THE EFFECTS OF PROLONGED STATIC INFLATION ON THE DISCHARGE CHARACTERISTICS OF PULMONARY STRETCH RECEPTORS IN TURTLES

by

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Both the tonic and phasic discharge characteristics of single slowly adapting pulmonary stretch receptors (SARs) were examined before and after a one hour period of maintained lung volume in freshwater turtles, *Pseudemys scripta* and *Chrysemys picta*. Lung volume was maintained at either resting volume (airway pressure = 0 cmH2O) or at an elevated lung volume (airway pressure = 10 cmH2O). Pressure inflations were performed with both air and 5% CO2 in air.

Two populations of receptors were recorded from: low threshold SARs (those that exhibited tonic discharge at resting lung volume) and high threshold SARs (those that did not exhibit tonic discharge at resting lung volume). During the one hour period of maintained lung inflation with air, low and high threshold SARs adapted up to 80% and 30% respectively. Following this period, the peak discharge rate attained with step inflation was unchanged in both groups. The low threshold SARs demonstrated a decrease in the phasic component of discharge associated with dynamic lung inflations following one hour of maintained lung inflation with air but the high threshold receptors did not.

During one hour of maintained lung inflation with 5% CO2 in air, low and high threshold SARs adapted more than they did during maintained lung inflation with air. Furthermore, there was an overall decrease in both the peak discharge attained with static lung inflation and the phasic responses to dynamic lung
infal tions following maintained lung inflation with 5% CO2 in both groups of receptors.

During the one hour period of maintained lung inflation with air, there were significant increases in both lung gas and blood gas levels of CO2, decreases in arterial pH and decreases in lung gas oxygen levels. The decreases in tonic and phasic components of SAR discharge seen during the one hour period of maintained lung inflation with air are due in part to an accumulation of metabolic (lung gas) CO2.
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INTRODUCTION

The function of breathing is to ensure that there is an adequate delivery of oxygen to, and removal of carbon dioxide from the gas exchange surface. The respiratory system, in conjunction with the cardiovascular system, provide the cells with the oxygen required for processes vital to their metabolism. In addition, these systems establish a means by which carbon dioxide, the primary metabolite of oxidative reactions, is removed from the body. The overall level of minute ventilation is actively adjusted through a number of control mechanisms to maintain adequate exchange over a wide range of metabolic states. These control mechanisms also serve to establish the breathing pattern. The amount of air moved in and out of the lungs each minute (minute ventilation, $\dot{V}$ (ml/min)) is the product of tidal volume (VT (mls)) and breathing frequency (min $^{-1}$). The frequency component of $\dot{V}$ is in turn a function of the inspiratory interval (TI) and the expiratory interval (TE). The relative levels of VT, TI and TE establish a breathing pattern (Bradley, 1977).

CONTROL OF VENTILATION:

The overall level of minute ventilation is controlled partially through afferent information arising from the peripheral and central chemoreceptors (Mitchell, 1980). In mammals there are two populations of peripheral chemoreceptors: one located at the bifurcation of the common carotid artery (carotid body chemoreceptors) and the other located near the
aortic arch (Daly, 1983). The chemoreceptors are distinct not only in their anatomical location, but also in their responses to respiratory stimuli. Both carotid and aortic body chemoreceptors readily respond to steady-state decreases in arterial blood oxygen tension by increasing their discharge. However, steady-state increases in arterial blood carbon dioxide tension and/or decreases in arterial pH elicit a greater increase in discharge from the carotid body chemoreceptors than from the aortic body chemoreceptors (Lahiri et al., 1983). Central chemoreceptors are situated near the ventrolateral surface of the medulla (Loeschcke, 1983) and respond to changes in the carbon dioxide tension of the extracellular fluid (ECF) in the brain. Molecular carbon dioxide (CO2) freely diffuses across the blood-brain barrier to the ECF, is readily hydrolyzed and dissociates to produce hydrogen ions (H+) and bicarbonate ions (HCO3-) (Slonim & Hamilton, 1971). The specific stimulus for the central chemoreceptors is thought to be the increased concentration of H+ ions near the area of the receptors (Loeschcke, 1983). The reflex response from the stimulation of both the central and peripheral chemoreceptors is manifest through a change in the overall level of ventilation as well as concomitant changes in breathing pattern (Mitchell, 1980).

CONTROL OF THE BREATHING PATTERN:

Air-breathing vertebrates demonstrate two types of breathing patterns, rhythmic and arrhythmic. Under normal physiological conditions, rhythmic breathing patterns are seen in fish, birds
and mammals while arrhythmic patterns are characteristic of most reptiles and some amphibians. The majority of the studies pertaining to the generation and maintenance of the breathing pattern have been conducted on mammals.

Generation of respiratory rhythm is a complex phenomenon involving extensive contributions from many motor neuron pools (for review see Euler, 1986). The primary respiratory rhythm generators are situated in the medulla and the pons. In the medulla, there are at least two distinct respiratory neuron groups closely associated with the central respiratory rhythm generator: the ventral respiratory group (VRG) located near the nucleus retroambigualis and the nucleus para-ambigualis and the dorsal respiratory group (DRG) located near the nucleus tractus solitarius (Euler, 1986). The DRG contains primarily inspiratory neurons whereas both inspiratory and expiratory neurons are found in the VRG (Mithcell, 1980). The pontine region has two respiratory neuron pools (the nucleus parabrachialis medialis and the Kolliker Fuse nucleus) which are not involved in the generation of respiratory rhythm per se, but are instrumental in influencing the timing of inspiration and expiration. Pattern generating neurons are also found in the phrenic motor nucleus of the spinal cord. This spinal rhythm generator is capable of maintaining respiratory rhythm in the absence of higher centers but in the intact animal, the central rhythm generators are of primary importance (Mitchell, 1980).

The rhythm produced by the central pattern generators is
modified by a number of factors. Parasympathetic afferent fibers of the tenth cranial (vagus) nerve projecting from the pulmonary receptors to the dorsal respiratory group located near the nucleus tractus solitarius are important in the control of respiration (for review see Sant'Ambrogio, 1982). From here, the DRG sends fibers to the phrenic motor nucleus in the ventral horns of the spinal cord (cervical segments 3, 4, and 5), the respiratory airways, as well as rostrally to inspiratory and expiratory neuronal pools within the ventral respiratory group. From the inspiratory and expiratory neurons in the VRG, efferent axons extend contralaterally to the intercostal and the phrenic motor neuron pools (Mitchell, 1980).

**Pulmonary Receptor Characteristics**

Maintenance of the normal breathing pattern is largely dependent upon afferent information arising from pulmonary receptors. There are three basic types of pulmonary receptors; slowly adapting pulmonary stretch receptors, rapidly adapting pulmonary stretch receptors and juxta-pulmonary capillary receptors (for review see Paintal, 1977).

Rapidly adapting pulmonary stretch receptors (RARs) were first described by Larrabee and Knowlton (1946). RARs are located exclusively in the larger diameter airways (> 0.3 mm) and respond to large changes in transmural pressure. Unlike slowly adapting pulmonary stretch receptors, these mechanoreceptors adapt quickly and completely to a maintained stimulus (Paintal, 1973).

Rapidly adapting pulmonary stretch receptors are also
stimulated by many noxious inhalents and are therefore commonly referred to as irritant receptors. Ammonia, aerosols and cigarette smoke are particularly effective in stimulating RARs. The typical reflex elicited by the stimulation of RARs is the cough reflex as well as an increase in minute ventilation (Paintal, 1977).

Juxta-pulmonary capillary receptors (J-receptors) are mechanoreceptors which are located in the interstitial lining of the lungs close to the pulmonary capillary bed (Paintal, 1969). The natural stimulus for these receptors is an increase in interstitial volume. Any condition (pathological or otherwise) that leads to pulmonary edema may result in the stimulation of J-receptors. Vigorous exercise frequently produces pulmonary edema and it has been postulated (Paintal, 1970) that stimulation of J-receptors may result in termination (or at least reduction) of exercise through central, reflex inhibition of the limb muscles. However, there is not much evidence to support this postulated reflex and the physiological significance of J-receptor stimulation remains a controversial issue.

Both rapidly adapting pulmonary stretch receptors and juxta-pulmonary capillary receptors are only activated under peculiar circumstances. Neither the RARs nor the J-receptors are involved in establishing the normal breathing pattern. Unless otherwise stated, all further discussion of pulmonary receptors and their contribution to the control of the breathing pattern will pertain only to slowly adapting pulmonary stretch receptors.
since these are the main contributors to breathing pattern control under most conditions.

Slowly adapting pulmonary stretch receptors (SARs) are mechanoreceptors that relate information concerning the total volume of gas in the lung (static discharge information) as well as the rate at which the lungs are filled (dynamic discharge information) (Bartlett et al., 1976). They actually respond to the rate and extent of deformation of pulmonary membranes in which they are situated (Knowlton and Larrabee, 1946; Davis et al., 1956). Classically, slowly adapting pulmonary stretch receptors were thought to be invoked in the Hering-Breuer inspiratory off-switch reflex. Their input is inhibitory to inspiration such that once a threshold level of afferent information is attained, inspiration is terminated and expiration is promoted (Euler et al., 1970). Slowly adapting pulmonary stretch receptors were first described by Adrian (1933) who recorded from these receptors by way of fibers running in the vagal nerve tract using both cats and rabbits. He identified SARs as units that display a regular (tonic) level of discharge at end-expiratory lung volume or functional residual capacity (FRC) and increase their rate of discharge with spontaneous increases in lung volume. It has since been shown that some slowly adapting pulmonary stretch receptors are tonically active at functional residual capacity while others only respond when lung volume exceeds FRC (for review see Sant'Ambrogio, 1982). Studies on mammals have revealed that SARs that show different discharge
thresholds are anatomically distinct receptor populations. Slowly
adapting pulmonary stretch receptors that do not exhibit a tonic
level of discharge at FRC tend to be concentrated in the distal
intra-pulmonary airways while SARs that do exhibit a tonic level
of discharge at FRC are found primarily in the larger diameter
(usually extrapulmonary) airways (Paintal, 1977).

Since the original description of slowly adapting pulmonary
stretch receptors (Adrian, 1933), it has been shown that receptor
discharge corresponds more closely with transmural or
transpulmonary pressure than with lung volume (Davis et al.,
1956; Sant'Ambrogio et al., 1974; Bartlett et al., 1976;
Davenport et al., 1981). In order for a mechanoreceptor to
respond to changes in pressure, a net force must be developed
across the tissue wall in which the receptor sits. In animals
such as turtles, the structure of the lung and the location of
the pulmonary stretch receptors is such that the receptors do not
see a change in transpulmonary pressure with lung
inflation/deflation cycles (Gans and Hughes, 1967; Jones and
Milsom, 1979). In light of this phenomenon, it is not surprising
then to find that turtle SAR discharge parallels changes in lung
volume rather than (artificially induced) changes in
transpulmonary pressure (Jones and Milsom, 1979).

Whether the discharge of a pulmonary mechanoreceptor
corresponds more readily to changes in transpulmonary pressure or
to changes in lung volume is likely to be dependent on the
orientation of the receptor within the pulmonary tissue.
Receptors that respond to changes in transpulmonary pressure appear to be situated parallel to pulmonary muscle fibers and are therefore activated when they are stretched during muscle extension (Bartlett et al., 1976). Receptors whose discharge corresponds more readily to changes in lung volume are likely to be located in series with pulmonary muscle fibers and are activated by tissue compression with changes in lung volume.

**Interactions Between the Pneumotaxic Center and SARs**

Stimulation of the nucleus parabrachialis medialis, located in the mid-pontine region of the brainstem, results in the premature termination of the inspiratory phase of the breathing cycle. A more pronounced stimulus is required to terminate inspiration in the early phase of the breathing cycle than is required in the later portion (Euler et al., 1976). This region of the brainstem, commonly referred to as the pneumotaxic center, plays a major role in ventilatory timing (Mitchell, 1980).

Neurons within the nucleus parabrachialis medialis only assume an independent respiratory rhythm in the absence of vagal input. During normal respiration, the pneumotaxic center works in conjunction with afferent impulses arising from slowly adapting pulmonary stretch receptors to help determine the timing (duration of the inspiratory and expiratory phases) of the breathing cycle (Mitchell, 1980).

Several models have been proposed to explain the interaction between pulmonary afferent information (from SARs) and the pneumotaxic center, and their subsequent roles in the production
and maintenance of the breathing pattern (Clark and Euler, 1972; Feldman, 1976; Agostoni et al., 1985). The fundamental basis for the control of ventilatory timing is by no means agreed upon. However, there is no doubt that vagal information arising from slowly adapting pulmonary stretch receptors plays an important role in the maintenance of a normal breathing pattern (Bradley, 1977).

**Influences on SAR Discharge - Effects of Hypercapnia**

Just as many factors affect the final output of the central rhythm generator, several factors affect the discharge characteristics of pulmonary stretch receptors. One such factor is CO2. Slowly adapting pulmonary stretch receptor discharge is decreased by variable amounts with increases in the CO2 concentration of inspired air (Mustafa and Purves, 1972; Bartlett and Sant'Ambrogio, 1976; Jones and Milsom, 1979; Mitchell et al., 1980). In mammals, intrapulmonary (bronchial) slowly adapting pulmonary stretch receptors show a much more marked decrease in discharge with a hypercapnic stimulus than do extrapulmonary (tracheal) SARs (for review see Sant'Ambrogio, 1982). Furthermore, bronchial SAR discharge decreases much more during local hypercapnic exposure (increased levels of inspired CO2) than with systemic hypercapnic exposure (Bartlett and Sant'Ambrogio, 1979). Green et al., (1986) have demonstrated that SARs located in the lungs of dogs are in fact sensitive to increased levels of pulmonary arterial PCO2. Since they observed no concomitant change in tracheal pressure, they assumed that CO2
evoked the decrease in SAR discharge by acting directly on the receptor itself.

The actual mechanism by which CO2 exerts its effects on SAR discharge is unknown. It has been proposed that CO2 may affect the microenvironment of the extracellular fluid surrounding the stretch receptor. Sant'Ambrogio et al. (1974) have postulated that the decrease in pH of the microenvironment arising from the increase in the (H+) associated with hypercapnia may be instrumental in the reduction of SAR discharge. Another possible mechanism proposed by Bartlett and Sant'Ambrogio (1976), is that the ionic composition of the ECF may be altered by a hypercapnic induced release of protein-bound Ca++ from the receptor membrane. This change in ECF composition may be instrumental in diminishing the response of slowly adapting pulmonary stretch receptors in the presence of increased levels of inspired CO2 (Bartlett and Sant'Ambrogio, 1976). Still another postulated mechanism is that CO2 affects the tone of the smooth muscle in which the receptor is situated whereby affecting its discharge (Mitchell et al., 1980; Richardson et al., 1984).

Influences on SAR Discharge - Effects of Adaptation

Slowly adapting pulmonary stretch receptor discharge decreases over time with a maintained stimulus of elevated lung volume (VLE) (Adrian, 1933). This process of stretch receptor adaptation is a complex phenomenon which has both a mechanical and an ionic basis. The mechanical basis of mechanoreceptor adaptation usually involves a change in the visco-elastic
properties of the tissue in which the stretch receptor is located (Davenport et al., 1981; Muza and Frazier, 1983). The ionic basis involved in stretch receptor adaptation can act either at the level of the sensory ending (which would affect the spike generator potential) or at the level of the spike encoder (which would elicit postspike decreases in receptor excitability) (Grigg, 1986). Sensory ending stretch receptor adaptation may involve cation gated mechanisms (possibly Ca++ gated K+ channels) which are activated by the changes in membrane potential associated with depolarization. These cation gated mechanisms would serve to repolarize the receptor membrane and therefore reduce the generator potential thus leading to adaptation. Stretch receptor adaptation at the spike encoder level is thought to be the result of an electrogenic Na+ pump that is stimulated by the Na+ influx during the depolarizing phase of the previous action potential (for a review see Grigg, 1986).

The rate at which slowly adapting pulmonary stretch receptors adapt to a maintained lung inflation is commonly used as a basis for SAR classification (Knowlton and Larrabee, 1946; Davis et al., 1956). These early calculations of SAR adaptation indices were based on very short periods of a maintained elevated lung volume stimulus (seconds to minutes). More recent studies undertaken to examine the adaptation responses of SARs to longer term maintained lung inflations have produced some very interesting and seemingly controversial results.
J. Breuer postulated that the tonic component of SAR discharge influences the control of ventilatory frequency in the absence of any phasic component (Bartoli et al., 1973). Bartoli et al., (1973) undertook experiments to examine the hypothesis that changing the tonic level of SAR discharge (by changing the end-expiratory lung volume) influences the timing of the breathing cycle. In their study, central respiratory rhythm (ventilatory effort) was assessed by way of a phrenic neurogram while the effect of changing FRC on ventilatory timing was examined in paralyzed dogs on cardiopulmonary bypass, in the presence and absence of vagal information. Abolishing the phasic component of PSR discharge by neuromuscular blockade (elimination of breathing movements) prolonged the inspiratory phase (TI) of the breathing cycle. There was no consistent effect on the expiratory phase (TE) and the overall decrease in ventilatory frequency with ensuing paralysis was attributed to an increase in TI. Alterations of functional residual capacity (maintained for 40 to 120 seconds) in the absence of breathing movements had no affect on TI but did change overall ventilatory frequency by exerting a profound effect on TE. In both protocols, bilateral vagotomy abolished the effects of changes in FRC. These results strongly indicate that at least in dogs, phasic information primarily affects TI and tonic information affects TE. Furthermore, TI and TE are under different control mechanisms.

Grunstein et al., (1975) performed additional experiments to further assess the effect of positive end-expiratory loading on
ventilatory timing relationships while recording from slowly adapting pulmonary stretch receptors in the cat. The results obtained from these studies were in close agreement to those obtained by Bartoli et al., (1973). Since studies performed by Bartoli et al., (1973) showed that increasing FRC had no effect on TI, Grunstein et al., (1975) postulated that there was either a peripheral (SAR) and/or a central (respiratory rhythm generator) adaptation to the new level of lung volume. They examined the discharge of slowly adapting pulmonary stretch receptors in cats that were spontaneously breathing from functional residual capacity and then from an elevated lung volume (VLE). When animals were breathing from FRC, occlusion of the trachea at end-expiratory lung volume did not bring about discharge from the stretch receptors. Occlusion at end inspiration however, did elicit discharge from the SARs (there was tonic SAR discharge at the end-inspiratory lung volume but not at FRC). When animals were breathing from an elevated lung volume (achieved by positive end-expiratory pressure), similar results were obtained. Upon tracheal occlusion at end-expiratory volume, there was no tonic SAR discharge, whereas tracheal occlusion at end-inspiratory volume was accompanied by discharge.

Lung volumes at end-inspiration when breathing from FRC were not appreciably different from lung volumes at end-expiration while breathing from VLE. Since slowly adapting pulmonary stretch receptors demonstrated tonic discharge at end-inspiration but not at end-expiration at VLE, the tonic component of SAR discharge
must have adapted to the elevated lung volume. Grunstein et al., (1975) concluded that the tonic component of the vagal mechanism controlling TI adapted such that only phasic information was important in determining ventilatory timing i.e. TI was independent of functional residual capacity. The conclusions of Grunstein et al., (1975) also explain why in the study of Bartoli et al., (1973), changes in functional residual capacity had no effect on TI.

The study of Grunstein et al., (1975), however, has also produced conflicting results concerning the role of tonic SAR discharge in the modulation of ventilatory timing. One one hand, they have shown that the tonic component of SAR discharge adapted to the new (elevated) lung volume. On the other hand, the duration of the expiratory phase of the breathing cycle was extended when the animals were breathing from this elevated FRC. Therefore, TE must be dependent not only upon phasic lung information (as was previously demonstrated by Clark and Euler, 1972), but on a separate vagal mechanism which is sensitive to absolute end-expiratory lung volume (Grunsterin et al., 1975).

In preliminary studies examining central pattern generator contributions to breathing pattern changes induced by alterations in FRC, Stanley et al., (1975) have demonstrated that with extended periods of maintained inflation (up to 8 minutes), the phrenic activity (monitoring central respiratory breathing efforts) returned toward normal values. Time course analysis indicated that this central adaptation was independent of the
adaptation seen in the slowly adapting pulmonary stretch receptors. Extending these findings, one might postulate that the changes in breathing pattern (the TI and TE timing relationship) observed with maintained VLE in the experiments of Bartoli et al., (1973) and Grunstein et al., (1975) were only transient, and in time they would revert to the normal pattern.

Jammes et al., (1983) have suggested that part of the central adaptation seen during maintained VLE is due to the activation of proprioceptive afferents in the expiratory muscles. These afferents project onto supraspinal structures localized to the medullary inspiratory neurons of the DRG. Sufficient stimulation of these afferents will prematurally terminate TI (Shannon, 1980). If these afferent fibers are stimulated during the expiratory phase, TE will also be extended (Remmers and Martilla, 1975). Intercostal proprioceptive afferent fibers have been shown to be activated by increases in functional residual capacity (through the process of end-expiratory loading) and cannot be ignored as a possible contributor to central respiratory rhythm habituation.

While the studies that demonstrate an adaptation or resetting of the central respiratory rhythm generator (Stanely et al., 1975; Jammes et al., 1983) remain nearly uncontested, a controversy still exists as to the degree of adaptation demonstrated by the slowly adapting pulmonary stretch receptors with maintained VLE. Grunstein et al., (1975) concluded that the tonic component of SAR discharge completely adapts to a change in
lung volume and these receptors essentially reset their threshold level of discharge. These results are in contrast to other studies which show that SARs only partially adapt to maintained elevated lung volumes.

D'Angelo and Agostoni (1975) undertook studies to determine the effects of changing functional residual capacity on lung volume—ventilatory timing relationships. They wanted to assess the contribution of slowly adapting pulmonary stretch receptors to the breathing pattern changes associated with these alterations in FRC. Experiments were conducted on anesthetized, spontaneously breathing cats, dogs and rabbits. Functional residual lung volume was altered by having the animals breathe at either continuous positive or negative pressure. Clark and Euler (1972) have previously demonstrated that the normal tidal volume—inspiratory duration (VT-TI) relationship is a hyperbolic function. D'Angelo and Agostoni (1975) showed that changing the functional residual lung volume of these animals changed the slope of this hyperbolic function and resulted in alterations in the breathing pattern. When FRC was increased, there was an increase in tidal volume and a decrease in breathing frequency (primarily produced by an extension of the expiratory phase of the breathing cycle). These pattern changes resulted in an increase in the slope of the VT-TI relationship. Bilateral cervical vagotomy eliminated these responses to changes in FRC indicating that vagal information arising from slowly adapting pulmonary stretch receptors was responsible for these changes in
breathing pattern. Furthermore, because these breathing pattern changes were persistent (lasting at least 10 minutes) the SARs could not be adapting to the imposed changes in FRC. If the SARs were adapting (as was suggested by Grunstein et al., 1975), then the central respiratory rhythm generator must be influential in maintaining these breathing pattern changes.

Davenport et al., (1981) investigated the adaptation responses of slowly adapting pulmonary stretch receptors located in the extrathoracic trachea of dogs. Upon stimulation (by elongation of the trachealis muscle), these receptors dramatically increased their discharge rate. When muscle stretch was maintained, the receptors showed a rapid adaptation response so that after 3 minutes of muscle stretch the rate of discharge had adapted to within 50% of the pre-stretch values. Davenport et al., (1981) attributed the majority of this adaptation response to changes in the mechanical properties of the muscle in which the receptors were situated.

Muza and Frazier (1983) further investigated SAR adaptation by examining the response of these receptors to prolonged shifts in functional residual capacity in spontaneously breathing cats. They recorded from single unit SARs and monitored the discharge of these receptors while the animals underwent spontaneous breathing episodes at resting and then at artificially elevated lung volumes. Results from this study are consistent with those from Davenport et al., (1981) in that they indicate that the receptors underwent only partial (albeit significant) adaptation.
The conflicting results regarding the adaptive properties of slowly adapting pulmonary stretch receptors have led to different conclusions on the relative importance of the tonic (volume related) and the phasic (rate related) components of SAR discharge in the control of the breathing pattern, particularly at lung volumes other than functional residual capacity. Studies which have shown slowly adapting pulmonary stretch receptors to adapt completely to maintained changes in lung volume would tend to suggest that the important component of SAR discharge is the phasic component (that which monitors changes in lung volume). This conclusion, in combination with results demonstrating that the central respiratory rhythm generator often adapts to changes in lung volume leads one to the conclusion that total lung volume actually has very little importance in the control of ventilation under steady-state conditions. In light of the other studies that show only a partial adaptation of slowly adapting pulmonary stretch receptors to maintained VLE, the role of the tonic component of SAR discharge is far from defined.

In mammals, adjustments in posture or body position often produce minor deviations in resting lung volume (Grunstein et al., 1975). However, it is unlikely that these animals experience very severe changes in FRC under normal physiological conditions. Animals such as turtles on the other hand actively undergo significant changes in their resting lung volumes. Turtles are aquatic animals that spend a great deal of time passively floating at the surface of the water. They are also capable of
undergoing very long dives and remain at various depths in the water column for extended periods of time. These animals are able to attain these various buoyancy states by altering their specific gravity through adjustments in lung volume. Regulation of lung volume is brought about by changes in pulmonary smooth muscle tonus (Milsom, 1975).

The normal breathing pattern of turtles consists of a series of breaths separated by a variable non-ventilatory (breathhold) period beginning at the end of inspiration. The overall frequency component of this periodic breathing pattern is a combination of the number of breaths within the ventilatory episode and the number of breathing episodes per unit time. Several studies have now shown that the duration of the nonventilatory period (or the number of breathing episodes per unit time) is the major controlled variable determining breathing frequency (Glass et al., 1978; Benchetrit and Dejours, 1980; Milsom and Jones, 1980).

Control of the duration of the nonventilatory period in animals exhibiting a periodic breathing pattern is a problem that has received a good deal of attention. Since blood gas tensions must change during the breathhold period, peripheral and central chemoreceptor reflex information may be an important factor in determining the breathhold length (Burghgren et al., 1978; Ackerman and White, 1979; Glass et al., 1983). However, no clear blood gas tension thresholds have been defined.

Johansen (1970) has suggested that the progressive decrease in lung volume over the duration of the breathhold period (due to
cutaneous CO2 elimination and blood and tissue CO2 storage) may be instrumental in terminating the breathhold. However, correlation studies have revealed that there is a high degree of variability between resting lung volumes and breathhold duration (Milsom and Johansen, 1975; Burggren and Shelton, 1979; Ackerman and White, 1979). It is likely that breathhold duration is controlled through a combination of chemoreceptor information and afferent information arising from slowly adapting pulmonary stretch receptors (Milsom and Chan, 1986).

Milsom and Chan (1986) examined the effects of chronic changes in resting lung volume (VLR) on the ventilatory pattern of turtles. When the body weight of these animals was altered through the attachment of either weights or floats to their shells, turtles increased or decreased their resting lung volume. They underwent this physiological adaptation in order to maintain neutral buoyancy which was normally attained within 24 to 48 hours (Milsom and Chan, 1986). Results from this study indicate that chronic alterations in resting lung volume had no effect on the overall levels of minute ventilation, tidal volume or breathing frequency. There was however, a distinct change in the breathing pattern of these animals. With an increase in resting lung volume, the turtles showed a decrease in the relative tidal volume (calculated as tidal volume per ml resting lung volume), an increase in the duration of the breathhold period and an increase in the number of breaths within each ventilatory period. Increases in VLR may allow the animal to extend the breathhold.
period (due to an increase in lung oxygen stores) but, in order to maintain an adequate turnover of the respiratory medium in light of the decrease in the relative tidal volume, the number of breaths within each breathing episode must be increased. Unlike the transient changes in the mammalian breathing pattern associated with alterations of functional residual capacity, the pattern changes in turtles persisted for many days (Milsom and Chan, 1986).

The results of Milsom and Chan (1986) demonstrate that the breathing pattern trends associated with chronic alterations in lung volume are likely to be due to the effect of these volume changes on pulmonary stretch receptor output.

If in fact slowly adapting pulmonary stretch receptors play a major role in producing and maintaining the breathing pattern changes associated with long term lung volume alterations in these animals, one would postulate that these receptors must not adapt completely during maintained lung inflation. Thus the present study was undertaken to determine the effects of maintained lung inflation on the discharge of slowly adapting pulmonary stretch receptors. Since increased levels of inspired CO2 are known to diminish SAR discharge (Jones and Milsom, 1979), the effects of prolonged inflation with hypercapnic gas (5% CO2 in air) on the discharge of these receptors was also investigated.
MATERIALS & METHODS

Animals:

Experiments were performed on freshwater turtles (*Pseudemys scripta* and *Chrysemys picta*) ranging in weight from 500 to 1000 grams. The turtles were housed at room temperature in plexi-glass tanks filled to a depth of approximately 40 cm with fresh running water. Wooden floats and heat lamps maintained on a 12 hour light cycle were provided for basking. Throughout the winter months the turtles rarely ate while during the summer months they were offered a diet consisting of raw meat (ground beef, liver and brine shrimp).

Surgical Procedure:

Turtles were single-pithed and restrained. A mid-line incision was made on the ventral surface of the neck and the trachea was exposed. A cannula was inserted into the trachea as low in the neck as possible and tied in place with surgical silk. The incision was then sutured shut and the animals were artificially ventilated with air using a Harvard Respirator. To connect a pressure transducer (*Statham P23V*) to the tracheal cannula, a small hole was drilled into the closed end of a plastic 3-way stopcock and a piece of PE90 tubing was inserted into this opening and secured with epoxy glue. The tube was filled with water and connected to the pressure transducer for measurements of intratracheal pressure. The pressure signal was simultaneously recorded on magnetic tape (Hewlett-Packard 3968A...
Instrumentation Recorder) and on a chart recorder (Beckman). The animals were then positioned in dorsal recumbancy to prepare for nerve recordings.

Measurement of Pulmonary Stretch Receptor Activity:

An incision was made in either the right or left side of the neck beginning just below the ear and extending down the neck for approximately 4 cm. The vagosympathetic nerve (tenth cranial nerve) was kept intact and dissected free from the surrounding tissue. The nerve was laid across a metal base plate and covered with mineral oil. The nerve was transected and then desheathed using fine watch makers forceps. A small cut was made in the nerve from which fiber slips were teased away from the vagal trunk.

Single or pauci unit recordings arising from receptors modulated by lung inflation were made using bipolar silver electrodes. The electrical activity from these receptors was amplified, filtered (FRAMP general purpose amplifier; F. Smith, Vancouver, B.C.) and recorded on magnetic tape. The filtered signal was passed through a window discriminator (W.P. Instruments - Model 121) and the output from the window discriminator was counted with a rate meter (EKE Electronics - Model RT 682). The outputs from both the window discriminator and the rate meter were also recorded on the chart recorder while only the signal from the window discriminator was stored on magnetic tape. Throughout the experiments, both the filtered and the unfiltered electrical signals arising from the receptors, the
window discriminator output and the pressure signal were viewed on a storage oscilloscope (Tetronix 5111A) and either the filtered or the window discriminated signals were played through an audio amplifier (Grass AM8). The rate meter was calibrated with a stimulator (Grass - Model S6C) prior to the recording procedure and the pressure transducer was calibrated with a water manometer (C.F. Palmer, London).

Measurement of Blood and Lung Gases:

Lung gas was sampled from the tracheal cannula using a 50 ml glass syringe equipped with a 3-way stopcock. With the pump ventilator off and the lungs at resting volume, gas was drawn out of the lungs by manipulating the syringe and the stop cock so that only the end-tidal gas was saved for measurements. The fractional concentration of oxygen and carbon dioxide in the lung gas was determined using an O2 analyzer (Beckman OM-11) and a CO2 analyzer (Beckman LB-2).

For blood sampling, a small hole was drilled in the upper middle portion of the carapace and the left subclavian artery was cannulated. The cannula was drawn out of the animal through a small hole made just below the front left leg and the hole in the carapace was then resealed with dental acrylic. The oxygen and carbon dioxide electrodes were calibrated using gases of varying CO2 concentrations mixed with a precision gas mixing pump (Radiometer, GMA 2). The pH electrode was calibrated using standardized buffering solutions (Radiometer; S1500 and S1510). All calibrations and measurements were done at room temperature (22°C).
**Experimental Protocol:**

The experimental procedure consisted of three separate protocols as illustrated in figure 1. The short term (150 seconds) maintained lung inflations and the dynamic lung inflations occurred at the same point in each protocol. The difference between the protocols resided in the one hour period of maintained lung volume. During the control protocol the lungs were maintained at resting volume for one hour, during the test protocol the lungs were maintained at an elevated volume for one hour and during the CO2 test protocol the lungs were maintained at an elevated volume for one hour after the animal had been ventilated with 5% CO2 in air. Between each protocol (control, test and CO2 test), the animals were pump ventilated with air for a 45 minute recovery period.

Resting lung volumes in *P. scripta* and *C. picta* have been found to be approximately 12 ml/100 grams (Jackson, 1971; Milsom, 1975). Resting lung volume is defined as the equilibrium volume at which the opposing forces of the thorax and the lungs are balanced (Jackson, 1971). In turtles this volume is reached when the animals are lying on their ventral surface with the glottis open. Resting lung volume results in an intratracheal pressure of 0 cmH2O. For the purpose of this study, elevated lung volume has been defined as the volume associated with an intratracheal pressure of 10 cmH2O. The elevated lung volume was maintained by a continuous positive pressure of 10 cmH2O. Animals were ventilated with 10 breaths at a standardized tidal volume
FIGURE 1  Outline of Nerve Recording Protocol

Panel A  Static and dynamic inflations prior to long term maintained lung volume

Panel B  Long term maintained lung volume at resting (control protocol) and elevated (test protocol) levels

Panel C  Static and dynamic inflations following long term maintained lung volume

The CO2-test protocol consisted of static and dynamic inflations on air (panel A) followed by 5 minutes of pump ventilations on 5% CO2 in air. After this equilibration period, the test protocol was performed (all inflations were with 5% CO2 in air).
CONTROL PROTOCOL

A

150s. vent. 30s.

B

150s. vent.

C

150s. vent. 30s.

TEST PROTOCOL

A

150s. vent. 30s.

B

150s. vent.

C

150s. vent. 30s.

60 minutes at $V_{L\text{REST}}$

60 minutes at $V_{L\text{ELEVATED}}$
(2.5 ml/100 grams) which was superimposed on both resting and elevated lung volumes.

When a single unit slowly adapting pulmonary stretch receptor was identified, the protocol was begun. Slowly adapting pulmonary stretch receptors are easily recognized as receptors that respond not only to an increase in lung volume with an increase in discharge rate, but also show a slow rate of adaptation to a maintained elevation in lung volume (Adrian, 1933; Knowlton and Larrabee, 1946; Davis et al., 1956). In addition, slowly adapting pulmonary stretch receptors demonstrate a discharge overshoot upon a sudden increase in lung volume as well as an off-response where discharge is absent for a short period of time upon lung deflation (Sant'Ambrogio, 1982). Ideally, all 3 components of the protocol were performed on each single unit receptor. To complete this task recordings had to be made continuously for at least 6 hours. Since this was often impossible, much of the data is comprised of recordings from receptors during only 1 or 2 components of the protocol.

Since the nerve recording apparatus is extremely sensitive to movement, the blood and lung gases were analyzed during a separate series of experiments on a different group of turtles to avoid the risk of damaging the recording preparation. Blood samples were withdrawn before beginning the protocol as well as prior to and immediately following the equilibration period (see figure 2). Again, animals were ventilated with either air or 5% CO2 in air. The blood and lung gas values obtained during
equilibration at resting lung volumes were not significantly different from those obtained during equilibration at elevated lung volumes and only the data from the elevated lung volume experiments are presented. Subsequent studies were performed using the basic protocol with a 6 hour equilibration period. In these experiments, blood samples were removed as described above with additional samples taken every 2 hours throughout the extended equilibration period.

Data Analysis:

Since the data obtained from the two subspecies of aquatic turtles used in this study were not significantly different, the results were combined. Experiments were conducted in both summer (April to September) and winter (October to March) months. Even though the metabolism of these animals tends to be lower during the winter months (Bennett and Dawson, 1976), there were no seasonal differences in the data obtained, probably owing to the extreme state of cerebral disarray of the animals.

To analyze the data, filtered electrical signals arising from slowly adapting pulmonary stretch receptors that were previously stored on magnetic tape were played back. These signals were rediscriminated and then counted using the rate meter. The signals from the window discriminator, the rate meter and the previously recorded signals from the pressure transducer were then transferred to a Gould chart recorder.

Analysis of the static discharge component involved examining the rate of occurrence of action potentials in response to
FIGURE 2  Outline of Blood Gas and Lung Gas Protocol

Test Protocol:

Panels A, B and C correspond to figure 1 captions

CO2-test Protocol:

Panel A  Static and dynamic inflations on air
Panel B  Long term maintained inflation after at least 5 minutes of pump ventilation on 5% CO2 in air
Panel C  Static and dynamic inflations following long term maintained elevated lung volume

Symbols:  ♠ denotes lung gas sampling
          ♦ denotes blood gas sampling
TEST PROTOCOL

CO₂ - TEST PROTOCOL

CO₂ ADDITION (5 min)
maintained increases and decreases in lung volume. Discharge rate was analyzed at the following points in the protocol:

a. resting lung volume prior to static lung inflation
b. peak discharge with static lung inflation
c. for 2 1/2 minutes at elevated lung volume following the initial lung inflation (2, 4, 6, 8, 10, 20, 30, 60, 90 and 150 seconds)
d. for 30 seconds following pump ventilation at elevated lung volume (2, 4, 6, 8, 10, 20, and 30 seconds)
e. for 2 1/2 minutes at resting lung volume following lung deflation (as in c)
f. for 30 seconds following pump ventilation at resting lung volume (as in d)
g. prior to the equilibration period
h. at 5 minute intervals throughout the equilibration period.

Figure 3 illustrates the points at which static receptor discharge was analyzed in each component of the protocol.

Analysis of the dynamic discharge associated with pump ventilation involved examining the rate of occurrence of action potentials before the ventilatory cycles (baseline discharge), at peak inspiratory lung volume and end-expiratory lung volume. The absolute number of action potentials fired during the inspiratory and expiratory portions of each ventilatory cycle were also counted.
Two-way analysis of variance was used to test the statistical significance of the data in this study. Differences were considered significant at the $P<0.05$ level.
RESULTS

SLOWLY ADAPTING PULMONARY STRETCH RECEPTORS

i) Response to Maintained Lung Inflation and Deflation

Figure 3a illustrates the discharge characteristics of a slowly adapting pulmonary stretch receptor in response to maintained lung inflation. At FRC (0 cmH2O) the receptor exhibited a tonic discharge rate of 1 to 2 Hz. Upon static lung inflation to 10 cmH2O, the peak inflation discharge rate reached 10 Hz and then slowly declined so that the receptor was firing at a rate of 6 Hz after 150 seconds of maintained inflation period.

Figure 3b demonstrates the response of the same SAR to lung deflation. At maintained lung inflation, the SAR was discharging at a rate of 9 Hz. Upon deflation (to functional residual lung volume) the receptor discharge was abolished for 10 seconds, after which it returned to the previously recorded rate of 1 to 2 Hz. This off-response was characteristic of most of the slowly adapting pulmonary stretch receptors recorded from in this study.

ii) Response to Dynamic Lung Inflation and Deflation

Figure 4 illustrates the response of a slowly adapting pulmonary stretch receptor to 10 pump ventilation cycles superimposed upon resting (airway pressure = 0 cmH2O) and then elevated (airway pressure = 10 cmH2O) lung volume. Prior to dynamic inflation at resting lung volume, the receptor exhibited a tonic discharge rate of 2 Hz. With increases in lung volume during the inflation cycle, receptor discharge increased markedly
FIGURE 3  Response of SAR #11 to Static Lung Inflation and Deflation

3a maintained inflation at elevated lung volume for 150 seconds
3b deflation from elevated lung volume (10 cmH20) to resting lung volume (0 cmH20)
FIGURE 4  Response of SAR #11 to Dynamic Lung Inflations

4a  pump ventilation at resting lung volume

4b  pump ventilation at elevated lung volume
A) Resting Lung Volume

B) Elevated Lung Volume
(mean peak inspiratory discharge rate = 6.9 Hz +/- 0.32 S.D.M.). During lung deflation, the receptor exhibited no baseline discharge even though the same lung volume elicited a tonic discharge rate of 2 Hz prior to lung inflation.

At elevated lung volume the receptor fired at a tonic discharge rate of 6 Hz. The mean peak inspiratory discharge rate was 14.0 Hz (+/- 0.50 S.D.M.) and the mean expiratory discharge rate was 5.0 Hz (+/- 0.67 S.D.M.), somewhat less than the tonic rate at the same lung volume. Thus the off-response demonstrated in figure 3b also occurred during the dynamic inflation cycles.

Two populations of slowly adapting pulmonary stretch receptors were identified which we have designated low threshold SARs (n=13) and high threshold SARs (n=4). Low threshold SARs exhibited a tonic rate of discharge at FRC while high threshold SARs only responded when lung volumes exceeded FRC. Aside from volume thresholds, these two populations of receptors had differences in their adaptation characteristics as well as in their sensitivities to increased levels of inspired CO2.

### LOW THRESHOLD SLOWLY ADAPTING PULMONARY STRETCH RECEPTORS

1) **Responses to Maintained Lung Inflations with Air**

Figure 5 illustrates the static inflation responses of low threshold slowly adapting pulmonary stretch receptors. Panel A shows the response of these receptors to short term (150 seconds) lung inflations prior to the long term (1 hour) maintained inflation periods (panel B). Panel C shows the response of these
FIGURE 5  **Low Threshold Fibers; Response to Maintained Static Lung Inflations**

Panel A  Short term inflation (150 seconds)
Panel B  Long term maintained inflation (60 minutes)
Panel C  Short term inflation (150 seconds)

Discharge is represented as a per cent of peak discharge at the initial portion of the protocol (panel A)

PAW = airway pressure (0 - 10 cmH2O)
receptors to short term inflations following the 1 hour maintained inflation period (see figure 2 for protocol outline).

In figure 5 receptor discharge is represented as a per cent of the peak discharge rate. Peak discharge rate is that which was obtained with acute static lung inflation at the beginning of the protocol (panel A). In the control protocol, peak inflation is defined as 100% (point E, panel A) and slowly declines over the short term (150 second) inflation period. At 150 seconds (panel A), the mean discharge rate is 64% of peak. When the lungs were maintained at resting lung volume for 1 hour (panel B), discharge remained close to the baseline discharge level (point R, panel A). After the 1 hour equilibration period, static lung inflation resulted in a mean discharge value that was not statistically different to the same condition prior to the equilibration period (point E, panel C vs panel A).

In the test protocol, after 1 hour of maintained inflation on air the receptors adapted 80% or to within 20% of their baseline (functional residual lung volume) discharge levels (60 minutes, panel B). Most of this adaptation occurred during the initial 2.5 minutes (150 seconds) of the maintained inflation period. Even with the large degree of receptor adaptation observed over the 1 hour inflation period, deflation to resting lung volume (point R, panel C) resulted in essentially the same mean tonic rate of discharge (panel C). In addition, the mean discharge rates at peak inflation and at 150 seconds of maintained inflation were not significantly different before
(panel A) and after (panel C) long term maintained inflation. However, the rate at which the receptors adapted to the short term lung inflation stimulus were different.

Figure 6 shows adaptation indices for slowly adapting pulmonary stretch receptors during short term lung inflations prior to and following the long term maintained inflation periods. The adaptation index used in the analyses of these data was derived from that of Knowlton and Larrabee (1946) and Davis et al., (1956). Mean receptor adaptation indices were calculated for 2, 4, 6, 8, 10 and 150 seconds following peak inflation (point E) during the short term inflations prior to (panel A) and following (panel C) long term maintained lung inflation (panel B). In the test run, SARs demonstrated a more rapid rate of adaptation following long term lung inflation than prior to this inflation period. The mean adaptation rates to a short term lung inflation stimulus in the control protocol were essentially the same prior to and following a period of long term maintainance of resting lung volume.

ii) Responses to Maintained Lung Inflations with Increased Levels of Inspired CO2

After 1 hour of maintained inflation with hypercapnic air (5% CO2 in air), the slowly adapting pulmonary stretch receptors adapted 88% or to within 12% of their baseline discharge levels (figure 5, CO2-test protocol, panel B). Following the long term maintained lung inflation period on 5% CO2, deflation to resting lung volume later in the protocol resulted in essentially the
FIGURE 6 Adaptation Indices for Low Threshold Slowly Adapting Pulmonary Stretch Receptors

Adaptation indices for short term inflations (150 seconds) before and after the period of long term maintained lung volume are statistically different in the test run at 6, 8, and 10 seconds.

- prior to 1 hour maintained lung volume
- following 1 hour maintained lung volume
ADAPTATION INDEX = \( f(\text{PEAK}) - f(x\text{sec}) \times 100 \)
\( \frac{f(\text{PEAK})}{f(\text{PEAK})} \)

Control Protocol

Test Protocol

CO₂ Test Protocol

A.I. after 1 hour maintained lung volume

X = 2 sec. 4 sec. 6 sec. 8 sec. 10 sec. 150 sec.

X = 2 sec. 4 sec. 6 sec. 8 sec. 10 sec. 150 sec.

X = 2 sec. 4 sec. 6 sec. 8 sec. 10 sec. 150 sec.
same mean tonic rate of discharge (point R, panel C). In contrast to the test protocol, the mean peak inflation discharge rate in panel C of the CO2-test protocol was significantly less than the mean peak inflation rate prior to CO2 addition (panel A).

The mean values for the CO2-test adaptation indices (figure 6) were greater following long term maintained inflation on hypercapnic air than they were prior to this treatment.

iii) Responses to Dynamic Inflations with Air

Figure 7 illustrates the mean baseline (prior to pump ventilation), peak inspiratory and end expiratory discharge rates of the slowly adapting pulmonary stretch receptors. Long term (1 hour) maintenance of lung volume at resting levels (control protocol) did not affect the mean values for baseline, peak inspiratory and end expiratory discharge rates of the SARs at either elevated (A vs C) or resting (a vs c) lung volumes.

Long term maintenance of lung volume at elevated levels (test protocol) did result in significant differences between mean values for peak inspiratory and end expiratory discharge rates of the SARs at both elevated (A vs C) and resting (a vs c) lung volumes. There were no differences between mean baseline discharge values at either elevated or resting lung volumes prior to and following long term maintained lung inflation.

iv) Responses to Dynamic Inflations with Increased Levels of Inspired CO2

Long term maintenance of lung volume at elevated levels with hypercapnic air (CO2-test protocol) did not result in significant
Mean discharge rate (+/- S.D.M.) for pump ventilation cycles.

Control protocol (n=8 animals / 10 pump ventilations)
Test protocol (n=8 animals / 10 pump ventilations)
CO2-test protocol (n=7 animals / 10 pump ventilations)

A  mean discharge at elevated lung volume prior to long term maintained lung volume
C  mean discharge at elevated lung volume following long term maintained lung volume
a  mean discharge at resting lung volume prior to long term maintained lung volume
C  mean discharge at resting lung volume following long term maintained lung volume
DYNAMIC INFLATIONS

Elevated Lung Volume

Resting Lung Volume

Control

DISCHARGE (Hz)

Test

B = Baseline
I = Peak Inspiration
E = Expiration
differences between mean discharge values at elevated lung volumes before CO2 addition (panel A) or after maintained inflation with hypercapnic air (panel C). However, there was a significant difference in the respective baseline values at resting lung volumes (panel a vs panel c). Peak inspiratory and end-expiratory values were significantly different after long term maintained lung inflation on hypercapnic air both at elevated (A vs C) and at resting (a vs c) lung volumes.

v) Dynamic Inflations - Discharge Rate vs Absolute Number of Impulses

Figure 8 illustrates the absolute number of impulses fired during the inspiratory and the expiratory phases of the pump ventilation cycles. In the control protocol, there was a significant difference in the mean number of impulses fired during the inspiratory phase of the ventilatory cycle before and after the 1 hour period of maintained resting lung volume at both elevated (A vs C) and resting (a vs c) lung volumes. There was no change in the mean number of impulses during the expiratory phase. After 1 hour of maintained inflation on air (test protocol), there was a significant difference in the number of impulses fired during both the inspiratory and expiratory phases of the ventilatory cycles at both elevated (A vs C) and resting (a vs c) lung volumes. When the lungs were maintained on 5% CO2 for 1 hour (CO2-test protocol), there was a significant decrease in the number of impulses fired during inspiration and expiration at elevated lung volumes (A vs C) and during inspiration at
FIGURE 8  Low Threshold Fibers: Response to Dynamic Lung Inflations (Absolute Number of Impulses)

Mean number of impulses (+/- S.E.M.) for 10 pump ventilations

Control protocol (n=8 animals / 10 pump ventilations)
Test protocol (n=8 animals / 10 pump ventilations)
CO2-test protocol (n=7 animals / 10 pump ventilations)

A  mean number of impulses at elevated lung volume prior to long term maintained inflation
C  mean number of impulses at elevated lung volume following long term maintained inflation
a  mean number of impulses at resting lung volume prior to long term maintained inflation
C  mean number of impulses at resting lung volume following long term maintained inflation
DYNAMIC INFLATIONS

Elevated Lung Volume

Resting Lung Volume

Control

DISCHARGE (Impulses)

CO₂ Test

I = Inspiratory Phase

E = Expiratory Phase
resting lung volumes (a vs c). The decreases in the mean number of impulses fired during the ventilatory cycle in the CO2-test protocol appeared to be greater than the decreases seen in the test protocol.

HIGH THRESHOLD SLOWLY ADAPTING PULMONARY STRETCH RECEPTORS

i) Responses to Maintained Lung Inflations with Air

Figure 9 illustrates the static inflation responses of high threshold slowly adapting pulmonary stretch receptors. These receptors responded to an increase in lung volume with an increase in discharge rate as did the low threshold receptors. However, the tonic baseline (functional residual lung volume) discharge level of these receptors was always 0 Hz. After 1 hour of maintained inflation on air (test run), the receptors had adapted to within 75% of their baseline discharge level (panel B). Again, as with the low threshold SARs, most of this adaptation had occurred within the first 2.5 minutes (150 seconds) of the maintained inflation period but unlike the low threshold SARs, these receptors did not begin to adapt until 3 to 4 seconds after the onset of lung inflation.

The mean inflation rates at peak inflation and at 150 seconds of maintained inflation did not appear to be different before (panel A) and after (panel C) long term maintained inflation. Furthermore, the rates at which these receptors adapted to the new level of discharge did not appear to be different before or after long term maintained inflation. Because of the small sample
FIGURE 9  **High Threshold Fibers; Response to Maintained Static Lung Inflations**

Panel A  Short term inflation (150 seconds)
Panel B  Long term maintained inflation (60 minutes)
Panel C  Short term inflation (150 seconds)

Discharge is represented as a per cent of peak discharge at the initial portion of the protocol (panel A)

PAW = airway pressure (0 - 10 cmH2O)
size in this population of SARs, adaptation indices are not presented for this receptor group.

ii) Responses to Maintained Lung Inflations with Increased Levels of Inspired CO2

After 1 hour of maintained inflation with hypercapnic air (5% CO2 in air), the high threshold slowly adapting pulmonary stretch receptors had adapted 55% or to within 45% of their baseline discharge levels (figure 9, panel B).

The response of the SARs to static lung inflation following maintained inflation with 5% CO2 in air (panel C, point E) was less than the response to static lung inflation prior to CO2 addition (panel A, point E). The rate to which the receptors adapted during the short term maintained lung inflation was also lower than prior to CO2 addition (panel C vs panel A).

iii) Responses to Dynamic Inflations with Air

Figure 10 illustrates the mean baseline, peak inspiratory and end expiratory discharge rates of the high threshold slowly adapting pulmonary stretch receptors. Long term (1 hour) maintenance of lung volume at resting levels (control protocol) did not appear to affect the mean values for baseline and end expiratory discharge rates of the SARs at either elevated (A vs C) or resting (a vs c) lung volumes. The differences in mean peak inspiratory discharge at elevated lung volumes (A vs C) appear to be due to one particular fiber. Since the sample size of this receptor population is small (n=3), this fiber has succeeded in distorting the mean value.
FIGURE 10  High Threshold Fibers; Response to Dynamic Lung Inflations (Discharge Rate)

Mean discharge rate for pump ventilation cycles.

Control protocol (n=3 animals / 10 pump ventilations)
Test protocol (n=2 animals / 10 pump ventilations)
CO2-test protocol (n=2 animals / 10 pump ventilations)

A  mean discharge at elevated lung volume prior to long term maintained lung volume
C  mean discharge at elevated lung volume following long term maintained lung volume
a  mean discharge at resting lung volume prior to long term maintained lung volume
C  mean discharge at resting lung volume following long term maintained lung volume
DYNAMIC INFLATIONS

Elevated Lung Volume

Resting Lung Volume

A

C

A

C

B = Baseline
I = Peak Inspiration
E = Expiration
Long term maintenance of lung volume at elevated levels (test protocol) did not result in any differences between mean values for baseline, peak inspiratory or end expiratory discharge rates at either elevated or resting lung volumes.

iv) Responses to Dynamic Inflations with Increased Levels of Inspired CO2

Long term maintenance of lung volume at elevated levels with hypercapnic air (CO2-test protocol) did not result in any difference between peak inspiratory or end expiratory discharge rates at elevated lung volumes. It is interesting to note that at elevated lung volumes following long term maintained lung inflation (CO2-test protocol, panel C), the mean end-expiratory discharge rate is lower than the baseline rate demonstrating the presence of a dynamic undershoot in receptor discharge. Long term maintenance of lung volume in the CO2-test protocol did not appear to have any effect on the mean baseline, peak inspiratory or end expiratory discharge values at resting lung volume (a vs c).

BLOOD GAS AND LUNG GAS ANALYSIS

i) Maintained Inflation with Air

At peak inflation, the mean values for the fractional concentration of oxygen and carbon dioxide in the lungs were 20.27% (+/- .30 S.E.M.) and .99% (+/- .36 S.E.M.) respectively. At the end of the 1 hour period of maintained inflation on air, lung gas F02 decreased to 13.17% (+/- 1.19 S.E.M.) and lung gas FC02
increased to 2.60% (+/- .57 S.E.M.). When the period of maintained lung inflation was extended, at the end of 6 hours the fractional concentrations of oxygen and carbon dioxide were 11.84% (+/- 1.42 S.E.M.) and 4.41 (+/- 1.41 S.E.M.) respectively (see figure 11). Additional measurements of lung gas FC02 values are displayed on table 1.

At peak lung inflation, the mean arterial PC02 value was 12.00 mmHg (+/- 1.30 S.E.M.) and the mean corresponding pH value was 7.94 (+/- .13 S.E.M.). After 1 hour of maintained lung inflation, arterial PC02 increased to a mean value of 26.00 mmHg (+/- 2.45 S.E.M.) and pH decreased to a mean value of 7.71 (+/- 0.04 S.E.M.). When the maintained inflation period was extended to 6 hours, the mean arterial PC02 and pH values were 74.50 mmHg (+/- 7.28 S.E.M.) and 7.12 (+/- .03 S.E.M.) respectively (see figure 12). Additional arterial PC02 values are listed in table 1.

ii) Maintained Inflation with Increased Levels of Inspired CO2

Prior to CO2 addition, the mean values for the fractional concentrations of oxygen and carbon dioxide in the lung gas were 20.25% (+/- .39 S.E.M.) and .78% (+/- 0.55 S.E.M.) respectively. At peak inflation (after at least 5 minutes of pump ventilation with 5% CO2 in air), the mean values for lung gas PO2 and PCO2 were 20.67% (+/- 0.20 S.E.M.) and 4.59% (+/- 0.28 S.E.M.) respectively. After 1 hour of maintained lung inflation on hypercapnic air, lung gas PO2 decreased to 17.13% (+/- 1.53 S.E.M.) and lung gas PCO2 increased to 5.74% (+/- 0.44 S.E.M.).
FIGURE 11  Lung Gas Analysis - Maintained Inflation on Air

Fractional concentration of lung gas oxygen and carbon dioxide (%), present in the lungs at peak inflation, 1 hour of maintained lung elevation and 6 hours of maintained elevation.

Mean values (+/- S.E.M.)

n = 8 animals

● denotes lung gas F02
▲ denotes lung gas FCO2
### TABLE 1  Blood and Lung Gas Measurements

<table>
<thead>
<tr>
<th>Maintained Inflation on Air</th>
<th>PaCO2 (mmHg)</th>
<th>FACO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12.00 (1.30)</td>
<td>1.08 (0.36)</td>
</tr>
<tr>
<td>Peak Inflation</td>
<td>12.00 (1.30)</td>
<td>.99 (0.36)</td>
</tr>
<tr>
<td>150 sec. inflation</td>
<td>----</td>
<td>1.19 (0.35)</td>
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<tr>
<td>1 hour inflation</td>
<td>26.00 (2.45)</td>
<td>2.60 (0.57)</td>
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<td>2 hour inflation</td>
<td>45.25 (6.06)</td>
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</tr>
<tr>
<td>4 hour inflation</td>
<td>60.88 (6.19)</td>
<td>----</td>
</tr>
<tr>
<td>6 hour inflation</td>
<td>74.50 (7.28)</td>
<td>4.14 (3.95)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Maintained Inflation on CO2</th>
<th>PaCO2 (mmHg)</th>
<th>FACO2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to CO2 addition</td>
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</tr>
<tr>
<td>Baseline</td>
<td>33.14 (6.71)</td>
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<td>After 5 Min. on CO2</td>
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<tr>
<td>Peak Inflation</td>
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<td>150 sec. Inflation</td>
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<tr>
<td>1 hour inflation</td>
<td>47.42 (4.75)</td>
<td>5.74 (0.44)</td>
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<td>53.80 (6.26)</td>
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<td>4 hour inflation</td>
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</tr>
<tr>
<td>6 hour inflation</td>
<td>70.60 (8.40)</td>
<td>10.26 (1.36)</td>
</tr>
</tbody>
</table>

Mean Values (+/- S.E.M.)

PaCO2 = partial pressure of CO2 in arterial blood
FACO2 = fractional concentration of CO2 in alveolar lung gas
FIGURE 12  Blood Gas Analysis - Maintained Inflation on Air

Partial pressures (mmHg) of carbon dioxide and pH values of the blood at lung inflation; and 1, 2, 4, and 6 hours of maintained inflation.

Mean values (+/- S.E.M.)
n= 10 animals

● denotes arterial pH
▲ denotes arterial PCO2
When the period of maintained lung inflation was extended, at the end of 6 hours the fractional concentrations of oxygen and carbon dioxide were 8.18% (+/- 3.16 S.E.M.) and 10.26% (+/- 1.36 S.E.M.) respectively (see figure 13).

Prior to CO2 addition, the mean value for arterial PCO2 was 33.14 mmHg (+/- 6.71 S.E.M.) and the mean corresponding pH value was 7.55 (+/- 0.14 S.E.M.). At peak inflation (following 5 minutes of pump ventilation with 5% CO2 in air), arterial PCO2 had increased to 37.43 mmHg (+/- 4.84 S.E.M.) and the arterial pH had decreased to 7.46 (+/- 0.08 S.E.M.). After 1 hour of maintained inflation on hypercapnic air, arterial PCO2 had further increased to 47.42 mmHg (+/- 12.36 S.E.M.) and arterial pH decreased to 7.35 (+/- 0.06 S.E.M.). When the maintained lung inflation period was extended to 6 hours, arterial PCO2 had reached 70.60 mmHg (+/- 8.40 S.E.M.) and arterial pH had decreased to 7.09 (+/- 0.07 S.E.M.) (see figure 14).
FIGURE 13  Lung Gas Analysis - Maintained Inflation on CO2

Fractional concentration of oxygen and carbon dioxide (%) present in the lung gas prior to CO2 addition, 5 minutes after CO2 addition and at 1 and 6 hours following maintained lung inflation on 5% CO2 in air.

Mean values (+/- S.E.M.)

n=10 animals

● denotes lung gas FO2

▲ denotes lung gas FC02
FIGURE 14  Blood Gas Analysis - Maintained Inflation on CO2

Partial pressures (mmHg) of carbon dioxide and pH values of the blood prior to CO2 addition, 5 minutes after CO2 addition and at 1, 2, 4, and 6 hours of maintained inflation on 5% CO2 in air.

Mean values (+/- S.E.M.)

n = 10 animals

● denotes arterial pH
▲ denotes arterial PCO2
RAPIDLY ADAPTING PULMONARY STRETCH RECEPTORS

Figure 15 illustrates the discharge profile of a rapidly adapting pulmonary stretch receptor (RAR) during a maintained lung inflation stimulus. With the onset of lung inflation from functional residual lung volume (airway pressure = 0 cmH2O) to an elevated lung volume (airway pressure = 20 cmH2O), the receptor discharge rate increases dramatically. The peak inflation discharge rate is 20 Hz and it quickly decays to its baseline (resting lung volume) level of 1 to 2 Hz within 3 seconds. We recorded from 6 RARs but no detailed analysis were carried out on this receptor group.
FIGURE 15  Response of a Rapidly Adapting Pulmonary Stretch Receptor to Static Lung Inflation

PAW = airway pressure (0 to 10 cmH2O)
Several interesting results have been presented in this study which will be elaborated on in the following discussion. Slowly adapting pulmonary stretch receptors recorded from in this study did not completely adapt to long term maintained increases in lung volume. Furthermore, neither the discharge rate attained with static lung inflation nor the discharge rate to which the receptors adapted at 150 seconds of maintained inflation were affected by long term maintained lung inflations with air. However, both the rate of receptor adaptation and the response of the receptors to dynamic lung inflations were affected by one hour of maintained lung inflation with air. Maintained lung inflations with 5% CO2 in air resulted in an overall decrease in the level of discharge of the slowly adapting pulmonary stretch receptors.

**Distinction Between Low and High Threshold Slowly Adapting Pulmonary Stretch Receptors:**

Two populations of slowly adapting pulmonary stretch receptors were recorded from in this study; those that exhibited a tonic discharge at functional residual capacity (low threshold receptors) and those that only responded when lung volume exceeded FRC (high threshold receptors). In his recent review, Paintal (1983) has made a similar distinction; low threshold receptors are those that fire during both inspiration and
expiration and high threshold receptors are those that fire only during inspiration. Mammalian studies have demonstrated that most high threshold receptors are located in the larger diameter intrapulmonary airways (characteristic of the peripheral portions of the lung) while low threshold receptors are more widely distributed throughout the pulmonary airways (Sant'Ambrogio and Sant'Ambrogio, 1980; Paintal and Ravi, 1980). In this study there was no attempt to localize the SARs. Owing to the high degree of morphological variation between reptilian and mammalian lungs (Romer and Parson, 1977), it is difficult to say whether or not the low and high threshold SARs that were recorded from were in fact anatomically distinct populations.

The data presented in this study demonstrates that both the low and high threshold slowly adapting pulmonary stretch receptors have the same classical responses to changes in lung volume. However, there appears to be some differences in their adaptation responses as well as in their sensitivities to increased levels of inspired CO2.

LOW THRESHOLD SLOWLY ADAPTING PULMONARY STRETCH RECEPTORS

Tonic Response to Static Lung Inflation:

As illustrated in figure 5, 1 hour of maintained resting lung volume (control protocol) had no effect on either the peak discharge response to static lung inflation or the rate to which the receptors adapted during the short term inflation stimulus (panel C). Furthermore, there was no change in the adaptation
indices following one hour of maintained resting lung volume (figure 6, control protocol).

The control protocol has served to establish that maintaining the lungs at resting volume for a period of 1 hour (with no cyclic ventilation), had no effect on the static inflation discharge response of the slowly adapting pulmonary stretch receptors. Therefore any changes observed in this static inflation response after the lungs had been maintained at an elevated volume (test protocol) or at an elevated volume with 5% CO2 in air (CO2-test protocol), should be purely a function of the test condition.

After 1 hour of maintained inflation with air (test protocol), the slowly adapting pulmonary stretch receptors had adapted 80% from their peak discharge value (figure 5). Most of this adaptation occurred within the first 2.5 minutes of inflation. The only documentation of direct recordings made from SARs over an extended period of sustained stimulation was done by Davenport et al., (1981) on tracheal stretch receptors in dogs. They demonstrated that after 1 hour of sustained stimulation (by stretching the trachialis muscle), the tracheal stretch receptors had adapted to within 30% to 80% of their pre-stretch values. They also showed that most of the adaptation occurred within the first 3 minutes of the muscle stretching process. Thus results presented in this study agree well with those of Davenport et al., 1981.

The adaptation response of slowly adapting pulmonary stretch
receptors is a characteristic common to most mechanoreceptors. The complete mechanism involved in receptor adaptation is not fully understood but it is believed to have both a mechanical and an ionic basis. The mechanical basis of receptor adaptation pertains primarily to changes in the structural properties of the tissue in which the receptor sits (Patton, 1965). Davenport et al. (1981) have attributed the adaptation response of slowly adapting tracheal stretch receptors to changes in the mechanical properties of the trachealis muscle itself. Davenport et al. (1981) have stimulated the vagus nerve distally from the recording electrodes (antidromic stimulation) throughout the course of the muscle stretching process and found that this failed to alter the adaptation indices of these receptors. From these results, they concluded that stretch receptor adaptation was caused by changes in the mechanical properties of the tissue and was not an intrinsic property of the receptor membrane itself.

One cannot exclude the possibility of an ionically based receptor adaptation mechanism. In order to explain the ionic basis of receptor adaptation, one requires a basic knowledge of the mechanoreceptor stimulus modality. The mechanoreceptor acts as a transducer and in effect, transforms one form of energy into another. Deformations of the tissue in which the receptor sits are transformed into a graded generator (receptor) potential. The intensity of the generator potential is encoded by the spike encoder through modulation of the generator potential amplitude.
The spike encoder then transforms this graded potential into a series of frequency modulated action potentials (Patton, 1965).

According to Grigg (1986), the ionic mechanism of stretch receptor adaptation has two possible sites of action; at the level of the sensory ending (thus affecting the amplitude of the generator potential) and at the level of the spike encoder (by producing a post-spike decrease in the membrane excitability). Obviously any mechanism that succeeds in returning the generator potential to its resting value will contribute to receptor adaptation. The proposed ionic mechanisms are said to involve cation-gated channels which, when activated, serve to repolarize the receptor ending (Grigg, 1986). The most likely site of ionic receptor adaptation is at the level of the spike encoder. Again, the membrane is thought to be repolarized by an electrogenic Na+ pump that is stimulated by the Na+ influx at the onset of the preceding action potential.

Figure 5 (test protocol) demonstrates that the peak inflation discharge rate in response to static lung inflation was not significantly affected by the hour of maintained lung inflation, nor was the steady-state discharge rate to which the receptors eventually adapted. However, there was a difference in the adaptation indices calculated before and after the hour of maintained lung inflation (figure 6, test protocol). Since the receptors showed the same discharge response to static lung inflation before and after the control run, the difference in the adaptation indices seen in the test run must be a function of the
adaptive process that occurred during the maintained lung inflation period.

These differences in the receptor adaptation indices may have a mechanical basis. If the receptor adaptation observed over the hour long maintained lung inflation period is attributable to the ensuing changes in the structural properties of the pulmonary tissue surrounding the stretch receptor (Davenport et al., 1981), then perhaps the more rapid rate of receptor adaptation following maintained inflation is due to a perpetuation of this mechanical phenomenon.

After 1 hour of maintained lung inflation with 5% CO2 in air the slowly adapting pulmonary stretch receptors had adapted 88% (figure 5, CO2-test protocol). Following the period of maintained lung inflation with 5% CO2 in air, the peak discharge response of the SARs to the increase in lung volume was significantly lower than with the same inflation stimulus prior to CO2-addition, as was the steady-state level of discharge to which the receptors eventually adapted during the short term (150 seconds) inflation stimulus. Furthermore, the adaptation indices following the period of maintained lung inflation with 5% CO2 were larger than those prior to this period of maintained lung inflation (figure 6, CO2-test protocol).

These results show that the levels of receptor discharge attained throughout the CO2-test protocol following maintained inflation with 5% CO2 were consistently lower than those prior to the addition of CO2. Interestingly, the adaptation indices
following maintained inflation with 5% CO2 were not greater than those following maintained inflation with air. That SAR discharge is in some way modified by increased levels of inspired CO2 has been documented in mammals (Mustafa and Purves, 1972; Sant'Ambrogio et al., 1974; Bartlett and Sant'Ambrogio, 1976; Coleridge et al., 1978; Mitchell et al., 1980,) as well as in reptiles (Milsom and Jones, 1976; Fedde et al., 1977; Jones and Milsom, 1979). The results presented in this study are in agreement with the above authors. Unfortunately, the results from this study give no further insight into the mechanism involved in the CO2-induced decrease in SAR discharge.

**Phasic Response to Static Lung Inflation and Deflation:**

The slowly adapting pulmonary stretch receptors that were recorded from in this study exhibited similar discharge characteristics to those reported in mammals (Miserocchi and Sant'Ambrogio, 1974; Bartlett et al., 1976; Davenport et al., 1981; Sant'Ambrogio et al., 1983), in turtles (Jones and Milsom, 1979) and in lunged fish (Milsom and Jones, 1985). As illustrated in figure 5, an increase in lung volume resulted in a dramatic increase in SAR discharge followed by a slow rate of adaptation. The initial "overshoot" in discharge in response to sudden lung inflation is a rate dependent phenomenon known as the on-response. Although the maximum discharge rate achieved by lung inflation is a function of both the volume and the rate of lung filling, the level of adaptation attained with prolonged lung
inflation is independent of the inflation rate (Milsom and Jones, 1985).

When the lung inflation stimulus was removed (during deflation to resting lung volume), the receptor discharge ceased briefly and then returned to its normal discharge rate for that particular lung volume (figure 3b). This phenomenon, known as the off-response, is thought to be due to an exaggerated hyperpolarization of the receptor generator potential (Patton, 1965). The off-response is a uniform characteristic of most vertebrate mechanoreceptors including those found in nonpulmonary tissues (muscle, gut and baroreceptors (Patton, 1965) and photoreceptors (Kandel and Schwartz, 1981)).

Phasic Response to Dynamic Lung Inflations:

Adrian (1933) first described the responses of slowly adapting pulmonary stretch receptors as being volume-related such that spontaneous increases and decreases in lung volume resulted in respective increases and decreases in discharge. As illustrated in figure 7, pump ventilation superimposed upon an elevated lung volume resulted in significantly greater levels of peak inspiratory and end-expiratory levels of discharge than did pump ventilation at resting lung volume. These results agree well with those of Bartlett et al. (1976), Muza and Frazier, (1983) and Milsom and Jones, (1985).

The low threshold slowly adapting pulmonary stretch receptors that were recorded from in this study clearly demonstrated a
dynamic off-response. At both resting and elevated lung volumes, the mean end-expiratory discharge values were lower than the pre-inflation (baseline) discharge values even though the corresponding lung volumes were the same. This dynamic off-response has previously been shown to be a rate sensitive phenomenon probably due to an exaggerated hyperpolarization of the receptor generator potential (Patton, 1965; Milsom and Jones, 1985).

After 1 hour of maintained resting lung volume, the baseline (pre-inflation), peak inspiratory and end-expiratory discharge rates at both elevated and resting lung volumes remained unchanged from the corresponding rates prior to maintained resting lung volume (figure 7, control protocol). The absolute number of impulses fired during the inspiratory phase prior to and following the 1 hour period of maintained resting lung volume were less consistent (figure 8, control protocol). At both elevated and resting lung volumes, the mean number of impulses fired during inspiration was reduced by approximately 8% following the 1 hour period of maintained resting lung volume.

Results from the control protocol have served to establish that the rate of SAR discharge during the baseline, peak inspiratory and end-expiratory portions of the ventilatory cycle were not affected by maintaining the lungs at resting lung volume for a period of 1 hour. Furthermore, the absolute number of impulses fired during the expiratory phase of the ventilatory cycle did not change with the 1 hour period of maintained resting
lung volume. Any changes observed in the above components of the cycle following 1 hour of maintained lung inflation with air (test protocol) or 1 hour of maintained lung inflation with 5% CO2 in air (CO2-test protocol) should be a function of the test condition. However, care must be taken in interpreting data concerning the number of impulses fired during the inspiratory phase of the ventilatory cycle.

After 1 hour of maintained inflation with air, the dynamic discharge rates of the slowly adapting pulmonary stretch receptors were significantly reduced during peak inspiration and end-expiration at both elevated and resting lung volumes (figure 7, test protocol). Additionally, there was a decrease in the absolute number of impulses fired during both the inspiratory and expiratory phases of the pump ventilation cycle (figure 8, test protocol). There was no difference in the baseline discharge rates of these receptors following the period of maintained lung inflation. These results indicate that the hour of maintained inflation on air produced a decrease in both the rate of discharge and in the absolute number of impulses fired during the inspiratory and expiratory portions of the pump ventilation cycle at both resting and elevated lung volumes. However, from these data it is difficult to determine which factor was affected more, the rate of receptor discharge or the absolute number of impulses fired.

After 1 hour of maintained inflation with 5% CO2 in air, the baseline and the dynamic (peak inspiratory and end-expiratory)
discharge rates were also significantly reduced at both elevated and resting lung volumes (figure 7, CO2-test). There was also a dramatic decrease in the number of impulses fired during the inspiratory phase of the ventilatory cycle (figure 8, CO2-test protocol). The decreases in the discharge rates during the pump ventilation were greater than those following maintained inflation with air as were the decreases in the absolute number of impulses occurring during the inspiratory phase of the cycle. As previously demonstrated by Jones and Milsom (1979), turtle pulmonary stretch receptors show a dramatic decrease in their sensitivity to lung inflation with increased levels of inspired CO2. It is not possible to determine whether CO2 had a more pronounced effect on the rate of change of discharge or on the overall level of discharge rate. These results are also in close agreement with those presented by Mustfa and Purves (1972) and Bradley et al. (1974) for mammals.

HIGH THRESHOLD SLOWLY ADAPTING PULMONARY STRETCH RECEPTORS

Tonic Response to Static Lung Inflation:

As illustrated in figure 9, 1 hour of maintained resting lung volume (control protocol) had no effect on either the peak response to static lung inflation or the rate to which the receptors adapted during the short term inflation stimulus. Furthermore, the rate at which the receptors adapted to lung volume was unchanged by the 1 hour period of maintained resting lung volume. The control protocol has therefore established that
maintaining the lungs at resting volume for 1 hour had no effect on the static inflation response of the high threshold slowly adapting pulmonary stretch receptors. Therefore, any changes observed in this static inflation response after the lungs had been maintained at an elevated volume (test protocol) or at an elevated volume with 5% CO2 in air (CO2-test protocol), should be purely a function of the test condition.

After 1 hour of maintained inflation with air, the high threshold slowly adapting pulmonary stretch receptors had adapted to 75% of their peak discharge level. All of this adaptation occurred within the first 2.5 minutes of lung inflation. The peak discharge rate in response to static lung inflation was not significantly affected by the hour of maintained lung inflation, nor was the steady-state discharge rate to which the receptors eventually adapted (figure 9, test protocol). The rate of receptor adaptation did not seem to be affected by the test condition. Since the values of the adaptation indices for this population were highly variable (probably due to the small sample size), they are not presented.

The high threshold SARs did not adapt as much as the low threshold SARs (25% vs 80%) during the hour of maintained lung inflation with air. This decrease in adaptation sensitivity may be an inherent characteristic of the receptors themselves (ionic adaptation), or it may be attributable to changes in the physical properties of the tissues surrounding the receptors (mechanical adaptation). If one may assume that there is a significant
mechanical basis for the adaptation phenomenon, then perhaps the high and low threshold SARs recorded from in this study were situated in different tissue types which in turn exhibited different responses to volume induced perturbations. If this assumption is valid, then these receptors may in fact be anatomically distinct populations (as originally suggested by Painial, 1983). Since data regarding the precise location of the SARs recorded from in this study were not collected, this hypothesis must remain speculative.

After 1 hour of maintained inflation with 5% CO2 in air, the high threshold slowly adapting pulmonary stretch receptors had adapted 45% (figure 9, CO2-test protocol). The rate of discharge attained after 1 hour of maintained inflation with 5% CO2 in air was significantly lower than that attained after 2.5 minutes of lung inflation with air (panel A). Following the period of maintained lung inflation with 5% CO2 in air, the peak discharge response of the SARs to the increase in lung volume was significantly lower than with the same inflation stimulus prior to CO2 addition, as was the steady-state level of discharge to which the receptors eventually adapted during the short term (150 seconds) maintained inflation stimulus.

The decrease in discharge over the 1 hour period of maintained lung inflation that was due to the increased levels of inspired CO2 can be estimated as follows: the discharge rate at 60 minutes of maintained lung inflation with air minus the discharge rate at 60 minutes of lung inflation with 5% CO2 in
air. For the high threshold SARs, the decrease in discharge due to the increased levels of inspired CO2 (25%) was much greater than that calculated for the low threshold SARs (4%). These estimates indicate that the high threshold SARs were much more sensitive to increased levels of inspired CO2 than were the low threshold SARs.

**Phasic Responses to Static Lung Inflation and Deflation:**

Like the low threshold slowly adapting pulmonary stretch receptors, these high threshold SARs also exhibited a rate sensitive on-response. As illustrated in figure 9, an increase in lung volume resulted in a dramatic increase in SAR discharge followed by a slow rate of adaptation. When the lung inflation stimulus was removed (during deflation to resting lung volume), these receptors ceased their discharge rate and only fired occasionally at resting lung volume and as such did not demonstrate an off-response.

**Phasic Response to Dynamic Lung Inflations:**

As illustrated in figure 10, pump ventilation superimposed upon the elevated lung volume resulted in significantly greater levels of peak inspiratory and end-expiratory levels of discharge than did pump ventilation at resting lung volume. These results agree well with those of Bartlett et al., (1976); Muza and Frazier (1983) and Milsom and Jones (1985). Unlike the low threshold slowly adapting pulmonary stretch receptors, in most
cases these high threshold SARs did not demonstrate a significant
dynamic off-response at elevated lung volume.

After 1 hour of maintained inflation at resting lung volume,
and 1 hour of maintained inflation at elevated lung volume, the
baseline (pre-inflation), peak inspiratory and end-expiratory
discharge rates at both elevated and resting lung volumes
remained unchanged from the corresponding rates prior to the
periods of lung volume maintenance (figure 10, control and test
protocols). Maintained lung inflation with 5% CO2 only affected
the baseline discharge rate following the lung inflation period.

These results indicate that neither the maintained lung
inflation stimulus nor the hypercapnic stimulus had an effect on
the dynamic sensitivity of the high threshold slowly adapting
pulmonary stretch receptors. Increased levels of inspired CO2 did
however serve to reduce the overall level of discharge rate (as
seen by the changes in the baseline values). Why the CO2-induced
decrease in the overall level of discharge was not reflected in
corresponding decreases in the peak inspiratory and
end-expiratory discharge values is unknown.

**BLOOD AND LUNG GAS ANALYSIS**

Since the natural breathing pattern of turtles is periodic
(McCutcheon, 1943), these animals tend to show large variations
in arterial P02 and PCO2 levels during normal intermittent
breathing (Lefant et al., 1970) as well as during extended
periods of diving (Jackson and Silverblatt, 1974). The magnitude of these variations are further affected by intracardiac blood shunting associated with the periods of breath holding (Burggren et al., 1978). The ability to preferentially perfuse the systemic or the pulmonary circulation is a characteristic of the physiology of these animals and is possible primarily because of the incomplete division of the cardiac ventricle (Romer and Parsons, 1977). Because of the intermittent pulmonary perfusion, it is not surprising that measurements of blood gas tensions do not always closely follow measurements of the fractional concentrations of gases in the lung (Burggren and Shelton, 1979).

The primary aim of measuring arterial PCO2 and pH levels in this study was to monitor the metabolic state of the animal throughout the experimental protocol, particularly during the periods of maintained lung inflation. The measurements for arterial PCO2 and lung gas FC02 and FO2 obtained after 1 hour of maintained lung inflations with air (figures 11 and 12) exhibited the same trends as results documented by Burggren and Shelton (1979) on the same species of turtle, Pseudemys scripta during an hour long voluntary dive. However, the PCO2 and FC02 values presented in this study were consistently lower than those reported by Burggren and Shelton (1979) due to the relative hypocapnia induced by the pump ventilation sequences prior to commencement of the protocol and the lower metabolism of the pithed animals. In any case, results from this study show that during the hour long maintained inflation period there were
increases in arterial PCO2 and corresponding decreases in arterial pH (figure 12) as well as increases and decreases in the fractional concentration of lung gas CO2 and O2 respectively (figure 11).

The fractional concentration of CO2 present at the receptor sites during maintained lung inflation with air was within the same range as that of an animal undergoing a one hour voluntary dive (Burggren and Shelton, 1979). As a result, the FC02 present at the receptor sites during maintained lung inflation (or during maintained resting lung volume) was within the physiological range experienced by the animal under natural conditions.

**CONTRIBUTION OF CO2 TO PULMONARY STRETCH RECEPTOR ADAPTATION**

Increased levels of inspired CO2 are known to reduce the overall level of discharge of slowly adapting pulmonary stretch receptors in turtles. More specifically, Jones and Milsom (1979) have shown that the administration of 5% CO2 (in air) and 10% CO2 (in air) result in respective 35% and 45% reductions of both peak inspiratory and end-expiratory discharge. The alinearity of this response demonstrates that the SARs are more sensitive to levels of CO2 that might be experienced by the animal under normal physiological conditions (such as during an extended breathhold or during a dive). During an extended breathhold period, metabolic CO2 is stored not only in the blood and tissues of these animals, but in the lung gas as well (for review see
Shelton et al., 1986). As a result, as the breathhold progresses, the amount of CO2 in the vicinity of the receptor sites will increase.

The results of Jones and Milsom (1979) in combination with the results presented in this study allow us to predict the contribution of accumulated metabolic (lung gas) CO2 to the adaptation response of the slowly adapting pulmonary stretch receptors seen during the 1 hour period of maintained lung inflation with air.

Low Threshold Slowly Adapting Pulmonary Stretch Receptors:

Estimates of the contribution of the accumulated metabolic (lung gas) CO2 to the adaptation response seen in the low threshold pulmonary stretch receptors during the 1 hour of maintained lung inflation with air are graphically illustrated in figure 16.

The difference between the fractional concentration of CO2 present in the lungs at the onset of lung inflation and at the end of short term (150 seconds) maintained lung inflation was 2.20% (table 1). Based on the results of Jones and Milsom (1979), the difference between 0.99% CO2 and 1.19% CO2 will result in a 2% decrease in SAR discharge. Therefore, in this study, approximately 1% (2% of the 36% decrease) of the total reduction in discharge seen during the adaptation response to the short term maintained lung inflation was due to the accumulated metabolic CO2 and the remainder (35%) was due to receptor
FIGURE 16 Contribution of CO2 to Pulmonary Stretch Receptor Adaptation

Response of LOW THRESHOLD SARs

Bar 1  mean peak inflation discharge rate
Bar 2  mean discharge rate at 150 seconds of maintained lung inflation on air
Bar 3 air  mean discharge rate at 60 minutes of maintained lung inflation with air
Bar 3 CO2  mean discharge rate at 60 minutes of maintained lung inflation with 5% CO2 in air
Contribution of CO₂ to Pulmonary Stretch Receptor Adaptation

\[ P_{A\text{CO}_2} = 0.99\% \quad P_{A\text{CO}_2} = 1.19\% \quad P_{A\text{CO}_2} = 2.60\% \quad P_{A\text{CO}_2} = 5.70\% \]
adaptation.

Similarly, the difference between the fractional concentration of CO2 present in the lungs at the end of the short term maintained inflation was 1.41%. Extrapolating from the results of Jones and Milsom (1979) where the difference between 1.19% and 2.60% CO2 resulted in a 10% decrease in receptor discharge, one can estimate that in this study, slightly less than 2% (10% of the 16% decrease) of the further decrease in receptor discharge over the 1 hour period of maintained inflation was due to accumulated metabolic CO2 and the remainder (14%) was a result of receptor adaptation.

The difference in the level of discharge at the end of 1 hour of maintained inflation with 5% CO2 and at the end of 1 hour of maintained inflation with air (a 4% decrease), can be attributed to the difference in the fractional concentration of CO2 in the lung gas at this point in the protocol (3.1%).

These results indicate that the low threshold SARs recorded from in this study are mildly sensitive to increased levels of lung gas CO2 (from 0.99% to 5.7%).

HIGH THRESHOLD SLOWLY ADAPTING PULMONARY STRETCH RECEPTORS

I have already established that the high threshold SARs are more sensitive than the low threshold SARs are to increased levels of inspired CO2. Since I have calculated the CO2 contribution to the decrease in discharge in the low threshold
SARs based on the receptor CO2 sensitivity relationships reported by Jones and Milsom (1979), these relationships cannot be applied to predict the CO2 dependent reduction in discharge in the high threshold SARs. Despite the alinearity of the response sensitivities of SARs to increased levels of CO2, all predictions for the high threshold SARs will be based on measured differences in discharge between rates seen at the end of 1 hour maintained inflation with air (test protocol) and at the end of 1 hour maintained inflation with 5% CO2 in air (CO2-test protocol).

As previously illustrated in figure 9 (test protocol), there was no difference between the discharge rates at the end of the short term (150 seconds) maintained inflation period and at the end of the long term (1 hour) maintained inflation period. This relationship is also illustrated in figure 17. The difference in discharge at the end of long term maintained inflation with air and at the end of long term maintained inflation with 5% CO2 in air (a 25% decrease) can be attributed to the differences in the fractional concentration of CO2 in the lung gas of these animals at this point in the protocol (3.1% CO2) (see figure 17).

Since 3.1% CO2 resulted in a 25% reduction in discharge, the difference in FACO2 between peak inflation and 150 seconds of maintained inflation (0.20% CO2) should result in a 6% reduction (25% of the 25% reduction) in the overall level of discharge. Therefore, 6% of the reduction in discharge seen with short term maintained inflation was attributable to the accumulated metabolic (lung gas) CO2, and the remainder (19%), was due to
FIGURE 17 Contribution of CO2 to Pulmonary Stretch Receptor Adaptation

Response of HIGH THRESHOLD SARs

Bar 1  mean peak inflation discharge rate
Bar 2  mean discharge rate at 150 seconds of maintained lung inflation with air
Bar 3 air mean peak inflation at 60 minutes of maintained lung inflation with air
Bar 3 CO2 mean peak inflation at 60 minutes of maintained lung inflation with 5% CO2 in air
receptor adaptation.

The degree of discharge reduction due to CO2 during the short term maintained inflation (6%) is likely to be underestimated. As demonstrated by Jones and Milsom (1979), increased levels of inspired CO2 have the greatest effect on SAR discharge at the lower (physiological) levels. In any case, figures 16 and 17 demonstrate that although low threshold SARs showed a larger adaptation response over 1 hour of maintained lung inflation with air than the high threshold SARs did, the high threshold SARs were more sensitive to increased levels of lung gas CO2.

**EFFECT OF MINOR CHANGES IN LUNG VOLUME ON SLOWLY ADAPTING PULMONARY STRETCH RECEPTOR DISCHARGE VALUES:**

The present study was performed on pithed turtles undergoing artificially induced changes in lung volume. Data generated from this study is very useful for further understanding the adaptation response of slowly adapting pulmonary stretch receptors to maintained changes in lung volume, as well as their response to static and dynamic changes in lung volume following the period of adaptation. Further insight has also been gained into the effect of increased levels of inspired CO2 on the above responses of SARs. From these data I have been able to estimate the relative contribution of accumulated metabolic CO2 to the adaptation process. Extending the application of the results obtained from the low threshold slowly adapting pulmonary stretch
receptors, one can estimate the degree of receptor adaptation that may occur during a 1 hour breathhold period in a normal (intact) turtle.

Figure 18 is a graphical representation of the discharge rate at the end of the 1 hour period plotted against lung volume for a hypothetical 500 gram turtle. Lung volume at resting levels (functional residual capacity) was calculated as 12 ml/100 grams (Jackson, 1971; Milsom, 1975). For the hypothetical 500 gram turtle, resting lung volume is 60 mls. 1 hour of maintained resting lung volume will result in an average discharge rate of 36% of peak (from figure 5, control protocol). This is illustrated as point A in figure 18.

For the hypothetical turtle, elevated lung volume was calculated as resting lung volume plus the volume produced by a static lung inflation of 10 cmH2O. From the static compliance curves of Vitalis and Milsom (1986), one can determine that the average volume produced by a pressure of 10 cmH2O is 8.4 ml/100 grams. Therefore, the maintained elevated lung volume in our hypothetical turtle is 102 mls. After 1 hour of maintained elevated lung volume, the average discharge of the SARs will be 44% of peak (from figure 5, test protocol). This is illustrated as point B in figure 18.

When turtles are intact and engaged in a normal periodic breathing pattern, lung volume decreases slightly during the breathhold period (Lefant et al., 1970). This decrease in lung volume is due to a decrease in the respiratory exchange ratio
FIGURE 18  SAR Discharge vs Lung Volume in a Hypothetical 500 gram Turtle

Point (A) discharge rate at 60 minutes of resting lung volume (from figure 5, control protocol)

Point (B) discharge rate at 60 minutes at elevated lung volume (from figure 5, test protocol)

Point (C) discharge rate at 60 minutes of a breathhold with a 10 ml decrease in lung volume
(RE) which is represented as VCO2/VO2 where V is the volume of gas moved over time (Glass et al., 1983). In other words, throughout the duration of the breathhold, more oxygen diffuses out of the lungs than CO2 diffuses into the lungs. Ackerman and White (1979) have measured both the RE values of turtles over extended periods of breath holding as well as the decrease in lung volume associated with this breathhold period.

From the data of Ackerman and White (1979), I have estimated that over a 1 hour period, lung volume in the hypothetical turtle will be reduced by approximately 10 mls. Therefore, the turtle will have a lung volume of 92 mls after 1 hour of breath holding from a starting volume of 102 mls. This is illustrated as point C in figure 18. This volume change results in a discharge rate that is 42% of the peak value. It must be noted however, that the estimated values of changes in receptor discharge associated with changes in lung volume have been extrapolated from a unilaterally vagotomized turtle. In an intact animal, these values may be somewhat different.

This exercise demonstrates that the discharge values we measured at the end of 1 hour of maintained lung inflation (44%) were not appreciably different from those calculated for a 1 hour breathhold period in a normal (intact) turtle (42%). These results help validate the experimental protocol as a physiologically relevant means of examining the adaptation response of turtle slowly adapting pulmonary stretch receptors to maintained lung inflations.
NOTE ON RAPIDLY ADAPTING PULMONARY STRETCH RECEPTORS

As demonstrated in figure 15, rapidly adapting pulmonary stretch receptors respond to increases in lung volume with an increase in discharge. These receptors are easily stimulated by noxious inhalents and their reflex is manifest in the cough response (Paintal, 1977). Six rapidly adapting pulmonary stretch receptors were recorded from throughout the study, but no detailed analysis was conducted on this receptor group.

RELATIVE ROLES OF TONIC AND PHASIC DISCHARGE IN THE CONTROL OF BREATHING IN TURTLES AND GENERAL CONCLUSIONS

The control of breathing is achieved by central integration of information arising from chemoreceptors (both central and peripheral), respiratory muscle afferents and pulmonary receptors. Generally, the central and peripheral chemoreceptors govern the overall level of ventilation while the slowly adapting pulmonary stretch receptors interact with the central respiratory rhythm generator to produce a characteristic breathing pattern.

Pulmonary stretch receptors were classically invoked in the Hering-Breuer inspiratory off-switch reflex. Preliminary examinations into the functional characteristics of slowly adapting pulmonary stretch receptors have led to the conclusion that the vagally-mediated inhibitory information arising from the SARs interacts with the central respiratory rhythm generator to
terminate the inspiratory phase of the breathing cycle (Euler et al., 1970; Clark and Euler, 1972). Clark and Euler (1972) postulated that the phasic, rather than the tonic component of SAR discharge was of primary importance in the control of the breathing cycle. More recently however, studies have demonstrated that not only is tonic information important, particularly in regulating TE (Grunstein et al., 1975), but that expiratory duration and inspiratory duration may be regulated through separate reflex mechanisms (Agostoni et al., 1985).

There is no doubt that vagally-mediated information arising from SARs does play a major role in producing and maintaining the breathing pattern (Bradley, 1977). The controversy however lies in the relative importance of the tonic and phasic components of SAR discharge in the control of the breathing pattern. Results presented by Grunstein et al. (1975) indicate that the tonic component of SAR discharge adapts completely to maintained increases in lung volume. Other studies however, have demonstrated that there is only a partial adaptation of the tonic component of SAR discharge (D'Angelo and Agostoni, 1975; Davenport et al., 1981; Muza and Frazier, 1983).

Turtles often undergo chronic changes in functional residual capacity to combat changes in body weight in an attempt to maintain neutral buoyancy. In doing so, there is a dramatic and persistent change in the breathing pattern of these animals (Milsom and Chan, 1986). If the tonic (volume-related) component of SAR discharge completely adapts to changes in FRC as suggested
by Grunstein et al. (1975), then the persistent changes in breathing pattern observed by Milsom and Chan (1986) must be the result of changes in the central respiratory rhythm generator. If on the other hand, SARs do not completely adapt to changes in FRC as suggested by D'Angelo and Agostoni (1975), Davenport et al. (1981) and Muza and Frazier (1983), then one could postulate that the tonic (volume-related) component of SAR discharge is important in producing and maintaining the breathing pattern changes observed in turtles experiencing alterations in FRC.

This study has demonstrated that neither the low threshold nor the high threshold slowly adapting pulmonary stretch receptors adapt to long term (1 hour) maintained lung inflations. At the end of 1 hour of maintained elevated lung volume, the low and high threshold SARs have only adapted 80% and 30% from their peak discharge rates respectively. Furthermore, long term lung inflation with air produced only minor (albeit statistically significant) decreases in low threshold SAR dynamic inflation responses compared to those recorded prior to the period of maintained inflation. The dynamic inflation responses of the high threshold SARs were unchanged by 1 hour of maintained lung inflation with air.

In conclusion, slowly adapting pulmonary stretch receptors do retain significant tonic and phasic discharge with prolonged lung inflation. Consequently, the volume-related (tonic) component of SAR discharge is likely to be instrumental in producing and maintaining the changes in breathing pattern that are associated
with chronic alterations in lung volume in these animals. Results from this study tend to support those of D'Angelo and Agostoni (1975), Davenport et al. (1981) and Muza and Frazier (1983). It must be noted that I do not attribute these changes in breathing pattern solely to afferent input arising from slowly adapting pulmonary stretch receptors. The overall breathing pattern of these animals is likely to be produced by the integration of information from chemoreceptors, slowly adapting pulmonary stretch receptors and the central respiratory integrative centers.
LITERATURE CITED


