateral occlusion. These results are consistent with the hypothesis previously presented in this discussion

concerning non-additive interaction between bilateral vagal volume feedback. Further evidence supporting the hypothesis of non-additive interaction is the observation that unilateral vagotomy had less effect on spontaneous unoccluded respiratory rhythm than on reflex respiratory responses to airway occlusions. Similar observations have been reported by Phillipson et al. (1971). These results also suggest that PSR impulses, which are thought to initiate the Hering-Breuer reflexes, may not be solely responsible for the vagal modulation of respiration.

A major factor to consider in analyzing reflex responses to airway occlusion during hypoxia and hyperoxia is the central effect of O_2. Central effects of hypoxemia during 10% O_2 breathing were manifested as increases in the rate of change of lung volume and airway pressure during inspiration. According to the V_T-T_I relationship (Clark and von Euler, 1972), inspiration should be terminated sooner at higher lung volume during hypoxemia. T_I was shorter during hypoxic hypoxemia in the present study. However, V_T remained constant suggesting that hypoxemia directly or indirectly (via chemoreceptor afferent activity) affects bulbopontine mechanisms by shifting the V_T-T_I relationship to the left. In direct contrast, carbon dioxide is reported not to affect or displace the relationship between tidal volume and inspiratory duration. The presence of a significant frequency response to changes in inspired oxygen in bilaterally vagotomized dogs in the present study is also in direct contrast to results reported during

hypercapnia. von Euler et al. (1970) reported that the increased frequency response to a wide range of chemical drives (all CO_2 stimuli) was possible only when vagal circuits were intact. The differences between results of the present study with hypoxia and previous results with CO_2 may lie in the actions of O_2 on bulbopontine mechanisms, e.g. the I-OS threshold or rate of rise of CIA.

Most of the previous studies designed to investigate respiratory control mechanisms have used CO_2 to elicit ventilatory responses consisting of a range of tidal volume and frequency combinations. Animals or subjects are generally kept hyperoxic in an attempt to eliminate peripheral chemoreceptor input. The ventilatory patterns which ensue are assumed to result from central CO_2 chemoreceptors and normal mechanical vagal volume feedback. It is now well-recognized that CO_2 alters pulmonary stretch receptor discharge (Banzett et al., 1978). Furthermore, the present studies suggest that O_2, directly and indirectly, may alter the 'set-point' of bulbopontine respiratory pattern control mechanisms.

As stated, BVX did not affect the tachypneic response to hypoxia. However, following BVX, the ventilatory response to hypoxia was associated with an increase in tidal volume. An increased V_T associated with an increased respiratory rate in response to hypoxia in vagotomized dogs is consistent with the idea that hypoxia increases respiratory center output without increasing the I-OS threshold. Evidence that hypoxic hypoxemia increased the

rate of rise of CIA without altering the I-OS threshold is provided by the data showing an increase in rate of change of airway pressure without a concomitant increase in peak inspiratory airway pressure. Some direct evidence (Folgering and Smolders, 1979) from intracellular recordings supports this suggestion. These differences between O_2 and CO_2 demonstrate the pervasive importance of controlling both O_2 and CO_2 in studies designed to investigate the neurochemical control of respiration.

Reflex respiratory patterns elicited by mechanical loading, with and without additional chemical loading in the present study, support the hypothesis concerning intrapulmonary chemoreception of oxygen. Similarities during hypoxic hypoxemia and DV normoxemia for responses to specific airway occlusions as well as steady state breathing patterns imply that intrapulmonary and arterial O_2 chemoreceptors act synergistically. Several lines of evidence suggest that F_IO_2 reflexly adjusts the ventilatory pattern by altering pulmonary stretch receptor activity. This explanation could explain the paradoxical ventilatory response to DV when p_aO_2 was actually slightly higher than during room air breathing.

An alternative explanation may involve intrapulmonary baroreceptor stimulation. Hypoxic pulmonary vasoconstriction is a local response, being confined to the lung or lobe which is hypoxic (Himmelstein et al., 1958; Fishman, 1961). In fact, Hales and Kazemi (1974) measured a 37% decrease in perfusion of the nitrogen ventilated hypoxic lung in differentially ventilated dogs. It is

reasonable to expect that a similar redistribution of pulmonary blood flow occurred in dogs differentially ventilated in the present study. The animals were kept isocapneic throughout the entire course of this study. This eliminated direct CO_2 and pH effects as well as CO_2-induced catecholamine release from altering the severity of hypoxic pulmonary vasoconstriction and subsequent shunting (von Euler and Liljestrand, 1958; Lloyd, 1966). Further evidence that shunting occurred in our dogs was suggested by the slightly increased mean pulmonary arterial pressure, right ventricular pressure and heart rate during differential ventilation. The less than expected pressor response to unilateral hypoxia might be explained by the idea that vasomotor activity within the hyperperfused hyperoxic right lung actually counteracted changes in mean pulmonary arterial resistance (Murray et al., 1969).

In addition to baroreceptor involvement in the ventilatory response to differential ventilation, indirect stimulation of PSR's by the pulmonary pressor response might have occurred. An increase in right ventricular systolic pressure during DV could indicate pulmonary vascular obstruction or vasoconstriction has occurred. These hemodynamic alterations can stimulate pulmonary stretch receptors (Bülbring and Whitteridge, 1945; Marshall and Widdicombe, 1958).

However, hyper- and hypoperfusion of the right and left lung respectively, may activate other intrapulmonary mechanisms which respond to small changes in oxygen tension. If such mechanisms do

exist, and if they mediate the ventilatory response to differential ventilation, it is unlikely that the afferent information courses in the vagus since the ventilatory response to DV was even more pronounced in BVX dogs. This latter observation precludes the possibility that PSR stimulation (either by increases in perfusion pressure or by changes in oxygen tension) or intrapulmonary baroreceptor activation are solely responsible for the steady state ventilatory patterns associated with differential ventilation. It is tenable that stimulation of intrapulmonary oxygen sensors causes release of humoral substances which alter respiratory center output and/or inspiratory threshold. As such, apparently normal sensory input becomes superimposed on different integrating mechanisms in the bulbopontine respiratory center(s).

The present experiments were performed in intubated, anesthetized, spontaneously breathing dogs. Therefore, explanations of the results may not necessarily apply to respiratory rate and depth control in awake animals. However, occlusion data obtained from conscious dogs in similar studies by Phillipson (1974) were comparable to results presented in this report.

While anesthesia does eliminate behavioral reactions to airway occlusions and changes in inspired O_2 tension, one must be careful in comparing the results of studies performed in animals anesthetized with different agents. Ventilation with low concentrations of trichloroethylene, ether, chloroform and halothane causes sensitization of pulmonary stretch receptors; higher

concentrations result in inhibition of PSR activity (Whitteridge and Bülbring, 1944; Paintal, 1957; Coleridge et al., 1968). For obvious reasons inhalant anesthetics are not appropriate in experiments designed to study mechanical lung volume reflexes. Similarly, the presence of general and specific depressant effects on central nervous system activity preclude the use of barbiturates in such studies. Alpha-chloralose is usually the best anesthetic agent in neurophysiologic studies because reflex activity is better retained than during various forms of barbiturate anaesthesia (Dripps and Dumke, 1943; Brown and Hilton, 1956).

The ventilatory responses to hypoxic and hyperoxic stimuli were readily apparent with the dose of α-chloralose/urethane (38 and 300 mg/kg respectively) used in this study suggesting that this combination does not depress chemoreflexes. Likewise, airway occlusions induced reflex adjustments in respiratory cycle characteristics which varied by less than 10% during a 9 hour period of room air breathing. This is in sharp contrast to Hering-Breuer reflexes studied under pentobarbital anesthesia which show time-related changes in reflex strength (Bouverot and Fitzgerald, 1969). Furthermore, mechanical and chemical reflexes were still apparent under very deep anesthesia with α-chloralose/urethane, suggesting minimal central respiratory depression.

SUMMARY

1. Intrapulmonary O_2 chemoreceptor mechanisms effectively participate in the neurochemical control of respiratory rate and depth.
   a. Changes in alveolar oxygen tension (independent of arterial oxygenation) alter the spontaneous breathing pattern as well as the reflex respiratory responses to airway occlusion of anesthetized dogs.
   b. These mechanisms may also be involved in hypoxic and hyperoxic ventilatory responses of vagally intact dogs.
   c. Directional changes in T_E and T_I during unilateral occlusion maneuvers of the nitrogen and oxygen ventilated lungs during DV are identical to those observed during bilateral hypoxia and hyperoxia, respectively.

2. Expiratory duration is NOT solely dependent upon mechanisms (namely phasic pulmonary stretch receptor discharge) which dictate inspiratory duration.
   a. Changes in respiratory frequency are brought about primarily by altering the expiratory duration with minimal changes in inspiratory time.

3. Vagally mediated tonic PSR, as well as extravagal afferents arising from the diaphragm, chest wall and chemoreceptors have a greater effect on T_E than T_I.

a. Tonic PSR activity during inspiration acts to prematurely shorten both inspiratory and expiratory time.

b. Chest wall afferent bulbopontine input appears to raise the I-OS threshold such that T_I is prolonged and inspired volume is increased.

c. Peripheral chemoreceptor input (hypoxic stimulus) shortens T_I with or without affecting T_E, suggesting that arterial chemoreceptor afferents act directly on the inhibitory off-switch threshold.

4. The degree of matching between threshold lowering effects of hypoxemia and threshold elevating effects of chest wall distension determines the timing relationship between inspiration and expiration which will occur in a given experimental situation.

5. Central interpretation of left and right lung vagal volume feedback is not simply additive. Alternatively, it could be that pulmonary vagal innervation (afferent and efferent) is not strictly ipsilateral.

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APPENDIX A: SUMMARY OF TABULATED DATA

Table A1. Mixed venous blood-gas and acid-base analysis during steady-state hypoxic, hyperoxic, and differential ventilation with vagi intact

		Hypoxia (n=12)	Hyperoxia (n=14)	Diff. Vent. (n=18)
pH (units)	N	7.26 ± 0.05[a]	7.25 ± 0.05	7.24 ± 0.04
	SS	7.30 ± 0.04	7.24 ± 0.06	7.25 ± 0.07
pCO_2 (mmHg)	N	60.8 ± 6.8	62.9 ± 7.6	59.8 ± 5.4
	SS	56.2 ± 6.2	63.2 ± 10.9	57.1 ± 9.6
pO_2 (mmHg)	N	52.3 ± 5.7	51.2 ± 9.8	54.7 ± 11.3
	SS	23.1 ± 7.8***	74.9 ± 17.5**	57.0 ± 5.7
BE (mEq/L)	N	-1.4 ± 2.7	-1.5 ± 3.4	-3.1 ± 1.7
	SS	1.4 ± 3.1	-2.7 ± 2.6	-3.4 ± 2.2
HCO_3^- (mEq/L)	N	26.7 ± 2.9	26.4 ± 3.2	24.8 ± 1.3
	SS	23.7 ± 3.2	25.7 ± 2.7	24.0 ± 1.8

[a]Values represent mean ± SD. Significant difference between normoxic (N) values preceding exposure to the test gas and steady-state (SS) experimental data indicated as : **P < 0.01, ***P < 0.001.

Table A2 Summary of arterial and mixed venous pO_2, pCO_2 and pH changes during hypoxia, hyperoxia and differential ventilation in bilaterally vagotomized dogs

		Hypoxia (n=9)		Hyperoxia (n=8)		Diff. Vent. (n=11)	
		N	SS	N	SS	N	SS
pH (units)	a	7.42 ± 0.03[a]	7.47 ± 0.03	7.35 ± 0.07	7.35 ± 0.09	7.28 ± 0.04	7.28 ± 0.06
	$\bar{v}$	7.38 ± 0.01	7.42 ± 0.04	7.32 ± 0.06	7.31 ± 0.07	7.26 ± 0.06	7.25 ± 0.05
pCO_2 (mm Hg)	a	42.3 ± 5.2	39.6 ± 6.8	41.9 ± 8.8	40.9 ± 11.9	46.3 ± 6.7	46.7 ± 10.5
	$\bar{v}$	49.6 ± 3.2	47.3 ± 6.4	47.3 ± 6.7	50.1 ± 10.5	52.4 ± 7.6	52.9 ± 10.6
pO_2 (mmHg)	a	76.1 ± 3.1	42.6 ± 0.6***	80.5 ± 9.1	326.6 ± 94.2***	74.2 ± 16.8	84.5 ± 33.6
	$\bar{v}$	56.6 ± 5.0	28.2 ± 2.3***	53.3 ± 4.5	68.4 ± 10.8**	44.4 ± 10.2	49.4 ± 5.4

[a]Values represent Mean ± SD for arterial (a) and mixed venous ($\bar{v}$) blood samples obtained during normoxia (N) preceding exposure to the test gas and during steady state (SS) breathing of the test gas. Significant difference between normoxia and the experimental test gas values represented as: **P < 0.01, ***P < 0.001.

Table A-3. Effect of left, right and bilateroral vagotomy on respiratory cycle characteristics during spontaneous steady state room air ventilation

Variable[a]	LEFT VAGOTOMY (n=12)		RIGHT VAGOTOMY (n=8)		BILATERAL VAGOTOMY (n=12)	
	Before	After	Before	After	Before	After
T_I (msec)	1344 ± 22[b]	1447 ± 78	353 ± 61	1201 ± 28	1130 ± 41	2023 ± 62*
T_E (msec)	5071 ± 165	4364 ± 51	4911 ± 269	2937 ± 128*	3730 ± 78	4267 ± 112
T_{TOT} (msec)	6415 ± 176	5811 ± 526	6264 ± 413	4138 ± 292*	4860 ± 588	6291 ± 622
T_I/T_{TOT} (%)	25.1 ± 1.5	29.2 ± 2.2	25.4 ± 0.4	34.8 ± 1.5**	28.1 ± 1.1	39.6 ± 1.6**
T_E/T_{TOT} (%)	74.9 ± 0.5	70.8 ± 2.2	74.6 ± 1.7	65.2 ± 1.5**	71.9 ± 1.2	60.4 ± 0.8**
T_E/T_I	3.83 ± 0.12	3.14 ± 0.34	3.81 ± 0.26	2.40 ± 0.22*	3.23 ± 0.12	1.90 ± 0.09*
V_{T_L} (ml)	152 ± 3	173 ± 12*	190 ± 6	191 ± 8	174 ± 9	289 ± 7*
V_{T_R} (ml)	205 ± 3	203 ± 8	207 ± 12	240 ± 8*	218 ± 4	355 ± 12*
V_T (ml)	357 ± 4	376 ± 14	397 ± 9	431 ± 9	392 ± 9	644 ± 14*
V_{T_L}/V_T (%)	41.8 ± 0.6	45.1 ± 0.4	47.1 ± 0.2	43.8 ± 0.8	43.7 ± 0.4	45.1 ± 0.3
V_{T_R}/V_T (%)	58.2 ± 0.7	54.9 ± 0.9	52.9 ± 0.9	56.2 ± 1.0	56.3 ± 1.1	54.9 ± 0.8
V_{T_L}/T_I (ml/sec)	114 ± 3	122 ± 7	146.8 ± 4	158.7 ± 5	162 ± 6	154 ± 7
V_{T_R}/T_I (ml/sec)	167 ± 4	148 ± 7	163.5 ± 4	202.0 ± 5	211 ± 7	187 ± 5
V_E (L/min)	4.31 ± 0.13	4.65 ± 0.37	4.53 ± 0.12	7.42 ± 0.37*	6.21 ± 0.22	7.86 ± 0.36
$I\text{-}P_{AW_L}$ (cm H_2O)	0.87 ± 0.03	1.02 ± 0.07	1.28 ± 0.04	1.42 ± 0.03	1.38 ± 0.06	1.64 ± 0.02
$I\text{-}P_{AW_R}$ (cm H_2O)	0.98 ± 0.04	1.09 ± 0.10	1.79 ± 0.02	2.15 ± 0.04	2.01 ± 0.04	2.31 ± 0.05
$E\text{-}P_{AW_L}$ (cm H_2O)	1.43 ± 0.02	1.80 ± 0.04**	1.42 ± 0.04	1.51 ± 0.03*	1.45 ± 0.01	1.77 ± 0.02**
$E\text{-}P_{AW_R}$ (cm H_2O)	1.26 ± 0.03	1.54 ± 0.03	1.91 ± 0.05	1.97 ± 0.06	1.80 ± 0.04	2.31 ± 0.03**
$I\text{-}P_{AW_L}/T_I$ (cmH_2O)	0.68 ± 0.04	0.75 ± 0.09	1.06 ± 0.07	1.25 ± 0.04	1.34 ± 0.03	0.93 ± 0.03
$I\text{-}P_{AW_R}/T_I$ (cm H_2O)	0.80 ± 0.06	0.85 ± 0.06	1.51 ± 0.07	1.94 ± 0.08	2.03 ± 0.06	1.29 ± 0.04
P_{ES_L} (cm H_2O/sec)	8.26 ± 0.20	- - - - - -	8.36 ± 0.24	9.41 ± 0.32	9.46 ± 0.34	9.58 ± 0.28
$I\text{-}F^L$ (L/min)	11.6 ± 0.2	12.6 ± 0.7	14.9 ± 0.4	15.8 ± 0.3	15.3 ± 0.1	15.9 ± 0.6
$I\text{-}F^R$ (L/min)	13.9 ± 0.3	13.8 ± 0.8	13.9 ± 0.2	16.0 ± 0.2*	17.2 ± 0.6	17.3 ± 0.3
$E\text{-}F^L$ (L/min)	16.5 ± 0.1	18.6 ± 0.9	16.7 ± 0.2	17.6 ± 0.3*	15.5 ± 0.2	15.5 ± 0.4
$E\text{-}F^R$ (L/min)	17.5 ± 0.20	18.6 ± 0.4	15.5 ± 0.3	16.7 ± 0.4*	17.3 ± 0.5	20.1 ± 0.2
E^L (cm H_2O)/L)	5.8 ± 0.1	6.0 ± 0.3	7.2 ± 0.2	8.1 ± 0.3	7.9 ± 0.2	5.7 ± 0.3*
E^R (cm H_2O/L)	5.0 ± 0.2	5.5 ± 0.4	8.9 ± 0.2	9.6 ± 0.4	9.3 ± 0.4	6.6 ± 0.3*

[a]Refer to ABBREVIATIONS.

[b]Values represent Mean + SEM. Measurements obtained from every breath over a 3 min period 25-40 min after vagotomy. Significant difference between vagotomized state and intact state represented by *$P<0.05$, **$P<0.01$.

Table A-4. Effects of hypoxic, hyperoxic, and differential lung ventilation on steady state respiratory cycle characteristics in vagally intact dogs

Variable[a]	HYPOXIA (n=12)		HYPEROXIA (n=14)		DIFF.VENT (n=18)	
	Before	During	Before	During	Before	During
T_I (msec)	1254 ± 27[b]	839 ± 21***	1088 ± 32	1099 ± 48	1197 ± 26	1128 ± 53
T_E (msec)	4454 ± 462	1355 ± 161**	3408 ± 216	4261 ± 228*	3343 ± 316	2714 ± 514*
T_{TOT} (msec)	5708 ± 164	2193 ± 87***	4496 ± 101	5360 ± 64	4539 ± 62	3842 ± 73*
T_I/T_{TOT} (%)	25.6 ± 0.2	38.3 ± 1.0***	27.7 ± 0.6	25.0 ± 0.8	29.3 ± 0.8	33.1 ± 1.0*
T_E/T_{TOT} (%)	74.4 ± 0.5	61.7 ± 0.4***	72.3 ± 0.9	75.0 ± 0.8	70.7 ± 0.7	66.9 ± 0.4*
T_E/TI	3.61 ± 0.42	1.65 ± 0.11**	3.13 ±	3.83 ± 0.28*	2.74 ± 0.42	2.27 ± 0.36**
V_{T_L} (ml)	187 ± 6	168 ± 4	180 ± 6	203 ± 9	170 ± 6	168 ± 7
V_T (ml)	218 ± 8	195 ± 7	205 ± 4	242 ± 3*	201 ± 6	211 ± 5
V_{T_L} (ml)	405 ± 7	363 ± 7	385 ± 6	446 ± 7*	371 ± 7	379 ± 6
V_{T_L}/V_T (%)	46.0 ± 6	46.8 ± 5	46.6 ± 4	45.5 ± 7	45.5 ± 3	44.0 ± 8
V_{T_R}/V_T (%)	54.0 ± 7	53.2 ± 9	53.4 ± 3	54.5 ± 6	54.5 ± 4	56.0 ± 6
V_{T_L}/TI (ml/sec)	156 ± 6	208 ± 5**	169 ± 7	185 ± 3*	148 ± 8	159 ± 4
V_T/TI (ml/sec)	184 ± 8	237 ± 11*	196 ± 7	221 ± 4*	179 ± 3	198 ± 9
V_E (L/min)	5.11 ± 0.61	10.08 ± 1.22***	5.89 ± 0.54	5.79 ± 0.79	5.66 ± 0.32	6.94 ± 0.41*
$I\text{-}PAW^L$ (cmH_2O)	1.34 ± 0.03	1.56 ± 0.06**	1.23 ± 0.04	1.29 ± 0. 03	1.23 ± 0.04	1.29 ± 0.02
$I\text{-}PAW^R$ (cmH_2O)	1.92 ± 0.06	2.30 ± 0.04*	1.82 ± 0.05	2.07 ± 0.07	1.82 ± 0.04	2.07 ± 0.08
$E\text{-}PAW^L$ (cmH_2O)	1.45 ± 0.03	1.43 ± 0.04	1.48 ± 0.02	1.67 ± 0.05*	1.37 ± 0.02	1.47 ± 0.03
$E\text{-}PAW^R$ (cmH_2O)	1.92 ± 0.42	1.89 ± 0.46	1.81 ± 0.31	1.89 ± 0.55	1.79 ± 0.41	2.01 ± 0.22*
$I\text{-}PAW^L/T_I$ (cmH_2O/sec)	1.13 ± 0.4	1.84 ± 1.0***	1.41 ± 0.9	1.47 ± 1.2	1.01 ± 0.3	1.23 ± 0.4*
$I\text{-}PAW^R/T_I$ (cmH_2O/sec)	1.65 ± 0.5	2.77 ± 1.1*	1.20 ± 0.3	2.16 ± 0.9	1.51 ± 0.4	2.00 ± 0.2*
P_{ES_L} (cmH_2O)	8.79 ± 0.21	10.40 ± 0.32	8.52 ± 0.16	9.28 ± 0.28*	7.43 ± 0.18	9.13 ± 0.26*
$I\text{-}F^L$ (L/min)	15.2 ± 0.1	18.8 ± 0.3**	15.0 ± 0.2	15.7 ± 0.1*	13.5 ± 0.3	14.1 ± 0.4
$I\text{-}F^R$ (L/min)	14.7 ± 0.1	17.8 ± 0.2**	16.3 ± 0.4	17.6 ± 0.3*	14.9 ± 0.4	17.1 ± 0.7*
$E\text{-}F^L$ (L/min)	16.8 ± 0.3	16.3 ± 0.2	16.2 ± 0.3	17.1 ± 0.1*	15.5 ± 0.4	15.5 ± 0.2
$E\text{-}F^R$ (L/min)	16.0 ± 0.4	15.0 ± 0.5	16.6 ± 0.3	17.4 ± 0.4	15.9 ± 0.3	15.9 ± 0.6
E^L (cmH_2O/L)	7.4 ± 0.2	9.2 ± 0.3*	8.2 ± 0.2	7.7 ± 0.5	6.9 ± 0.3	7.2 ± 0.3
E^R (cmH_2O)/L)	9.1 ± 0.2	11.0 ± 0.4*	9.7 ± 0.3	9.1 ± 0.4	8.4 ± 0.2	8.6 ± 0.3

[a]Refer to ABBREVIATIONS.

[b]Values represent Mean ± SEM. Significant difference between the Before and During test gas breathing periods represented by *P<0.05, **P<0.01, and ***P<0.001.

Table A5. Effects of hypoxic, hyperoxic and differential lung ventilation on steady-state respiratory cycle characteristics in bilaterally vagotomized dogs

Variable[a]	(n=9) Hypoxia	(n=8) Hyperoxia	(n=11) Diff. Vent.
T_I (msec)	1542 ± 21[b]	1956 ± 18	1730 ± 32
T_E (msec)	1610 ± 48*	3924 ± 122	3932 ± 83
T_{TOT} (msec)	3151 ± 120	5880 ± 221	5662 ± 186
T_I/T_{TOT} (%)	49.2 ± 0.9	34.2 ± 0.4	33.8 ± 0.3
T_E/T_{TOT} (%)	50.8 ± 1.1	65.8 ± 1.2	66.2 ± 0.9
T_E/T_I	1.04 ± 0.2*	2.02 ± 0.6	2.12 ± 0.5
V_T^L (ml)	338 ± 8	385 ± 6*	41 ± 8*
V_T^R (ml)	406 ± 9	461 ± 3*	535 ± 10*
V_T (ml)	744 ± 12	846 ± 9*	953 ± 12*
V_T^L/V_T (%)	45.8 ± 7	45.9 ± 4	4 ± 4
V_T^R/V_T (%)	54.2 ± 8	54.1 ± 6	56 ± 4
V_T^L/T_I (ml/sec)	218 ± 7*	214 ± 11	252 ± 6**
V_T^R/T_I (ml/sec)	263 ± 3*	258 ± 8	319 ± 9**
V_E (L/min)	14.04 ± 1.3*	10.01 ± 1.2*	11.9 ± 1.2**
$I\text{-}P_{AW}^L$ (cm H_2O)	1.59 ± 0.03	1.78 ± 0.04	2.25 ± 0.06
$I\text{-}P_{AW}^R$ (cm H_2O)	2.48 ± 0.07	2.43 ± 0.06	2.41 ± 0.08
$E\text{-}P_{AW}^L$ (cm H_2O)	1.92 ± 0.03	1.94 ± 0.02	2.15 ± 0.04
$E\text{-}P_{AW}^R$ (cm H_2O)	2.71 ± 0.05	2.33 ± 0.04	2.2 ± 0.06
$I\text{-}P_{AW}^L/T_I$ (cm H_2O/sec)	1.03 ± 0.4	1.1 ± 0.9	1.45 ± 0.4*
$I\text{-}P_{AW}^R/T_I$ (cm H_2O/sec)	1.62 ± 0.5	1.43 ± 0.6	1.53 ± 0.2
P_{ES} (cm H_2O)	12.6 ± 0.7	9.01 ± 0.3	10.89 ± 0.4
$I\text{-}F^L$ (L/min)	22.7 ± 0.6	18.5 ± 0.7	19.5 ± 0.6
$I\text{-}F^R$ (L/min)	19.9 ± 0.3	21.9 ± 0.5	26.5 ± 0.4
$E\text{-}F^L$ (L/min)	20.3 ± 0.4	20.5 ± 0.4	18.8 ± 0.3
$E\text{-}F^R$ (L/min)	22 ± 0.5	23.1 ± 0.2	27.6 ± 0.1
E^L (cm H_2O/L)	4.8 ± 0.3	4.5 ± 0.4	5.5 ± 0.5
E^R (cm H_2O/L)	6.1 ± 0.31	5.5 ± 0.6	4.6 ± 0.3*

[a]Refer to abbreviations.

[b]Values represent Means ± SEM with significant differences between normoxic BVX vs test gas BVX by paired comparisons designated as: *$p < 0.05$, **$p < 0.01$.

Table A6. Change in inspiratory duration of first effort breaths

Experimental Condition[a]	Type of Occlusion					
	RLO-EE	RLO-EI	LLO-EE	LLO-EI	BLO-EE	BLO-EI
I-Room Air	196 ± 22***[b]	222 ± 23***	200 ± 25***	221 ± 24***	811 ± 73***	650 ± 46***
I-Hypoxia	228 ± 60*	194 ± 94*	102 ± 33*	133 ± 31**	619 ± 82***	513 ± 83***
I-Hyperoxia	151 ± 32***	202 ± 31**	175 ± 25***	262 ± 24***	537 ± 64***	576 ± 53***
I-Diff. Vent.	133 ± 29***	262 ± 72**	162 ± 40**	348 ± 63***	723 ± 101***	784 ± 11***
LVX-Room Air	209 ± 84*	492 ± 304	94 ± 44*	45 ± 43	336 ± 103***	448 ± 52***
RVX-Room Air	-100 ± 27*	-10 ± 35	373 ± 90*	508 ± 73**	630 ± 110***	603 ± 219*
BVX-Room Air	25 ± 45	-95 ± 65	45 ± 55	-155 ± 25	205 ± 105	243 ± 168
BVX-Hypoxia	5 ± 50	10 ± 20	55 ± 15	10 ± 50	195 ± 15*	20 ± 40
BVX-Hyperoxia	-65 ± 185	22 ± 81	83 ± 57	-30 ± 120	253 ± 182	106 ± 137
BVX-Diff. Vent.	95 ± 45	-110 ± 280	5 ± 5	-20 ± 50	155 ± 45	250 ± 62*

[a]Refer to ABBREVIATIONS.

[b]Values given in units of time (msec, Mean ± SD) with significant differences between first effort and preceding control breaths designated as: *P < 0.05, **P < 0.01, and ***P < 0.001.

Table A7. Change in expiratory duration of first effort breaths

Experimental Condition[a]	Type of Occlusion					
	RLO-EE	RLO-EI	LLO-EE	LLO-EI	BLO-EE	BLO-EI
I-Room Air	-366 ± 375[b]	1350 ± 355***	297 ± 387	413 ± 250	196 ± 310	529 ± 268*
I-Hypoxia	5 ± 37	519 ± 131**	104 ± 42*	541 ± 166**	-144 ± 150	960 ± 176***
I-Hyperoxia	972 ± 564	2332 ± 985*	124 ± 222	1250 ± 306**	1822 ± 820*	4259 ± 464***
I-Diff. Vent.	233 ± 138	461 ± 451	203 ± 86*	1667 ± 471**	614 ± 160*	2473 ± 405***
LVX-Room Air	2192 ± 1126	1531 ± 664*	-820 ± 404*	-714 ± 511	190 ± 432	148 ± 269
RVX-Room Air	123 ± 79	-200 ± 192	473 ± 187	5463 ± 3078	723 ± 449	3140 ± 1054*
BVX-Room Air	-5 ± 365	-125 ± 105	275 ± 155	65 ± 105	-410 ± 70	-430 ± 122*
BVX-Hypoxia	-590 ± 570	-1 ± 170	-130 ± 60	-60 ± 60	-60 ± 20	-145 ± 115
BVX-Hyperoxia	490 ± 450	-118 ± 151	-133 ± 168	843 ± 655	410 ± 554	762 ± 618
BVX-Diff. Vent.	30 ± 360	-180 ± 120	-1 ± 240	-85 ± 155	-1245 ± 125*	-393 ± 603

[a]Refer to ABBREVIATIONS.

[b]Values expressed in units of time (msec; mean ± SD) with significant differences between first effort and preceding control breaths designated by: *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

Table A8. Change in total cycle duration of first effort breaths

Experimental Condition[a]	Type of Occlusion					
	RLO-EE	RLO-EI	LLO-EE	LLO-EI	BLO-EE	BLO-EI
I-Room Air	-170 ± 366[b]	1572 ± 354***	497 ± 392	634 ± 249*	1006 ± 311**	1180 ± 265***
I-Hypoxia	233 ± 61**	717 ± 172**	206 ± 43**	674 ± 196**	474 ± 152*	1491 ± 219***
I-Hyperoxia	1123 ± 575*	2533 ± 990*	298 ± 213	1512 ± 299***	2359 ± 844*	4836 ± 476***
I-Diff. Vent.	367 ± 130*	722 ± 425	366 ± 79***	2014 ± 471***	1336 ± 242***	3256 ± 400***
LVX-Room Air	2401 ± 1073*	2024 ± 652**	-726 ± 416	-669 ± 497	526 ± 381	597 ± 270*
RVX-Room Air	23 ± 89	-210 ± 179	847 ± 276*	5970 ± 3113	1353 ± 546*	3743 ± 1117*
BVX-Room Air	20 ± 320	-220 ± 170	320 ± 100	-90 ± 130	-205 ± 175	-187 ± 243
BVX-Hypoxia	-585 ± 575	10 ± 190	-75 ± 75	-50 ± 110	135 ± 35	125 ± 155
BVX-Hyperoxia	425 ± 265	-97 ± 99	-50 ± 199	813 ± 563	663 ± 604	868 ± 512
BVX-Diff. Vent.	125 ± 315	-290 ± 280	5 ± 235	-105 ± 105	-1090 ± 170*	-143 ± 540

[a] Refer to ABBREVIATIONS.

[b] Values given in units of time (msec, Mean ± SD) with significant differences between first effort and control breaths designated as: *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.

APPENDIX B: REPRESENTATIVE RECORDINGS OF CARDIOPULMONARY PARAMETERS DURING SPECIFIC EXPERIMENTAL PROCEDURES

Figure B1. Characteristic changes in the inspiratory and expiratory airflow patterns produced by bilateral vagotomy.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lung, esophageal pressure (P_{ES}) and a time scale. Note the changes in time scale before, during and after vagotomy (arrow). Vagal transection produces an apneic period followed by a bilateral increase in tidal volume and significant prolongation of total cycle duration. Fluctuations in inspiratory airflow are indicative of disrupted phrenic output. The increased slope of the expiratory flow trace results from removal of vagally mediated autogenic, i.e., laryngeal and pharyngeal, bronchomotor tone.

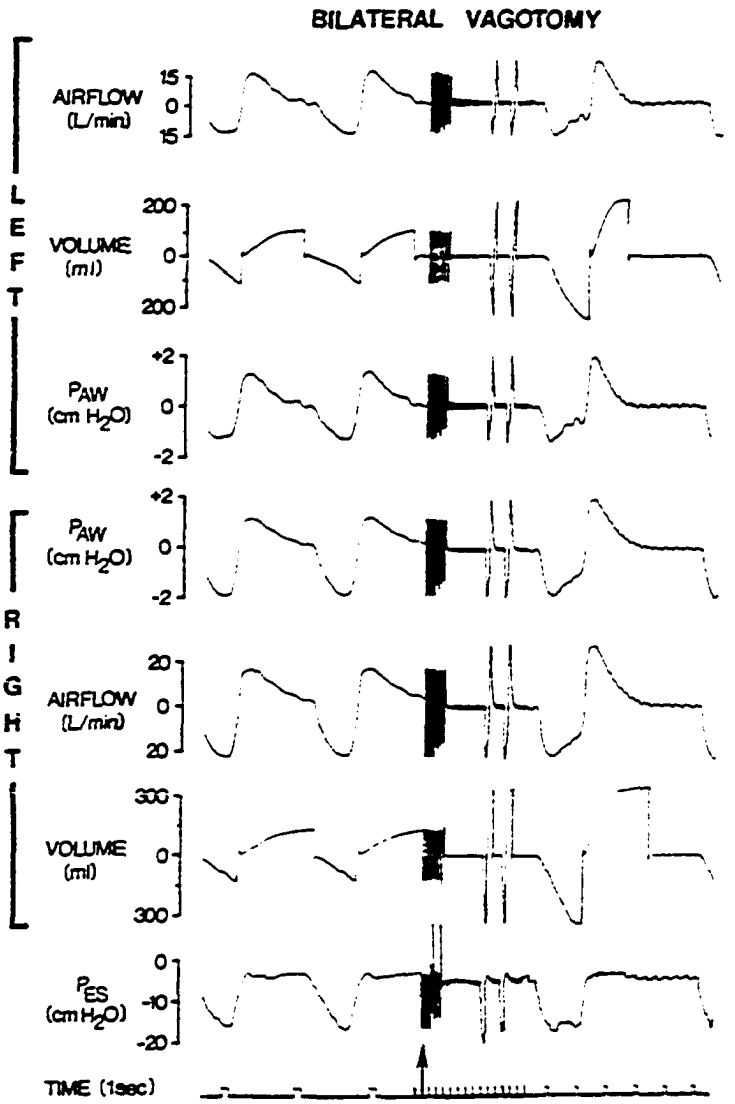

BILATERAL VAGOTOMY
LEFT
RIGHT
AIRFLOW (L/min)
15
0
15
VOLUME (ml)
200
0
200
PAW (cm H2O)
+2
0
-2
PAW (cm H2O)
+2
0
-2
AIRFLOW (L/min)
20
0
20
VOLUME (ml)
300
0
300
PES (cm H2O)
0
-10
-20
TIME (1sec)

Figure B2. Brief apneic response to right and bilateral vagotomy in anesthetized dog during room air breathing.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lungs, esophageal pressure (P_{ES}), pulmonary arterial blood pressure (PAP) and a time scale. Both procedures initially resulted in an immediate brief apneic period. However, right vagotomy produces small increases in tidal volume and respiratory rate while bilateral vagotomy produces a marked increase in volume and decrease in respiratory rate. The pulmonary pressor response to bilateral vagotomy was more apparent than that produced by cutting the right vagus, although neither was significant.

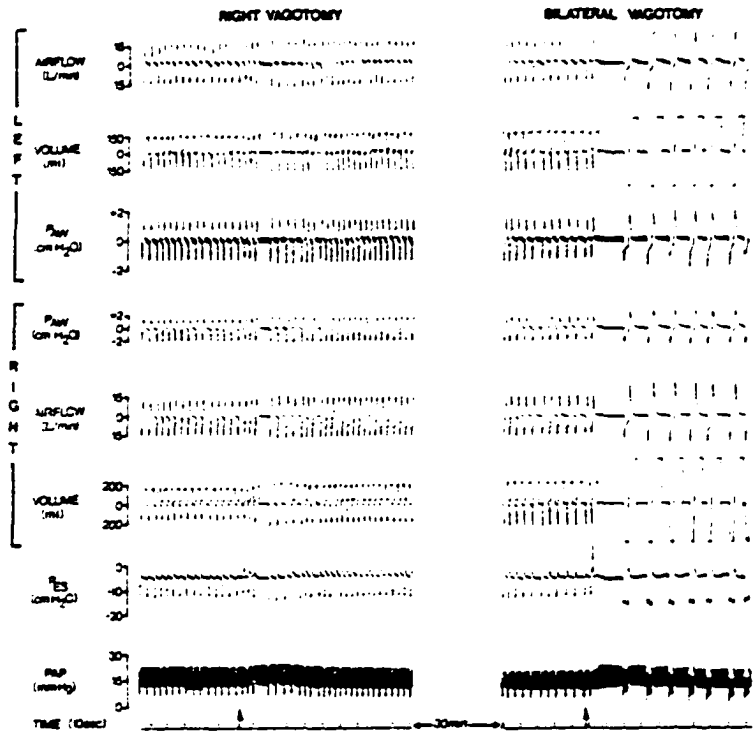

RIGHT VAGOTOMY
BILATERAL VAGOTOMY
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{aw} (cm H_2O)
P_{aw} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cm H_2O)
MAP (mmHg)
TIME (Osec)
30sec

Figure 83. Transient elimination of arrhythmic breathing patterns by severing one or both vagi.

Traces represent airflow, tidal volume and airway pressure (P_{AW}) of the left and right lungs, esophageal pressure (P_{ES}), pulmonary arterial blood pressure (PAP) and a time scale. Approximately 48 min elapsed between right vagotomy (RVX) and left or bilateral vagotomy (BVX) in this dog. Tidal volume is relatively unaffected by right vagotomy. Subsequent severing of the left vagus, i.e., BVX condition, produced a transient increase in tidal volume which rather quickly returned toward normal. Note that the changes in airflow are out of proportion to the changes in airway pressure indicating a decline in airway resistance following vagotomy. The resistance change occurs on the left as well as the right side following RVX which suggests cross-over innervation of the lungs.

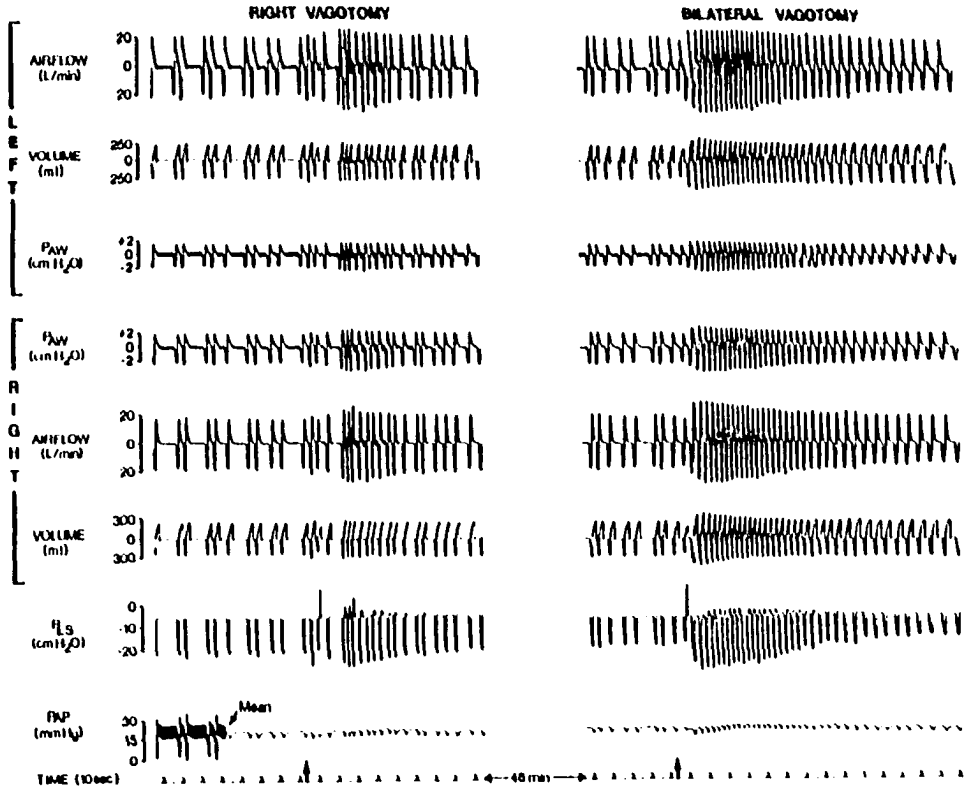
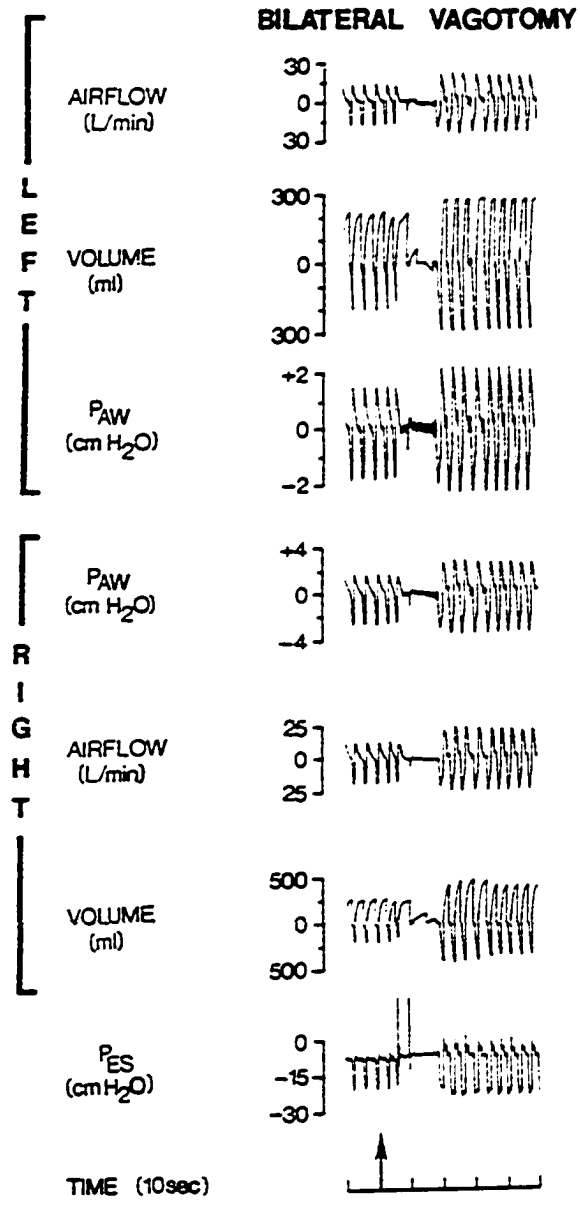

RIGHT VAGOTOMY
BILATERAL VAGOTOMY
LEFT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
RIGHT
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cm H_2O)
PAP (mm Hg)
Mean
TIME (10sec)
40 min

Figure B4. Volume changes in the absence of a frequency response to bilateral vagotomy.

Records show airflow, tidal volume and airway pressure (P_{AW}) of the left and right lungs, esophageal pressure (P_{ES}) and a time scale. Simultaneously severing both vagus nerves (arrow) produced a brief apneic period followed by a rhythmic respiratory pattern as usual. However, unlike in most dogs, the pattern was characterized by an unchanged breathing frequency with a concomitant increase in tidal volume.


BILATERAL VAGOTOMY
LEFT
RIGHT
AIRFLOW (L/min)
VOLUME (ml)
P_{AW} (cm H_2O)
P_{AW} (cm H_2O)
AIRFLOW (L/min)
VOLUME (ml)
P_{ES} (cm H_2O)
TIME (10sec)
30
0
30
300
0
300
+2
0
-2
+4
0
-4
25
0
25
500
0
500
0
-15
-30