VAGAL EFFECTS ON COLLATERAL FLOW RESISTANCE IN DOG LUNGS

By

Lynne E. Olson

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ABSTRACT

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A double lumen catheter wedged in a subsegmental bronchus isolated a lobe segment. 95% O_2 5% CO_2 entered the segment through the outer lumen ($\dot{V}$) and left via collateral pathways. The inner lumen measured pressure in the segment (P_S). Transpulmonary pressure (P_L) was measured at the trachea. Steady state resistance (R_{ss}) was determined with the vagi intact, sectioned and stimulated as:

$$R_{ss} = \frac{P_S - P_L}{\dot{V}}$$

When $\dot{V}$ is interrupted, P_S-P_L decays to zero. Modelling the segment as two series compartments demonstrates a fast (f) and slow (s) compartment each with its own resistance (R) and time constant (TC). Static lung pressure-volume characteristics were evaluated. Vagal stimulation decreases maximum lung volume without altering compliance. Stimulating the nerve ipsilateral to the segment increases R_{ss}, R_f, R_s, and TC_s without affecting TC_f. Contralateral stimulation has no effect. The slow compartment is believed to represent collateral channels, therefore increasing vagal tone increases collateral flow resistance.

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R_{ss}	Steady state resistance of lobe segment
ΔR_{ss}	Difference in steady state resistance between experimental and control state
$\hat{R}_{ss}$	Steady state resistance estimated from fitted control R_{ss} vs. P_L or R_{ss} vs. %VC curve
R_f	Resistance of the fast compartment
R_s	Resistance of the slow compartment
C_f	Compliance of the fast compartment
C_s	Compliance of the slow compartment
TC_f	Time constant of the fast compartment = $R_f C_f$
TC_s	Time constant of the slow compartment = $R_s C_s$
P_L	Transpulmonary pressure
P_S	Pressure in the isolated segment of lung lobe
$P_S - P_L$	Pressure difference between the segment and the remainder of the lobe
$\dot{V}$	Steady state flow into the isolated segment as measured with a flowmeter
VC	Vital capacity: volume necessary to inflate the lungs from $P_L = 0$ to $P_L = 30$ cm H_2O
%VC	Volume added to the lungs above residual volume ($P_L = 0$ cm H_2O) as a percentage of vital capacity
V_{max}	Maximum volume that can be added to the lungs above residual volume ($P_L = 0$ cm H_2O)
$\%V_{max}$	Maximum volume that can be added to the lungs above residual volume ($P_L = 0$ cm H_2O) as a percentage of vital capacity
α	Index of lung compliance

INTRODUCTION AND LITERATURE REVIEW

In the late 1800's the lungs were believed to be a series of dichotomously branching tubes which became progressively smaller, ultimately terminating in air sacs where gas exchange took place. This view is represented in the following excerpt from Kirkes Handbook of Physiology (1893).

> The vesicles of adjacent lobules do not communicate and those of the same lobule or proceeding from the same intercellular passage, do so as a general rule only near angles of bifurcation; so that, when any bronchial tube is closed or obstructed, the supply of air is lost for all the cells opening into it or its branches.

While interalveolar connections were described by Kohn in 1893, their existence was disputed by anatomists and their potential significance was ignored by physiologists until the 1930's. It was then observed that atelectasis does not always occur in lung tissue distal to an obstructed airway in man (Van Allen et al. per Macklem, 1971). Recognizing that this observation was incompatible with the then current anatomical description of the lung, Van Allen and co-workers began to investigate the transfer of air between adjacent lung lobules. A 5/16 inch diameter cannula with a dilatable tip was tied into a segmental bronchus of a collapsed isolated lobe of dog lung. Serial x-rays taken while air was infused into the cannula showed that the whole lobe can be inflated and that air leaves the inflated lobe via the mainstem bronchus. When the cannula was wedged into a lobe of dog lung in vivo and the other end of the cannula held under a water seal, water was drawn into the cannula on inspiration and air bubbled out on expiration. Van Allen and co-workers reasoned that the isolated segment receives ventilation either by diffusion or through some unknown anatomical pathways between lobules (Van Allen et al., 1930). This phenomenon was called collateral respiration, but has since been renamed collateral ventilation in keeping with physiological convention.

Van Allen et al. attempted to determine the size of the collateral pathways by infusing suspensions of bismuth subnitrate and india ink into isolated dog lobes via the bronchi. Visual examination of the lobes showed that india ink passes collaterally but bismuth subnitrate (15-30 μm) does not. Bismuth subnitrate particles were found in the alveoli indicating that the collateral pathways are smaller than terminal respiratory ducts and alveoli. As india ink could be transferred only when the parenchyma was expanded, they concluded that the channels are patent only when the lung is inflated. Expanding their investigations of collateral ventilation to include human, cat, rabbit, calf and pig lungs, they found that the collateral transfer of air at physiological pressures requires intimate fusion between lobules. In calf and pig lungs, in which the lobules are separated by complete fibrous septa, collateral transfer of air does not occur. The Pores of Kohn were proposed as the collateral pathways (Van Allen et al., 1931).

The phenomenon of collateral ventilation was largely ignored in the literature until 1948 when Baarsma reported two case histories of juvenile patients who had aspirated foreign objects. One patient in whom a foreign body completely obstructed the left lower section of the main bronchus and part of the lower lobe bronchus developed atelectasis. The other patient had a foreign body wedged beyond the first dorsal branch of the lower lobe bronchus and failed to develop atelectasis. The lack of atelectasis in the second case was explained by collateral ventilation occurring between segments of the lobe (Baarsma et al., 1948). These clinical findings led Baarsma to study collateral ventilation by wedging a catheter into the lungs of patients undergoing bronchoscopy and collecting collaterally transferred air in a spirometer. He confirmed his clinical observation that obstructing the main bronchus of a lobe prevents collateral ventilation while obstructing a side branch does not (Baarsma et al., 1948).

Alley and Lindskog (1948) reported on pharmacologic factors influencing collateral ventilation. A cannula with a dilatable tip was wedged into a lower lobe bronchus and connected to a Krogh spirometer by one-way valves, allowing exhalation only. The remainder of the lungs were connected by a tracheal cannula to a second spirometer. Collateral transfer of air was said to occur if air was transferred into the Krogh spirometer with each exhalation indicating that more air was expired than initially present in the isolated segment. Alpha-napthyl-thio-urea induced pulmonary edema and intravenous histamine abolish collateral ventilation according to these investigators. The Pores of Kohn were postulated as being the functional collateral pathways.

When evaluating data obtained from the dilatable tip cannula technique, a few possibilities must be considered. Air entering the segment via collateral channels can also leave the segment by the same route on exhalation. Therefore an estimate of the air moved collaterally from the volume transferred to the Krogh spirometer should be conservative. Any leak around the catheter will also lead to underestimation of collateral gas transfer although this is unlikely if the cannula is securely tied into a bronchus. Factors affecting airway resistance or lobe compliance might influence results if the entire lobe is subjected to a treatment without any attempt to determine where the primary change in resistance or compliance occurs.

Accessory bronchial-alveolar connections with diameters up to 30 have been described in normal human, cat and rabbit lungs (Lambert, 1955). These connections have no muscular wall of their own but interrupt the muscular wall of the terminal bronchioles they penetrate. Lambert's canals have been proposed as alternative pathways through which collateral ventilation might occur. These structures have not been described in dog lungs.

Martin showed that the size and frequency of interalveolar pores increases with age up to one year in the dog (Martin, 1963) but questioned whether the Pores of Kohn can explain the ease with which air is transferred collaterally. A calculation that a pressure of 192 cm H_2O would be necessary to open a closed pore of 5 μm diameter stimulated a search for alternative collateral pathways. Martin first determined that the collateral transfer of air in degassed excised dog lobes occurs at pressures within a physiological range (17-28 cm H_2O). By infusing a saline suspension of polystyrene spheres 50-710 μm diameter into a bronchus of excised dog lobe under 4 cm H_2O pressure and collecting the effluent, he determined that spheres as large as 120 μm diameter pass through collateral channels in the dog. If Lambert's canals exist in dog lungs, even in the absence of surface forces due to the saline infusion, they would have to be remarkably compliant to pass spheres four times their diameter. This led Martin to dust an isolated segment with india ink powder (1-3 μm) and make serial microscopic sections. In a remarkable reconstruction of 1600 serial sections, he followed the tortuous path of a respiratory bronchiole which connected two terminal bronchioles from adjacent lung segments. He postulated that these muscular walled anastomosing respiratory bronchioles (100-200 μm) could be the functional collateral pathways in the dog (Martin, 1966).

Such pathways have not yet been demonstrated in normal human lungs. Spheres of 60 μm diameter have been passed collaterally in normal excised human lungs, but these communications, as determined by resin casts, appear to be between alveolar ducts. No evidence for communications more proximal than the acinus was found (Henderson et al., 1968/1969). Silicone casts of human lung sections using a micropuncture technique have demonstrated interacinar ducts 200 μm diameter (Raskin & Herman, 1975), and rubber casts of human lungs have revealed alveolarized shunts distal to the terminal bronchioles with diameters of 100-500 μm and lengths of a few millimeters (Phelan, personal communication).

In summary, by the late 1960's the phenomenon of collateral ventilation had been demonstrated in many mammalian species. Dog lungs, which are unlobulated, have good collateral ventilation due to either size or number of collateral channels. Cow and pig lungs, which are distinctly lobulated, have little if any collateral ventilation. Three anatomical sites are considered to be possible collateral pathways as presented in Table 1.

Table 1. Description of Possible Collateral Pathways

Name	Site	Diameter
Pores of Kohn	Interalveolar pores	3-13 μm
Lambert's Canals	Bronchiole-alveolar connections	30 μm
Martin's Channels	Bronchiole-bronchiolar connections	up to 120 μm

In 1969, Brown et al. reported the results of impacting beads of known diameter into excised dog and pig lobes. Beads with a penetrating central hole were used to simulate partial and complete airways obstruction. Results using the oscillatory technique for determining airway resistance demonstrate that many airways less than 2 mm diameter have to be obstructed before a marked increase in total respiratory resistance can be demonstrated. However, obstructing a small number of airways 5-11 mm diameter produces large increases in total respiratory resistance due to their smaller total cross sectional area. Although the criteria for determining frequency dependence of compliance were not given, the authors report that obstructing small airways in dog lobes does not alter vital capacity or static compliance nor does it produce frequency dependence of dynamic compliance. This indicates that obstruction of large numbers of small airways in dog lobes does not alter tidal volume distribution regardless of respiratory frequency. Of the three pig lobes studied only one demonstrated a significant reduction in vital capacity and static compliance with small airway obstruction. In all three lobes, however, dynamic compliance was frequency dependent after obstruction of the small airways. In contrast to dog lungs, pig lungs are unable to maintain a normal distribution of ventilation with increased respiratory rate when small airways are obstructed. These results are attributed to differences in the efficiency of collateral ventilation in dog and pig lobes. The collateral time constant (T_{coll}) is defined as the product of collateral resistance (R_{coll}) and lung compliance (C). For collateral pathways to be effective in maintaining a normal distribution of ventilation with airways obstruction, the collateral time constant must be short relative to the duration of inspiration. Dog lungs were found to have short T_{coll}'s while pig lungs had very long T_{coll}'s.

The first quantitative description of the mechanical properties of collateral pathways appeared in 1969. Hogg et al. reasoned that lower lobe airways, collateral channels in incomplete interlobar fissures and upper lobe airways represent three resistances in series. To determine the resistance of collateral channels, a cannula was tied into a basal segmental bronchus, catheters inserted through the pleura above and below the fissure and a cannula tied into an apical segmental bronchus. Air was infused into the lobe through the basal cannula and left via the apical cannula. In a steady-flow state, knowing the pressure in each cannula permits the calculation of lower lobe, collateral channel and upper lobe resistances. This study was performed in 16 excised human lungs, 8 normal and 8 emphysematous. Collateral resistance is greater than upper lobe and lower lobe airway resistance in normal lungs but less than upper lobe and lower lobe airway resistance in emphysematous lungs. Hysteresis was demonstrated in the pressure-flow curve indicating that collateral resistance is less on deflation than inflation. It was postulated that the diameter of collateral pathways is a function of tissue and surface forces and lung volume. Assuming that collateral pathways collapse with increased surface forces as airways do, the reduced surface forces on deflation might explain these results (Hogg et al., 1969).

Theoretical considerations using electrical analogues were presented to help explain the frequency dependence of compliance seen in emphysema (Hogg et al., 1969). Hogg and co-workers reasoned that the ability of collateral pathways to maintain adequate ventilation to obstructed segments depends on their time constant. For collateral ventilation to be effective in delivering inspired gas to an obstructed segment, T_{coll} must be small relative to inspiration time. It was noted that until measurements of T_{coll} are made, these theoretical speculations cannot be confirmed. In his review article, Macklem (1971) credits two laboratories for independently developing methods for estimating the appropriate time constants.

Hilperts method consists of wedging a triple lumen balloon tipped catheter into a bronchus. The balloon is inflated to securely isolate the segment of lobe distal to it. Air can then only enter and leave the segment by collateral channels. Air is infused at a constant known flow rate ($\dot{V}_{coll}$) through one lumen of the catheter while another lumen simultaneously records pressure in the isolated segment (P_{seg}). Steady state collateral resistance (R_{coll}) is calculated as:

$$R_{coll} = \frac{P_{seg}-P_{el}}{\dot{V}_{coll}}$$

P_{el} represents the pressure in the remainder of the lobe. Therefore $P_{seg}-P_{el}$ is the driving pressure for the flow of gas in or out of the segment when $\dot{V}_{coll}$ is stopped. When $\dot{V}_{coll}$ is interrupted, the resulting pressure decay in the isolated segment approximates a single exponential. As in the electrical analogue, the collateral time constant is defined as the time necessary for $P_{seg}-P_{el}$ to decay to 37% of its initial value (Hilpert, 1970).

Woolcock and Macklem (1971) developed two methods for assessing collateral mechanical properties. The first method involves wedging a double lumen polyethylene catheter into a bronchus. A known volume of air is rapidly injected into the isolated segment as segment pressure is simultaneously recorded. Plotting the resulting pressure decay as a function of time on semi-logarithmic paper permits the recovery of up to three time constants using a curve stripping technique.

The second method utilizes a single lumen catheter wedged in a bronchus and a variable frequency oscillating pressure system and assesses dynamic characteristics of the collateral channels. These investigators recognize the errors in their data due to the experimental techniques, and discuss their findings accordingly (Woolcock and Macklem, 1971).

Several important conclusions were drawn from Woolcock and Macklem's data. They found that the repeatability of a given time constant measurement is enhanced by a strict volume history procedure prior to each determination. This implies that surface and tissue forces influence the mechanical properties of collateral pathways. Contrary to the report of Hogg et al. (1969), collateral resistance was lower after a full deflation. As constant volume history maneuvers were performed in both studies, there is no obvious reason for this discrepancy other than the method used to calculate R_{coll}.

Robinson and Sorenson (1978), reporting on excised dog lobes, found that when R_{coll} was plotted as a function of transpulmonary pressure (P_L), R_{coll} after a full inflation was less than R_{coll} after deflation, confirming the observation of Hogg et al. (1969). When plotted as a function of percent total lobe capacity (%TLC) however, R_{coll} after a full inflation was less than R_{coll} after deflation at lobe volumes less than 40%. The data as a function of %TLC are consistent with Woolcock and Macklem's report (1971). Unpublished data from the present study confirm Robinson and Sorenson's results when resistance was examined as a function of P_L. These discrepant findings emphasize the importance of a strict constant volume history prior to resistance determinations.

The introduction of suitable techniques for quantitating the mechanical properties of collateral pathways and the recognition of the physiological implication of the existence of alternate ventilatory pathways stimulated research into factors affecting collateral ventilation. Much of this research was into the effect of CO_2 and O_2 tensions on collateral channels in an attempt to determine how these pathways might affect the distribution of ventilation in chronic obstructive lung diseases.

Regardless of whether the method employed was calculation of R_{coll} by Hilperts method (Batra et al., 1975A; Batra et al., 1975B; Traystman et al., 1976) or measurement of the volume of collaterally transferred air (Chen et al., 1970; Sealy and Seaber, 1975; Johnson and Lindskog, 1971), the results of the effect of gas tension on collateral channels are compatible. Alveolar hypercapnia increases the effective collateral ventilation by decreasing the resistance of collateral channels or by recruiting additional channels. Alveolar hyperoxia decreases collateral ventilation, although the effect is not as marked or consistent as the effect of alveolar CO_2 tensions. The fact that atropine and dibenzylene attenuated but did not abolish the response of collateral channels to CO_2 suggests that these pathways are responsive to neural input (Batra, 1975A).

Woolcock and Macklem (1971) were the first to report an effect of the vagus nerve on collateral pathways. Results were obtained on two dogs only and actual values for R_{coll} and segment compliance (C_{seg}) presented for one dog. These results were obtained using the oscillatory technique for determining the dynamic properties of collateral channels. Vagal stimulation caused a large increase in R_{coll} and a smaller decrease in C_{seg}, resulting in a small increase in T_{coll}. When the lobe was excised and measurements repeated, there was a larger increase in T_{coll} over control resulting from increases in both R_{coll} and C_{seg}. It is at first anomalous that stimulating the vago-sympathetic nerve in the dog in vivo and excising the lung should both increase T_{coll} since the state of distension of the pulmonary vasculature is not thought to be the primary determinant of collateral resistance to gas flow (Menkes et al., 1976). Results could be explained on the basis of changes in alveolar gas tensions as alveolar hypocapnia and hyperoxia increase collateral resistance in vivo (Traystman et al., 1976).

As early as 1844 it was demonstrated that stimulating the vagus nerve caused bronchoconstriction (Widdicombe, 1963). Widdicombe cites a report by Volkmann in which a puff of air was discharged from the lungs with sufficient force to extinguish a candle held at a tracheostomy during stimulation of the vagus nerves. Since that time, numerous studies have been performed to elucidate the primary site of action, distribution of receptors and quantitative effect of the vagus nerve on respiratory mechanical and gas flow properties.

The development of the retrograde catheter technique permitted the quantitative partitioning of the total resistance of the lungs (R_{tot}) into peripheral and central components. In this method a flared tip polyethylene catheter is wedged in a bronchus so that the catheter extends peripherally through the parenchyma and pleura. Total lung resistance is measured using the oscillatory technique and partitioned by knowing the pressure drop occurring between the trachea and wedged catheter, and the wedged catheter and pleural cavity (Macklem and Mead, 1967). In this study and subsequent studies utilizing this technique, peripheral resistance (R_{per}) is defined as the resistance of all airways distal to the wedged catheter tip and central resistance (R_{cen}) as the resistance of airways proximal to the catheter tip. The distinction is therefore arbitrary and depends upon the size of the airway in which the retrograde catheter is placed.

Woolcock et al. (1969A, 1969B) utilized the retrograde technique to examine the effect of vagal stimulation on central vs. peripheral airways and on the elastic properties of the dog lung. Vagal stimulation increased R_{cen} and R_{per}, being most effective at low lung volumes. However, there was a large degree of interanimal variation. Differences in the distribution of parasympathetic receptors were postulated to explain much of this variation. It was stated that vagal stimulation caused large decreases in vital capacity although no composite data are presented (Woolcock et al., 1969A).

Both R_{tot} and R_{cen} were lung volume dependent, increasing as lung volume decreased. Beta adrenergic blockade with propranolol increased R_{per} significantly and potentiated the effect of vagal stimulation. With vagal stimulation following propranolol, R_{per} as a percentage of R_{tot} was more lung volume dependent than R_{cen} as a percentage of R_{tot}.

As R_{per} was relatively independent of lung volume prior to beta adrenergic blockade, it was postulated that there is sympathetic tone in the peripheral airways making them insensitive to lung volume changes (Woolcock et al., 1969B). Such a mechanism would serve to minimize airway resistance and dead space. Hoppin et al. (1978) using a modification of the retrograde catheter technique in which parenchymal pressure was directly measured in vivo and catheter response times carefully matched were unable to confirm the observation of Woolcock et al. (1969B) that R_{per} was independent of lung volume prior to beta adrenergic blockade. Composite data presented in the report by Hoppin et al. (1978) demonstrate that both R_{cen} and R_{per} are volume dependent. This volume dependence was not abolished by vagotomy indicating that it may be due to mechanical interdependence. Hoppin et al. (1978) suggest that the frequency response of the catheters and the inclusion of tissue resistance in the measurements, obscured changes in R_{per} with lung volume in the determinations of Woolcock et al. (1969B). This does not directly invalidate the postulate that peripheral airways possess sympathetic tone, however. In a clinical study on human volunteers, Ploy-Song-Sang et al. (1978) found that when infused separately, intravenous histamine or propranolol did not alter the mechanical properties of the lungs as assessed plethysmographically. When infused together, however, maximal flow during forced exhalation at 50% total lung capacity was significantly decreased suggesting peripheral airway constriction. The investigators conclude that histamine constricts peripheral conducting airways in man but that the effect is masked by sympathetic bronchodilation due to reflex catecholamine discharge by the adrenal glands.

Woolcock et al. (1969A, 1969B) report that with vagal stimulation, pressure volume (P-V) curves shift toward the pressure axis as compared to control curves. The difference between curves is greatest at transpulmonary pressures greater than 10 cm H_2O. Vital capacity (VC) decreases with both propranolol and vagal stimulation. Vagal stimulation following beta adrenergic blockade causes the largest percent decrease in VC, averaging 23% (Woolcock et al., 1969B). These results have been confirmed by Hahn et al. (1976) who utilized a bronchographic technique to demonstrate that while airway pressure-diameter curves are markedly shifted toward the pressure axis with vagal stimulation, the deflation limb of the P-V curve of the lungs are much less affected, although the shift toward the pressure axis was significant at P_L's greater than 5 cm H_2O. The relative shifts in the two curves indicate that airways may be somewhat independent of lung volume.

In conclusion, while all methods to date claim to measure collateral mechanical properties, there is no concrete evidence indicating that only collateral pathways are affected by the experimental treatments. It is equally likely that the airways within the isolated segment also contribute to the measured resistance and time constant.

When utilizing Hilperts method for determining collateral resistance, the catheter becomes wedged in a 4-7 generation bronchus, the trachea being generation 1. While at this point it is not clear what anatomical structures constitute collateral pathways, in the dog collateral channels are thought to occur at the level of respiratory bronchioles which begin at generation 17. These figures indicate that there may be 10 generations of airways distal to the catheter yet proximal to the collateral channels. The resistance of these airways is included in the determination of "R_{coll}". For this reason, in the present study, the resistance of pathways within the isolated segment determined using Hilpert's method is designated steady state resistance (R_{ss}) instead of collateral resistance (R_{coll}).

Furthermore, it is known that airway resistance changes as a function of lung volume. Volume shifts in the lung with experimental intervention must be carefully assessed to determine whether increases in collateral resistance may be attributed to changes in the pressure-volume (P-V) characteristics of the lungs.

Since it is known that vagal stimulation increases airway resistance, the problem becomes one of separating the effect of the vagus on collateral flow resistance from its effect on airway flow resistance. To control extraneous variables, a mixture of 95% O_2 5% CO_2 was infused into the segment to prevent hypocapnic broncoconstriction. A strict constant volume history was established prior to each determination and measurements made in duplicate. Pressure-volume curves were constructed to assess the effect of vagal stimulation on lung volume. Finally, the segment was mathematically modelled as two compartments in series to permit the separation of changes in airway vs. changes in collateral resistance with vagal stimulation.

MATERIALS AND METHODS

Surgical Preparation

Ten dogs (10-18 kg) of mixed breed, age and sex were anesthetized with a mixture of alpha chloralose (100 mg/kg body weight, i.v., ICN Pharmaceutical, Cleveland, OH) and urethane (500 mg/kg body weight, i.v., Sigma Chemical Co., St. Louis, MO). When necessary, succinyl choline (20 mg, i.v., E. R. Squibb & Sons, Inc., Princeton, NJ) was infused to prevent spontaneous ventilation during data collection. A polyethylene catheter filled with heparinized saline was inserted into a femoral artery and connected to a pressure transducer (P23Db, Statham Instruments, Hato Rey, PR) to monitor mean arterial blood pressure. A femoral vein was also cannulated and a slow drip of Lactated Ringers solution begun to assure the patency of the catheter. Supplements of the anesthetic, paralytic and blocking agent were infused via this cannula.

A tracheostomy was performed and a three-way connector tied into the trachea. The supine animal was placed on a heating pad to maintain body temperature and artificially ventilated with a constant volume ventilator (Model 613, Harvard Apparatus, Millis, MA). Tidal volume was selected so that peak inspiratory pressure measured at the trachea was about 12 cm H_2O. Respiratory frequency was adjusted to maintain end tidal CO_2 concentration between 4% and 5% as measured at the trachea with an infra-red CO_2 analyzer (LB-2, Beckman Instruments, Fullerton, CA) which was calibrated daily with a gas mixture of known CO_2 concentration.

The cervical vagus nerves were isolated, a ligature passed beneath each and warm mineral oil applied to prevent drying. The chest was widely opened with a transsternal thoracotomy in the sixth interspace. A variable speed blower attachment maintained a positive end expiratory pressure. Figure 1 is a schematic representation of the equipment used for the experiment.

Isolating a Segment of Lobe

In order to isolate a segment of lobe, the ventilator was switched off and the lung was fully inflated with the blower. A double lumen polyethylene catheter (flared tip = 5 mm o.d.) was passed through the sidearm opening of the three-way connector at the trachea and advanced until the tip became securely wedged in a subsegmental bronchus. The segment of lobe distal to the catheter tip ventilated only through collateral channels. The site of wedged catheter placement was verified by palpation. As placement of the catheter was random, the vagus nerve on the same side as the lobe containing the catheter was designated the ipsilateral (IL) vagus nerve and the other the contralateral (CL) vagus nerve.

Measurement of Lung Pressures

Transpulmonary pressure (P_L) was measured with a differential pressure transducer (PM 131, Statham Instruments, Hato Rey, PR) as the difference between tracheal and atmospheric pressures. With no flow,

Figure 1. Schematic representation of equipment used to determine resistance of isolated lung lobe segment. Transpulmonary pressure (P_L) and the pressure difference across the isolated segment (P_S-P_L) were monitored with differential pressure transducers and recorded on light sensitive paper. Gas flow into the segment ($\dot{V}$) was regulated with a flowmeter. Lung inflation pressure was maintained with a blower attachment through a Harvard ventilator. Percent CO_2 was continuously monitored with an infra-red CO_2 analyzer.

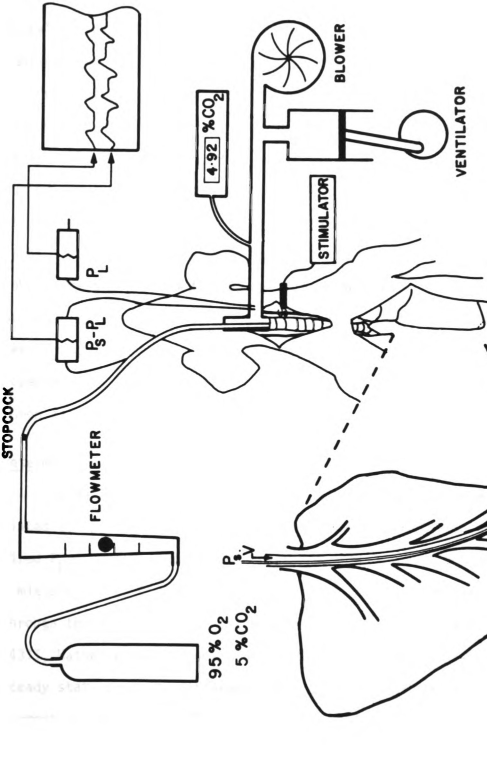
STOPCOCK
FLOWMETER
95 % O_2
5 % CO_2
P_S-P_L
P_L
4·92 % CO_2
STIMULATOR
BLOWER
VENTILATOR
P_s
V

Figure 1

tracheal pressure equals alveolar pressure. A second differential transducer measured the difference between segment pressure (P_S) at the distal end of the double lumen catheter and inflation pressure in the remainder of the lobe (P_L) as measured at the trachea. This pressure difference (P_S-P_L) was the driving pressure for flow between the isolated segment and the trachea (see Figure 1). The transducers were calibrated daily against a water manometer and the calibration periodically checked during the experiment. P_L and P_S-P_L were displayed simultaneously on an oscilloscope screen and recorded on light sensitive paper (VR-6, Electronics for Medicine, White Plains, NY). The catheter isolating the lobe segment was assumed to be securely wedged when P_L and P_S were out of phase during tidal breathing and the determination of steady state resistance of pathways within the segment (R_{ss}) using Equation 1 was repeatable at the same P_L. Ninety percent response time for the double lumen catheter was 0.06 sec.

Determination of R_{ss}

To determine R_{ss}, the ventilator was switched off, the lung inflated to P_L = 30 cm H_2O with the blower and then deflated to the desired P_L in order to establish an appropriate constant volume history. A mixture of 95% O_2 and 5% CO_2 was infused into the isolated segment through the outer lumen of the wedged catheter via a flowmeter (Model 7431T, Matheson Gas Products, Joliet, IL). Flow was adjusted until a steady state pressure difference of 3 cm H_2O existed across the isolated segment (P_S-P_L = 3 cm H_2O). Flow was then abruptly interrupted by turning a stopcock and P_S allowed to come to equilibrium with P_L as gas flowed from the isolated segment via collateral channels. In other words, P_S-P_L decayed to zero as shown in a representative trace in Figure 2. Steady state resistance was calculated knowing the steady state driving pressure (P_S-P_L) and the flow ($\dot{V}$) necessary to obtain that pressure.

$$R_{ss} = \frac{P_S - P_L}{\dot{V}} \qquad (1)$$

Experimental Design

The determination of R_{ss} was repeated at P_L's between 0 and 15 cm H_2O with the vagi intact before and after beta adrenergic blockade with propranolol (0.25-1.0 mg/kg body weight, i.v., DL-Propranolol HCl, Sigma Chemical Co., St. Louis, MO), with the vagi sectioned, and during alternate stimulation of the peripheral ends of the ipsilateral and contralateral vagus nerves (SD-9, Grass Medical Instruments, Quincy, MA). The stimulus parameters, 5V, 30H_z, 3msec, were sufficient to induce cardiac arrest. Most measurements were made in duplicate. Stimulation was initiated prior to the volume history maneuver and continued until the measurement was complete. Stimulus duration was approximately 20 seconds. Propranolol was infused by diluting the dose in 100 ml of normal saline and infusing it over a period of 10 minutes with an infusion pump (Model 600-000,Harvard Apparatus Co., Inc., Dover, MA).

In one animal atropine sulfate (0.4 mg/kg body weight, i.v., Bel-Mar Laboratories, Inc., Inwood, NY) was administered after the experimental protocol was completed and the determination of R_{ss} repeated.

A flow diagram of the experimental protocol is presented in Appendix A.

Figure 2. Representative trace of the pressure difference across the isolated segment (P_S-P_L) in cm H_2O, during stimulation of the ipsilateral vagus nerve, as a function of time in seconds. During a-b, 95% O_2 5% CO_2 is flowing into the segment at a constant rate establishing a 3 cm H_2O pressure difference. At b, flow is interrupted and P_S-P_L decays to zero as gas leaves the segment via collateral channels.

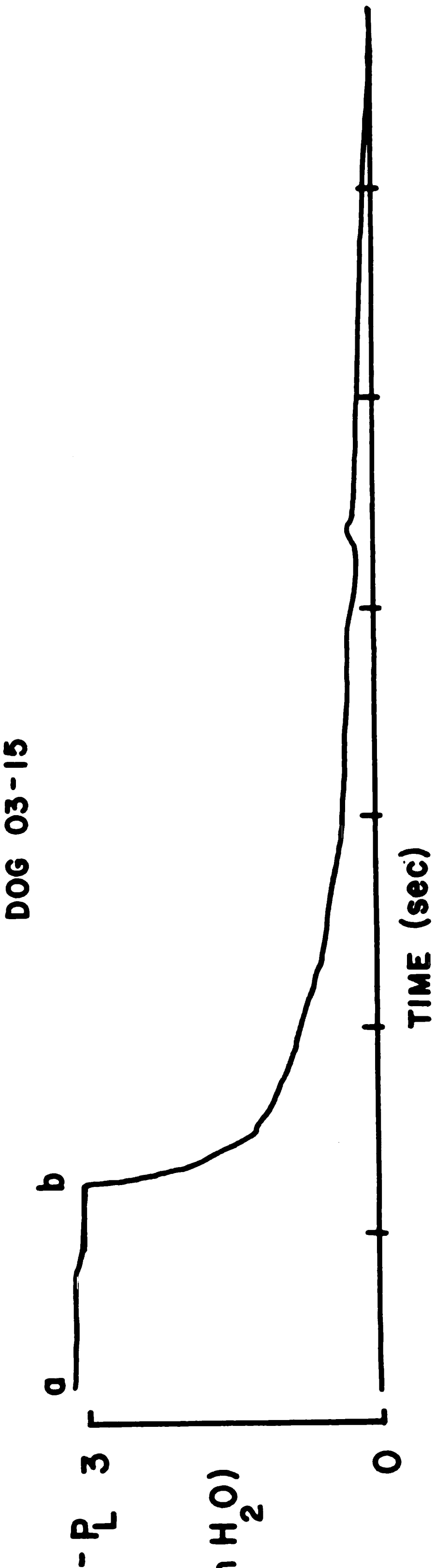

Figure 2

<u>Reduction of R_{ss} Data</u>

Because of the large interanimal variation in R_{ss}, vagal effects on pathways within the segment were analyzed by calculating a change in resistance (ΔR_{ss}) produced by vagal sectioning and stimulation. The change in steady state resistance was calculated as the difference between R_{ss} determined during experimental treatment and control R_{ss} at the same distending pressure ($\hat{R}_{ss}$). In order to establish a control curve for each dog, R_{ss} was determined over a wide range of distending pressures prior to sectioning the vagi, before and after propranolol. Since R_{ss} decreased as P_L increased, the relationship of R_{ss} to P_L was empirically described as a power function using the following equation:

$$\hat{R}_{ss} = aP_L^{\,b} + c \qquad (2)$$

Parameters a, b, and c were calculated and the residuals minimized utilizing a nonlinear least-squares curve fitting routine (Bevington, 1969) performed by a digital computer (LSI 11, Digital Equipment Corporation, Maynard, MA). The predictability of these curves was good with an average residual variance of 8.6×10^{-3} (cm H_2O/ml/sec)^2. A representative curve is shown in Figure 3.

Data for ΔR_{ss} are divided into three groups. Group I consists of three dogs in which no propranolol was given. Group II consists of seven dogs in which R_{ss} was determined after beta adrenergic blockade for all experimental conditions. In the latter group, ΔR_{ss} was calculated as the difference between experimental R_{ss} and $\hat{R}_{ss}$ determined from the control curve established one-half hour after the propranolol infusion ended.

Figure 3. Representative curve for one dog plotting steady state resistance of pathways within the isolated segment (R_{ss}) in cm H_2O/ml/sec as a function of transpulmonary pressure (P_L) in cm H_2O. Circles represent individual data points. The smooth curve was generated using Equation 2. The parameters of Equation 2 are given in the figure.

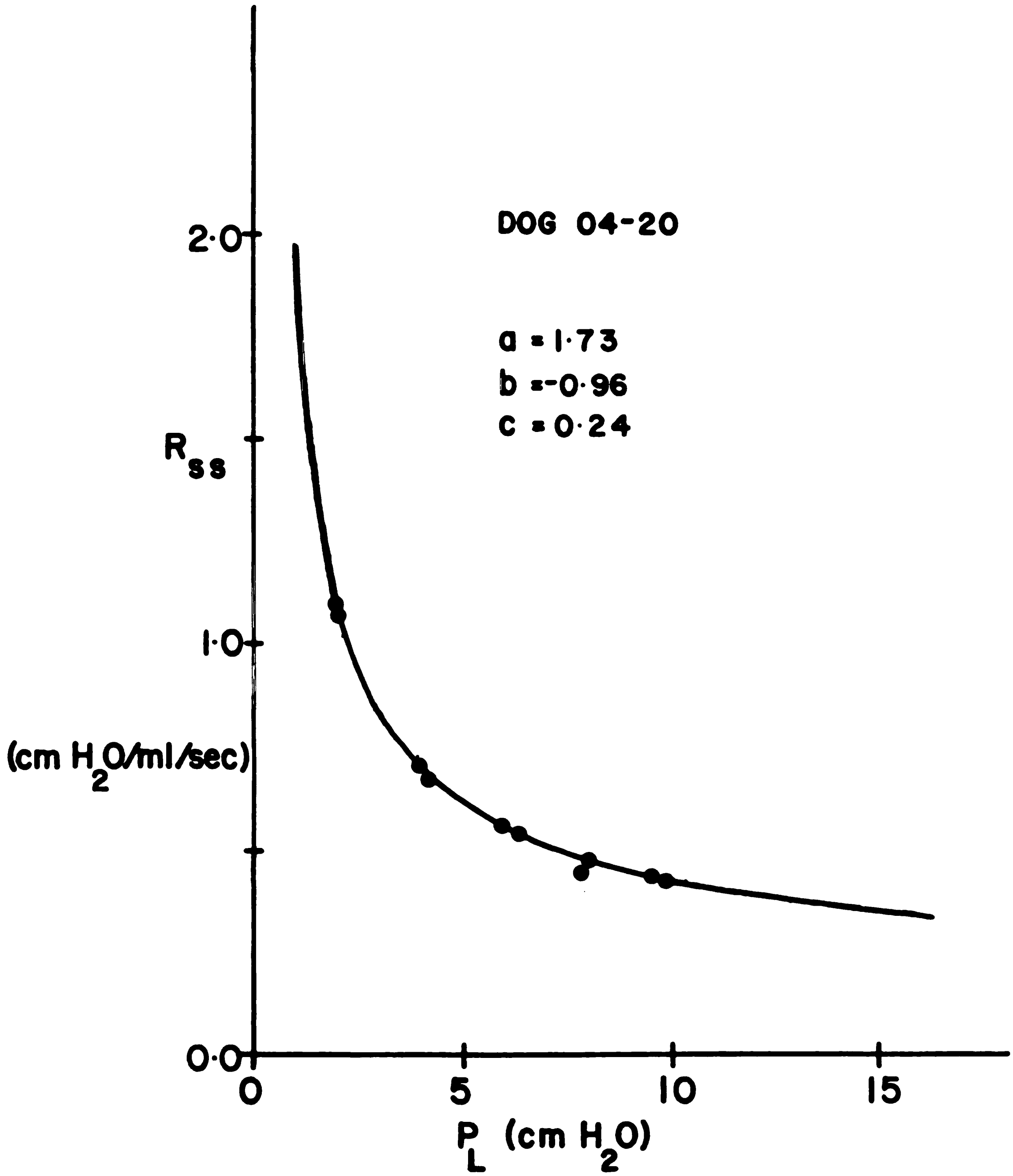
DOG 04-20
a = 1·73
b = -0·96
c = 0·24
R_{ss}
(cm H_2O/ml/sec)
2·0
1·0
0·0
0
5
10
15
P_L (cm H_2O)

Figure 3

For five of the seven dogs of Group II, pressure-volume (P-V) data were available during simultaneous stimulation of both vagus nerves. These five dogs represent Group III. Therefore, R_{ss} could be calculated at a given lung volume rather than at a given distending pressure, using the following equation:

$$R_{ss} = a\%VC^{b} + c \tag{3}$$

A representative curve is presented in Figure 4.

Analysis of Pressure Decay Curves

When steady state flow into the isolated segment was interrupted, P_S-P_L decayed to zero as in Figure 2. A total of 90 curves from 10 animals were analyzed as exponential decays using the nonlinear least squares routine and digital computer. Curves which were best fitted as single exponentials are described by the following equation:

$$(P_S-P_L)_t = (P_S-P_L)_{t=o}\bar{e}^{(1/RC)t} \tag{4}$$

The fit of these curves had an average standard error of the mean (SEM) of 5.45 x 10^{-4} cm H_2O. The time constant (RC) of the collaterally ventilated space was calculated from this equation. As 66% of the pressure decays studied were best described as double exponentials, the isolated segment was modelled as two compartments in series, each with its own resistance (R) and capacitance (C) as shown in Figure 5. These curves were described using Equation 5 and had a mean SEM of 2.76 x 10^{-4} cm H_2O.

$$(P_S-P_L)_t = (P_S-P_L)_{t=o}\frac{R_1}{R_1+R_2}\bar{e}^{(1/R_1C_1)t} + (P_S-P_L)_{t=o}\frac{R_2}{R_1+R_2}\bar{e}^{(1/R_2C_2)t} \tag{5}$$

Figure 4. Representative curve for one dog plotting steady state resistance of pathways within the isolated segment (R_{ss}) in cm H_2O/ml/sec as a function of percent vital capacity (%VC). Circles represent individual data points. The smooth curve was generated using Equation 3. The parameters of Equation 3 are given in the figure.

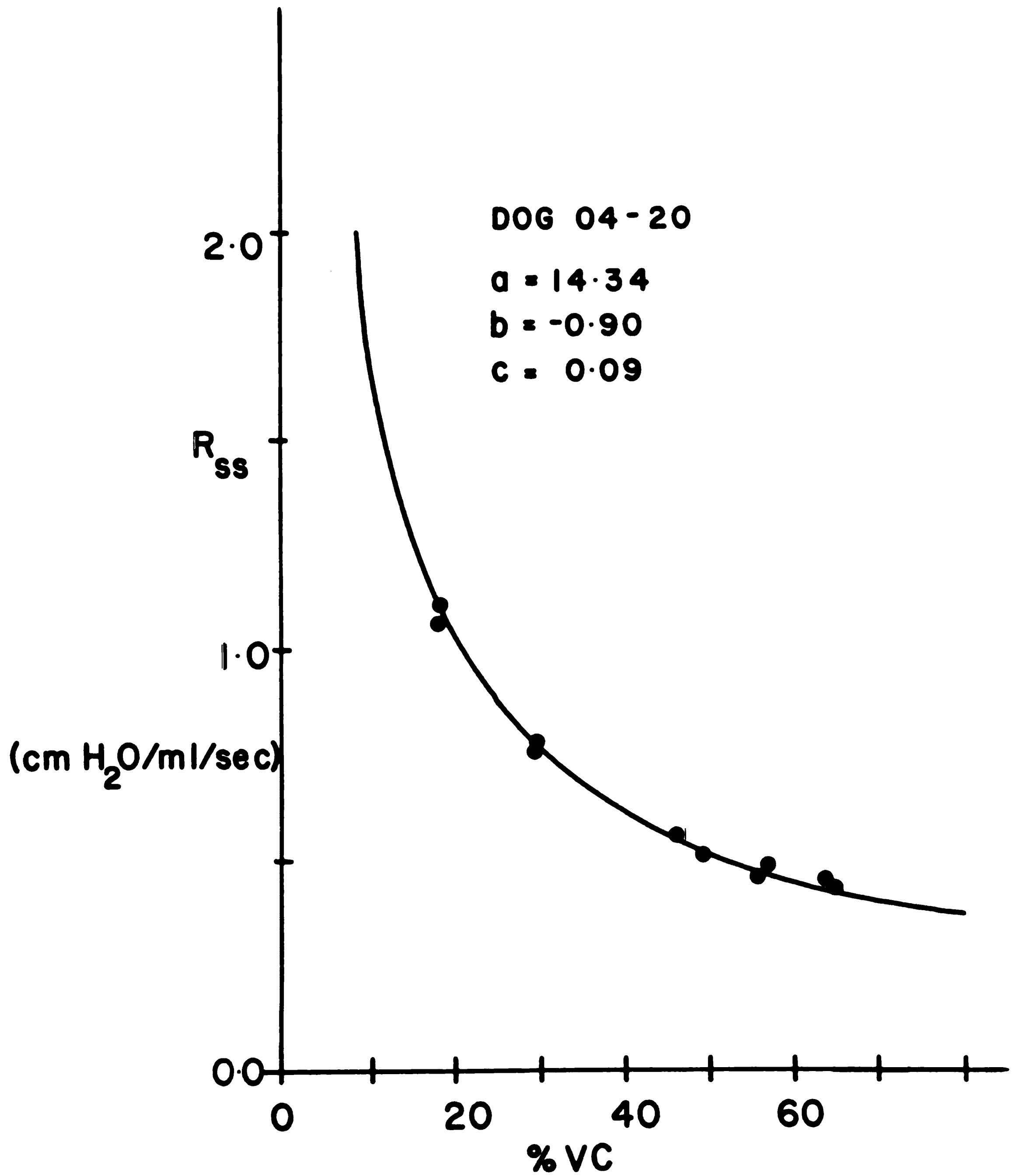

Figure 4

Figure 5. Electrical representation of the two compartment model proposed to represent the isolated segment. Driving pressure for flow through the system is the difference between the pressure in the isolated segment (P_S) and the pressure in the remainder of the lobe (P_L) as measured at the trachea.

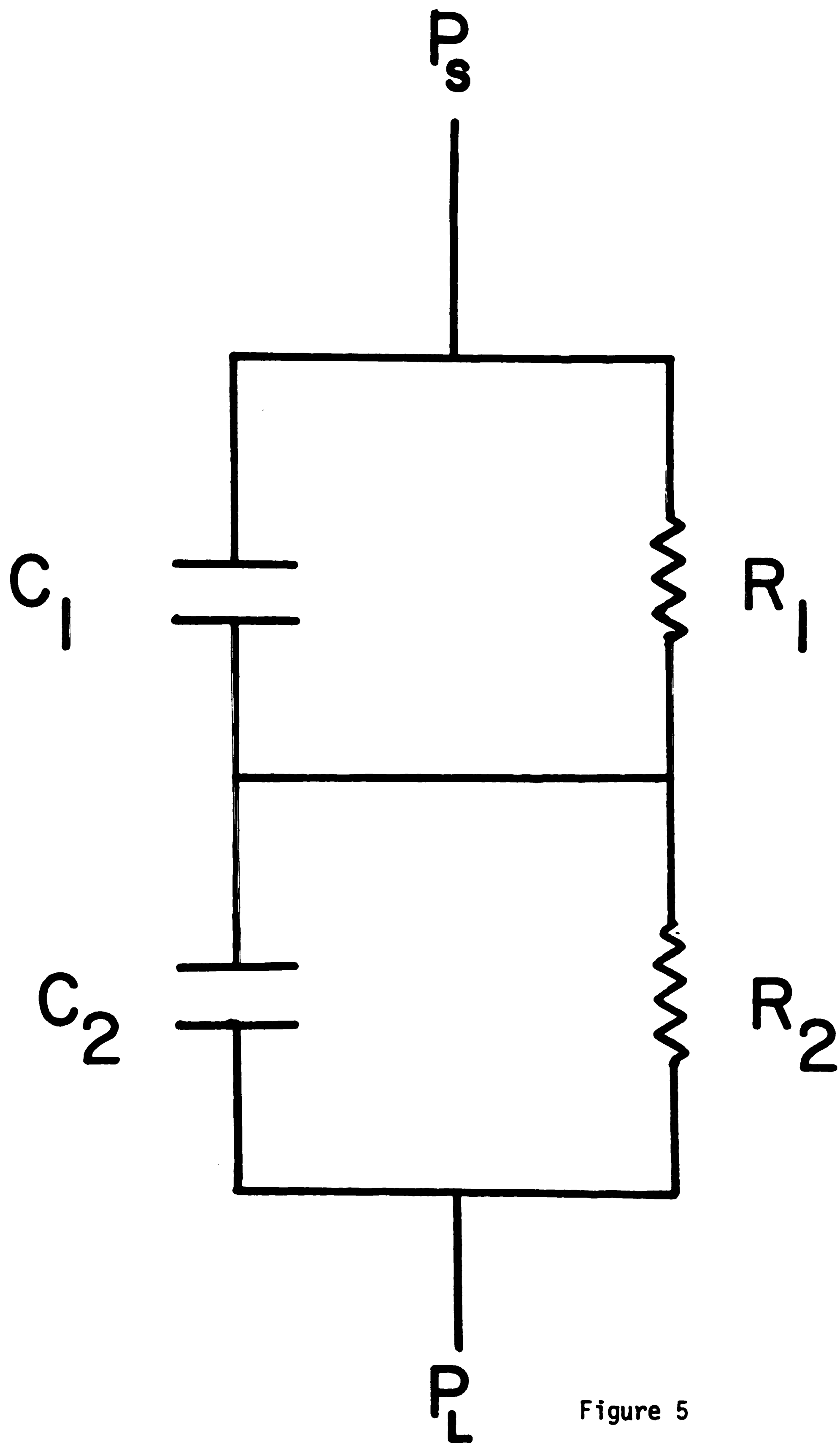

Figure 5

This equation permitted the calculation of two time constants (R_1C_1,R_2C_2) and two resistances (R_1,R_2). As the two compartments are in series, R_{ss} is equal to the sum of R_1 and R_2. A fast compartment (f) and a slow compartment (s) were found.

Recording of Lung P-V Curves

To determine whether the vagus nerve innervates structures which would affect the elastic properties of the lung, static P-V curves were constructed by stepwise injection and withdrawal of known volumes of air into and out of the lungs using a 1500 ml syringe (Model s1500, Hamilton Co., Inc., Reno, NV). Flow was permitted to stop between each step and P_L recorded simultaneously. The pressure-volume (P-V) characteristics of the lungs were determined with the vagus nerves intact before and after propranolol, with the vagus nerves sectioned, and in five animals during simultaneous stimulation of both vagus nerves. These curves permitted the description of R_{ss} as a function of %VC using Equation 3, by relating the P_L at which R_{ss} was determined to %VC.

Analysis of P-V Curves

The deflation limbs of the P-V curves were empirically described as single rising exponentials (Salazar and Knowles, 1964). Parameters were obtained using the nonlinear least squares procedure and a digital computer. Vital capacity (VC) is defined as the volume of air necessary to inflate the lungs from P_L = 0 to P_L = 30 cm H_2O (Figure 6). Knowing VC permitted the description of P-V curves as a percentage of VC (%VC) to account for differences in lung size using the following equation:

Figure 6. Representative deflation limb of the pressure-volume (P-V) curve for one dog plotting volume (V) added to the lungs above residual volume in liters as a function of transpulmonary pressure (P_L) in cm H_2O. Circles represent individual data points. The smooth curve represents predicted V from nonlinear least squares fit of the data points to the following equation:

$$V = V_{max}(1-e^{-\alpha P_L})$$

Parameters for this equation are given in the figure. Vital capacity (VC) is defined as V at P_L = 30 cm H_2O.

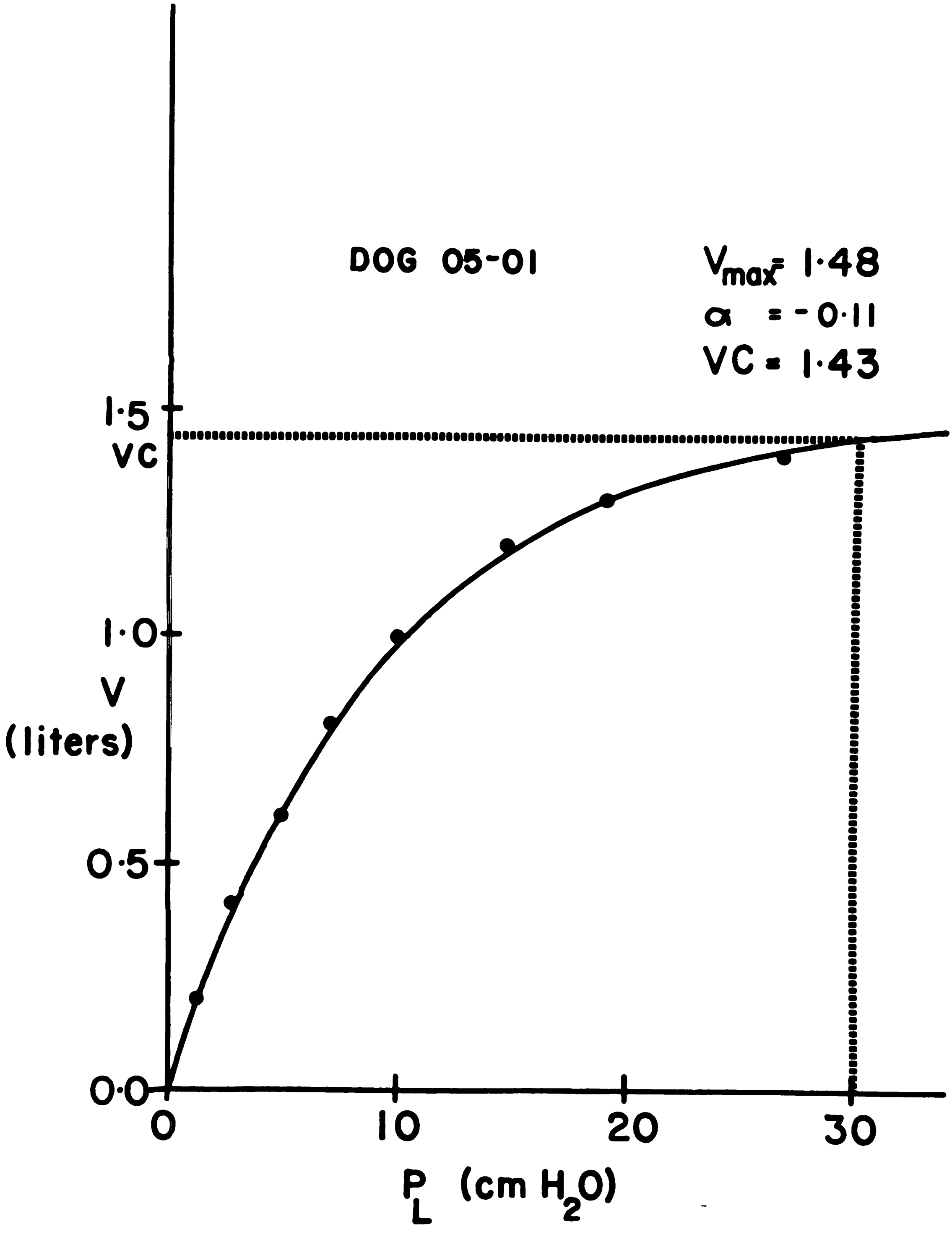
DOG 05-01
V_{max}= 1·48
α = -0·11
VC = 1·43
1·5
VC
1·0
V
(liters)
0·5
0·0
0
10
20
30
P_L (cm H_2O)

Figure 6

$$\%VC = \%V_{max}(1-e^{-\alpha P_L}) \qquad (6)$$

%VC is the volume of air above residual volume (P_L = 0 cm H_2O) as a percentage of VC necessary to inflate the lung to a given distending pressure. $\%V_{max}$ represents the maximum volume that can be added to the lung above residual volume as a percentage of VC. Alpha indicates the rate at which the curve rises and is therefore an index of lung compliance.

Statistical Treatment of Data

The change in steady state resistance was calculated for three experimental conditions:

1) vagi sectioned
2) ipsilateral vagal stimulation
3) contralateral vagal stimulation

A one-way analysis of variance (ANOVA) verified that there was no significant difference in the P_L or %VC at which ΔR_{ss} was determined for these conditions. The effect of lung volume on the magnitude of ΔR_{ss} is therefore the same for each condition in Groups I and II providing the P-V curve is not altered by vagal stimulation. In Group III, the normalization of ΔR_{ss} to %VC eliminated the effect of the vagus nerve on lung volume. A mean ΔR_{ss} was calculated for each experimental condition. Differences in ΔR_{ss} were calculated with a one-way ANOVA and differences in the mean ΔR_{ss} determined with the Student-Neuman-Keuls (SNK) analysis (Sokal and Rohlf, 1969; Rohlf and Sokal, 1969).

A one-way ANOVA verified that there was no difference in the P_L at which R_f,R_s,TC_f, and TC_s were calculated for four experimental conditions:

1) vagi intact (control)
2) vagi sectioned
3) ipsilateral vagal stimulation
4) contralateral vagal stimulation

Significant differences in compartmental resistances and time constants among experimental conditions were determined with a one-way ANOVA and SNK analysis. In addition, Wilcoxon's Two Sample Test for unequal sample sizes was used to evaluate the time constant data (Sokal and Rohlf, 1969).

The effect of the vagus nerve on the elastic properties of the lung was assessed by statistical analysis of the parameters $\%V_{max}$ and α. Treatment effects were determined using a two-way ANOVA and SNK analysis.

ANOVA tables and the results of Wilcoxon's Two Sample Test are presented in Appendix B. Significance was determined at the $P < 0.05$ level in all cases.

RESULTS

In all dogs studied, R_{ss} of pathways within the isolated segment was dependent on both lung volume and vagal input. Steady state resistance was greatest at low lung volumes and during ipsilateral vagal stimulation. Figure 7 shows the data from one dog.

In Group I, no propranolol was used and ΔR_{ss} was calculated at the same distending pressure. The change in steady state resistance during ipsilateral vagal stimulation was significantly greater than ΔR_{ss} with the vagi sectioned and ΔR_{ss} during contralateral vagal stimulation (Figure 8).

Ipsilateral vagal stimulation significantly increased ΔR_{ss} as compared to ΔR_{ss} with the vagi sectioned and during contralateral vagal stimulation in Group II also. In this group ΔR_{ss} was normalized to P_L as in Group I, however, all measurements were taken after beta adrenergic blockade with propranolol. Results are shown in Figure 9.

The effect of the vagus nerve on the elastic properties of the lung are presented in Table 2 and Figure 10.

Table 2. Pressure-volume Curve Parameters

	Vagi Intact	Vagi Sectioned	Vagi Stimulated
$\%V_{max}$	104.6	100.1	96.9*
α (mean)	-0.095	-0.107	-0.111

* = significantly different from vagi intact but not from vagi sectioned.
n = 10

Figure 7. Representative data from one dog plotting steady state resistance (R_{ss}) in cm H_2O/ml/sec as a function of transpulmonary pressure (P_L) in cm H_2O with the vagi intact (control), sectioned (cut), during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL). Symbols represent individual data points. The smooth curve represents the nonlinear least squares fit of Equation 2 to the control data points. Parameters for Equation 2 are given in the figure.

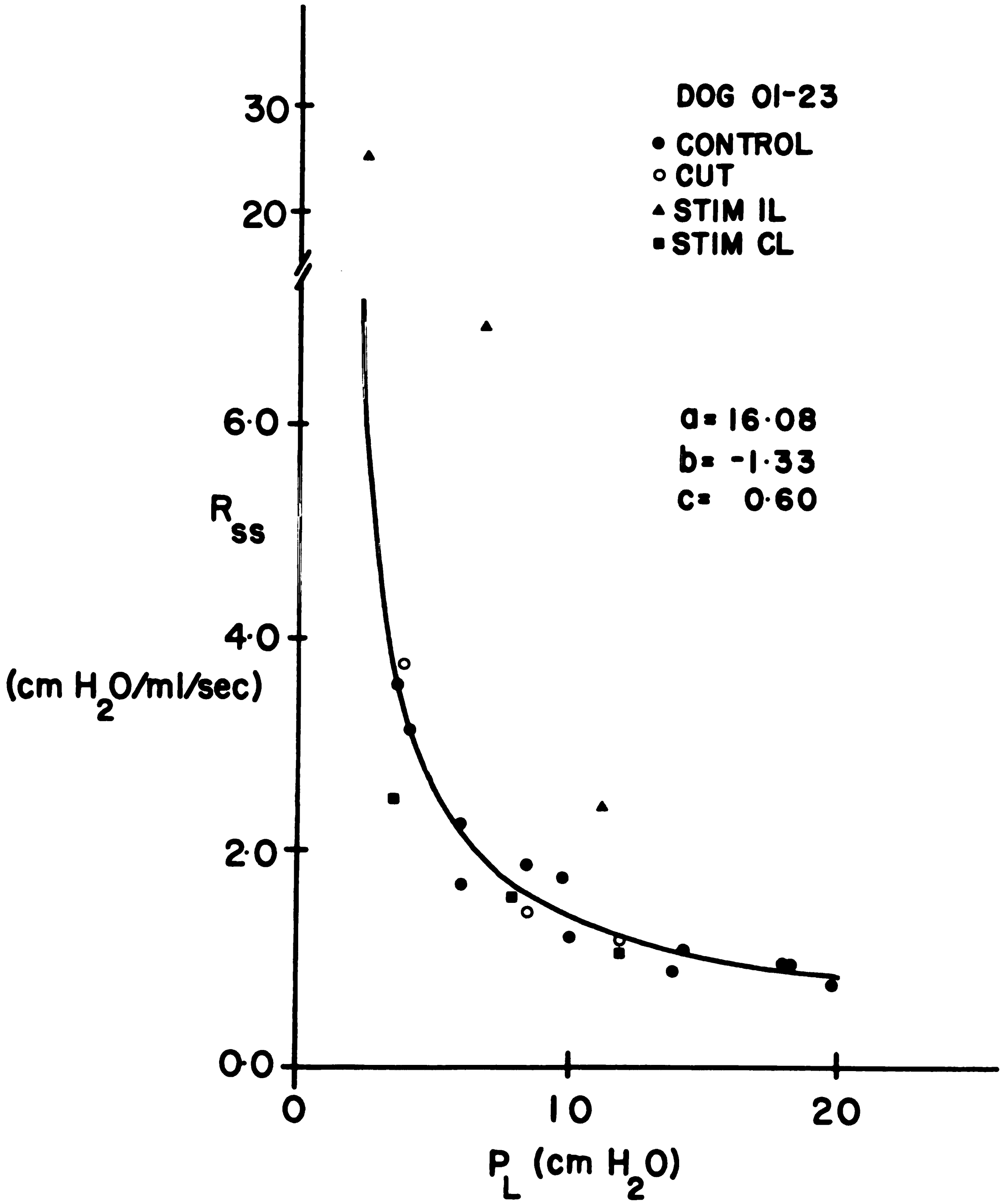
DOG 01-23
● CONTROL
○ CUT
▲ STIM IL
■ STIM CL
a= 16·08
b= -1·33
c= 0·60
30
20
6·0
4·0
2·0
0·0
R_{ss}
(cm H_2O/ml/sec)
0
10
20
P_L (cm H_2O)

Figure 7

Figure 8. Change in steady state resistance from control (ΔR_{ss}) in cm H_2O/ml/sec with the vagi sectioned (cut), during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL) for Group I. Group I consists of three dogs in which no propranolol was used and $\hat{R}_{ss}$ obtained at the same distending pressure using Equation 2.

(mean $\pm$ SEM)

* = significant at $P < .05$

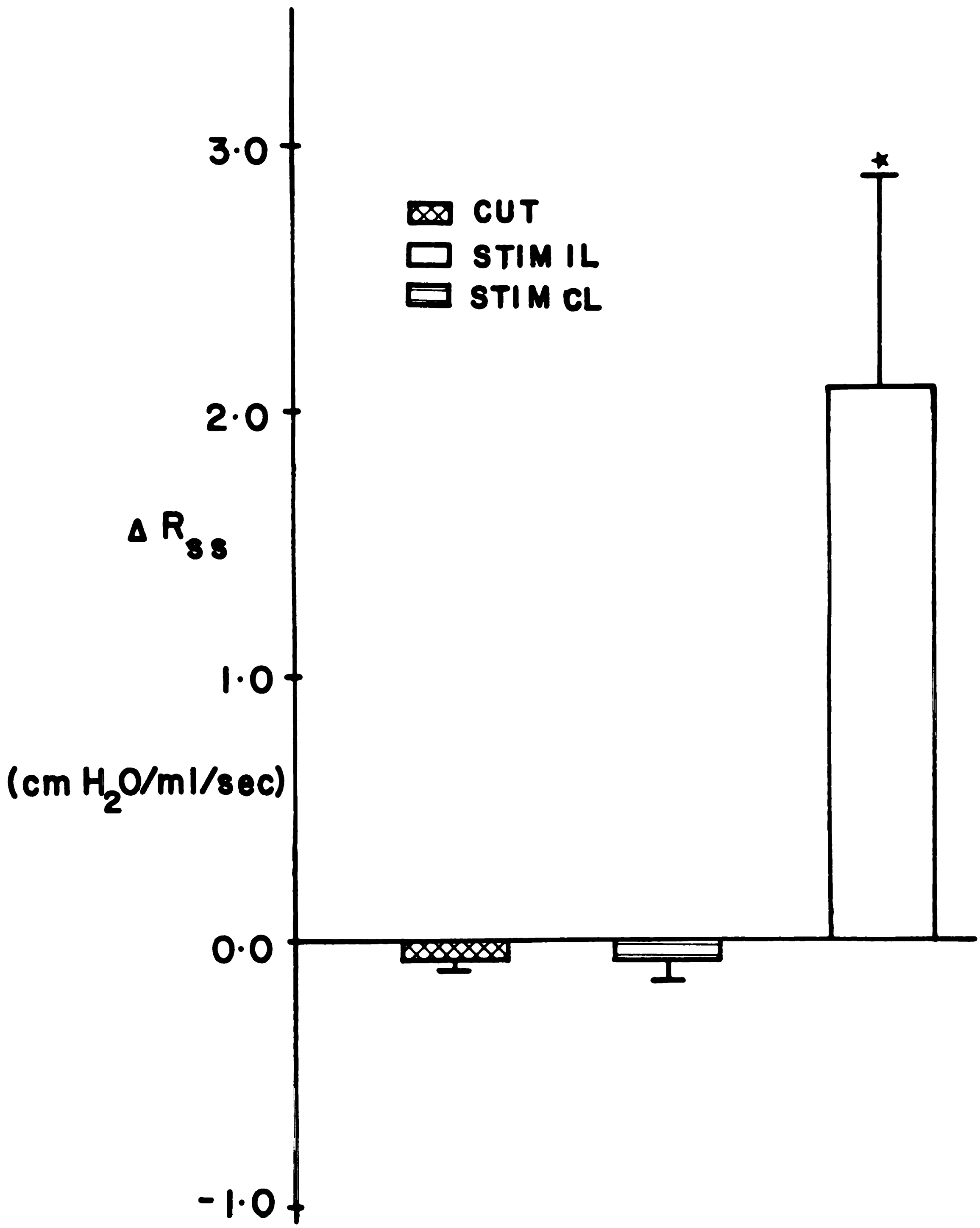

Figure 8

Figure 9. Change in steady state resistance from control (ΔR_{ss}) in cm H_2O/ml/sec with the vagi sectioned (cut, during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL) for Group II. Group II consists of seven dogs in which propranolol was given and $\hat{R}_{ss}$ obtained at the same distending pressure using Equation 2.

(mean $\pm$ SEM)

* = significant at $P < .05$

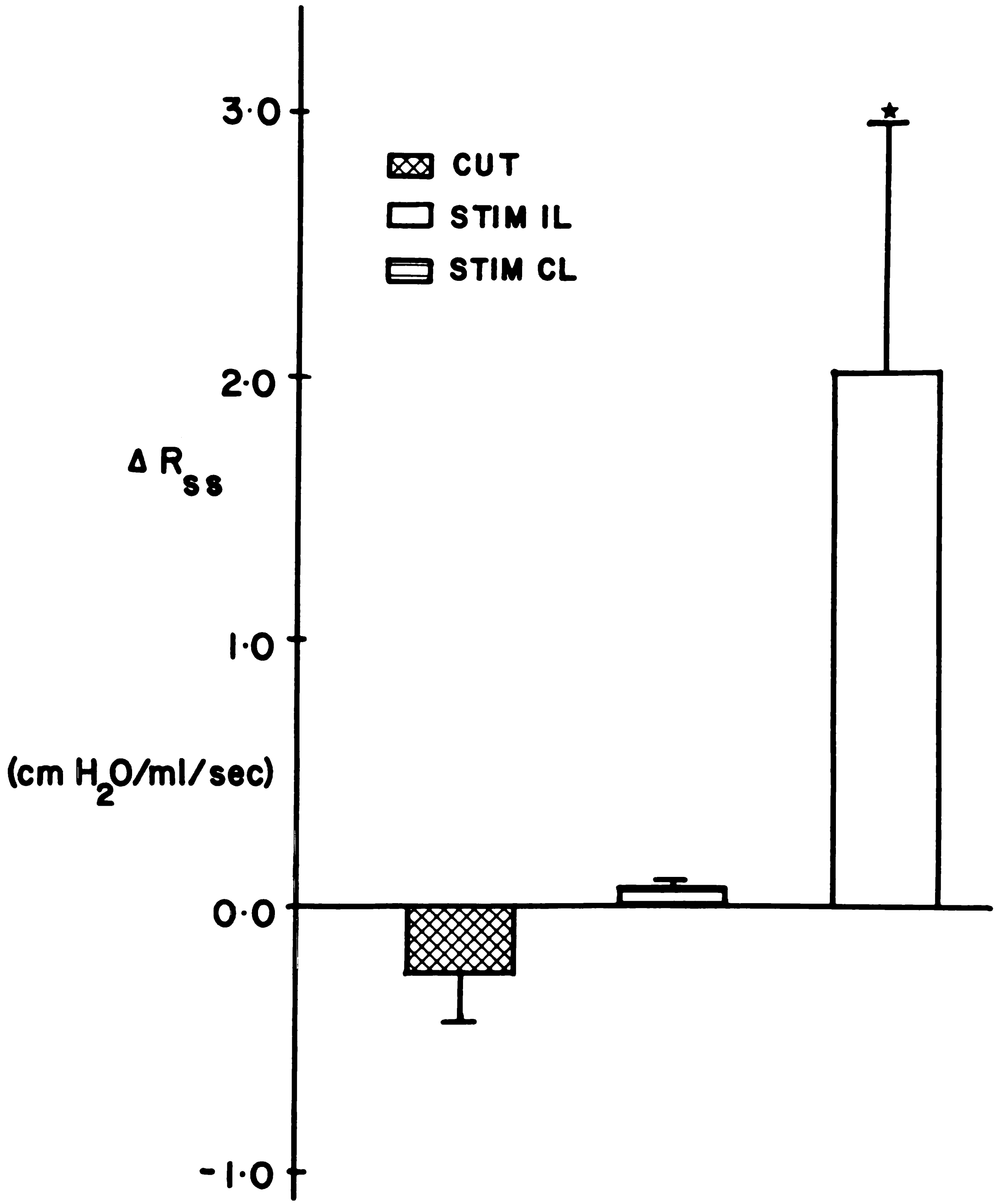

Figure 9

Figure 10. Percent vital capacity (%VC) as a function of transpulmonary pressure (P_L) with the vagi intact (control) sectioned (cut) and during simultaneous stimulation of both vagi (stim). Curves were generated using Equation 6 and averaging the results from 10 dogs. The parameters used are presented in Table 2.

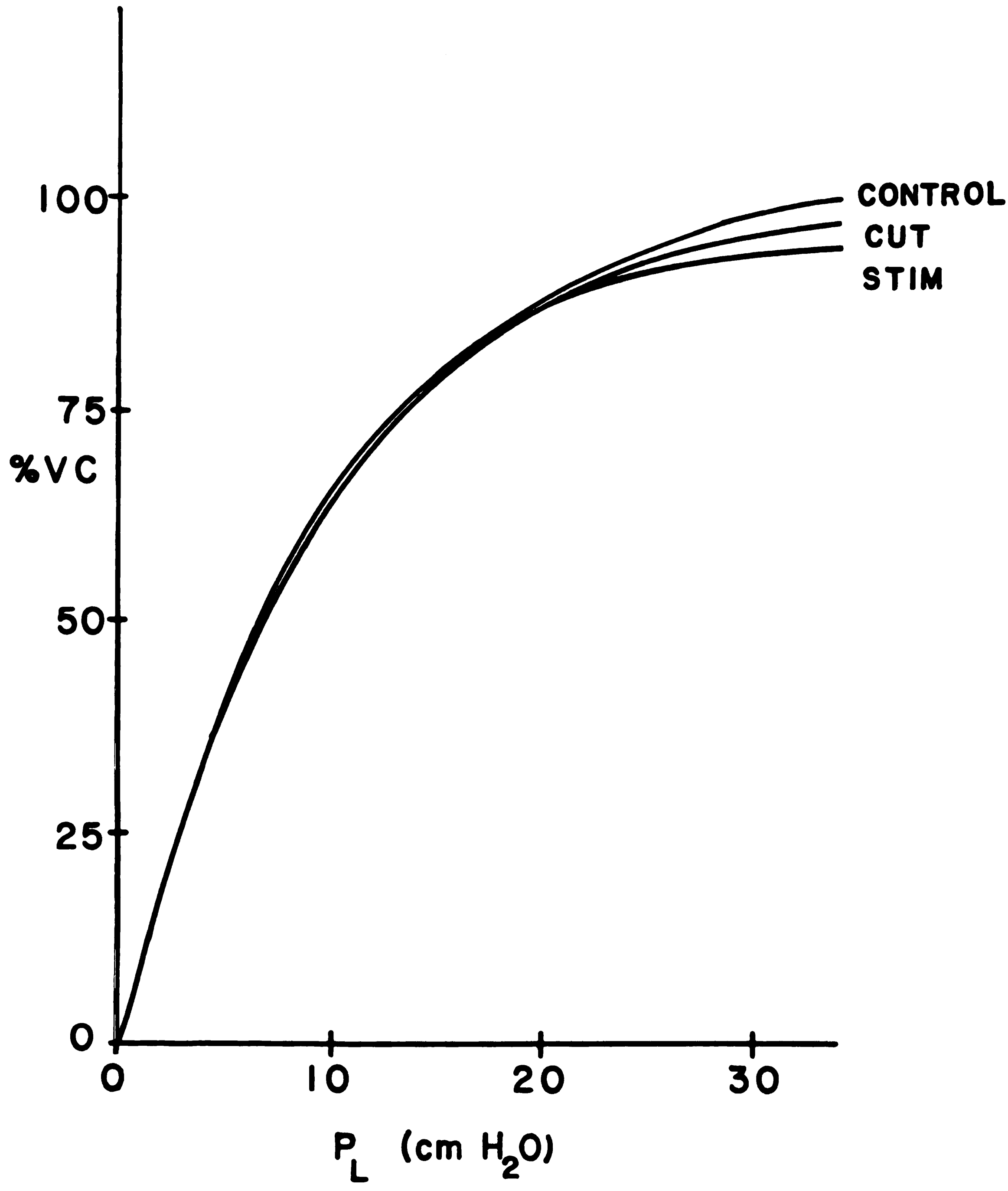

Figure 10

Vagal stimulation significantly decreased $\%V_{max}$ but had no effect on α. The decrease in %VC with vagal stimulation in the region of the P-V curve at which most R_{ss} determinations were made was insignificant when data from 10 dogs were pooled.

To eliminate the possibility that the vagal effects in Groups I and II were due to the shift in the P-V curve toward the pressure axis during vagal stimulation, ΔR_{ss} was normalized to lung volume instead of distending pressure in five dogs. These data comprise Group III and results are presented in Figure 11. As in Groups I and II, ipsilateral vagal stimulation significantly increased ΔR_{ss} as compared to ΔR_{ss} with the vagi sectioned and ΔR_{ss} during contralateral vagal stimulation.

Results from the two compartment model indicate that there is a fast compartment (f) and a slow compartment (s) within the isolated segment. The fast component was undetectable in 33% of the curves resulting in their being best described by Equation 4. In these cases, R_f and TC_f were assumed to be zero. The effect of the vagus nerve on R_f and R_s is presented in Figures 12 and 13. Ipsilateral vagal stimulation significantly increased both R_f and R_s over control values. Sectioning the vagus nerves and stimulating the contralateral vagus nerve had no effect on R_f or R_s.

Time constants for each compartment during experimental treatments were calculated using Equations 4 and 5, and results are presented in Figures 14 and 15. TC_f represents the time constant of the fast compartment and TC_s the time constant of the slow compartment. Due to the large interanimal variance, significant differences in TC_f and TC_s among

Figure 11. Change in steady state resistance from control (ΔR_{SS}) in cm H_2O/ml/sec with the vagi sectioned (cut), during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL) for Group III. Group III consists of five dogs in which propranolol was given and $\hat{R}_{SS}$ obtained at the same lung volume using Equation 3.

(mean $\pm$ SEM)

* = significant at $P < .05$

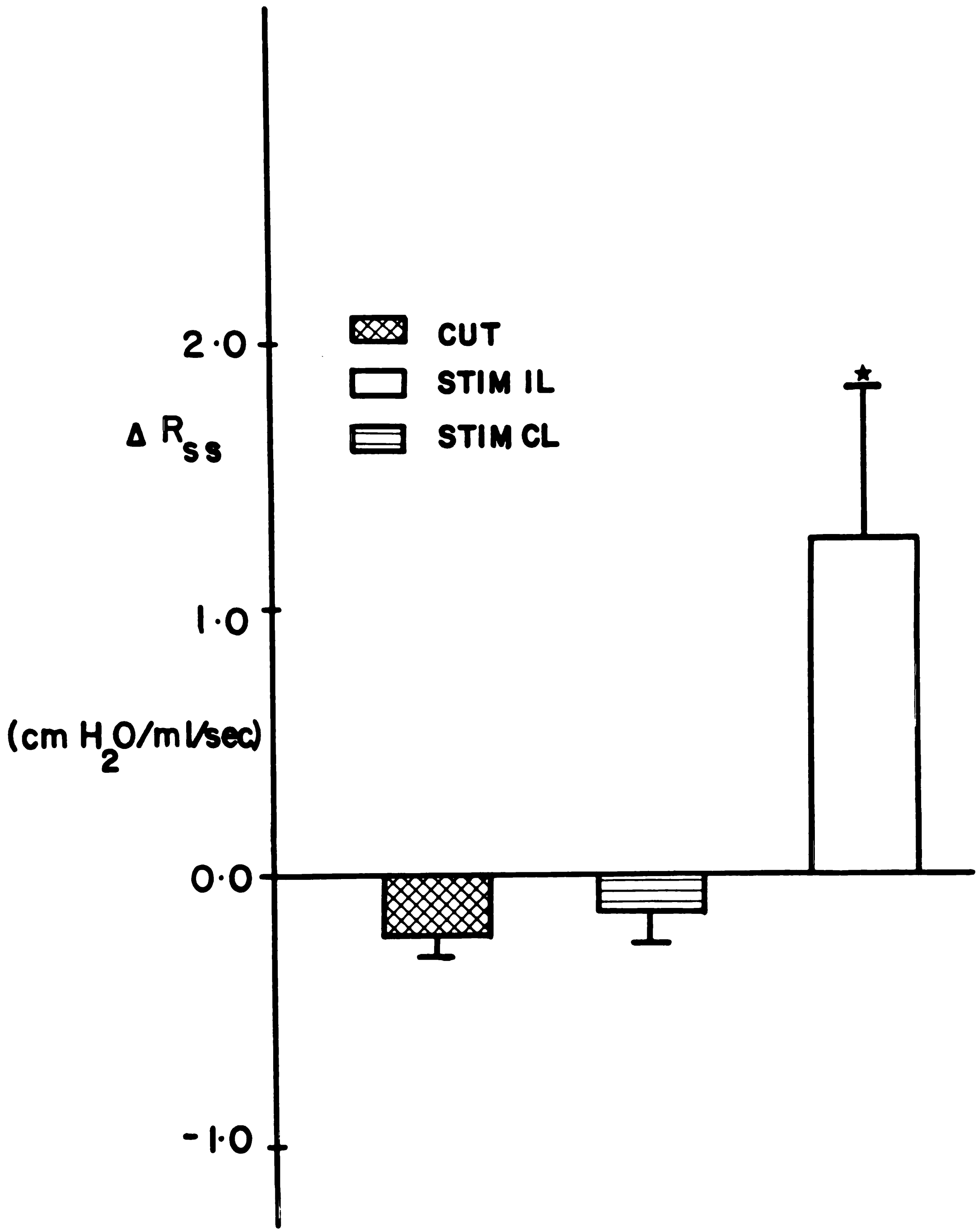

Figure 11

Figure 12. Resistance of the fast compartment (R_f) in cm H_2O/ml/sec with the vagi intact (control), vagi sectioned (cut), during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL). Data are from 10 dogs.

(mean $\pm$ SEM)

* = significant at $P < .05$

Figure 13. Resistance of the slow compartment (R_s) in cm H_2O/ml/sec with the vagi intact (control), vagi sectioned (cut), during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL). Data are from 10 dogs.

mean $\pm$ SEM)

* = significant at $P < .05$

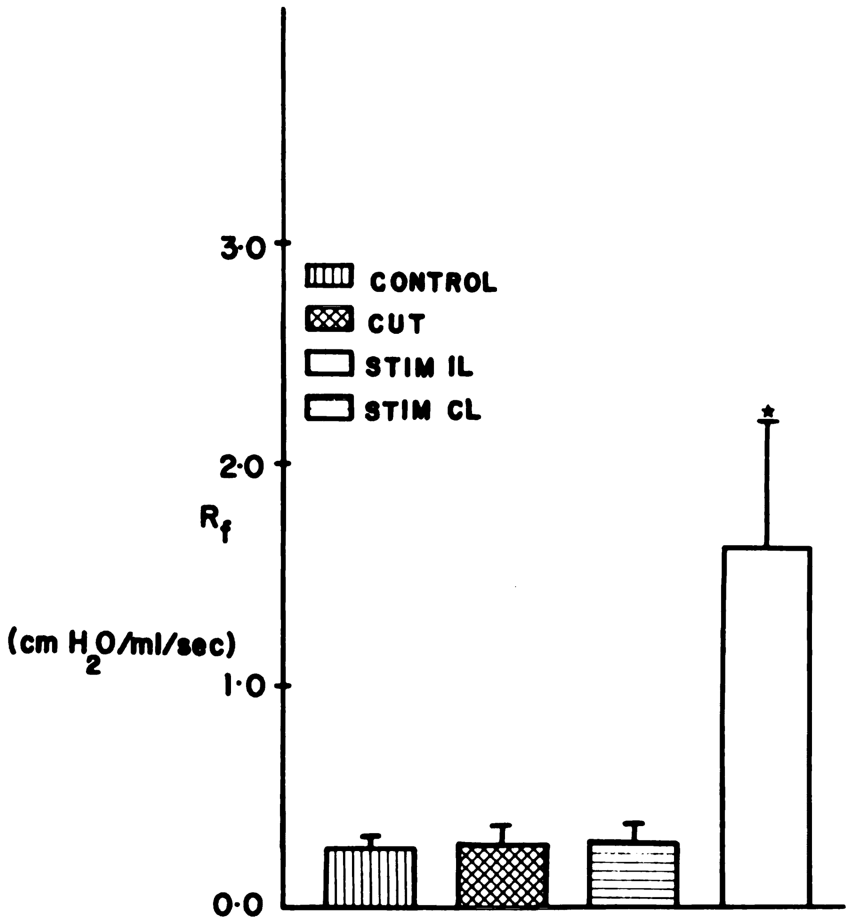

Figure 12

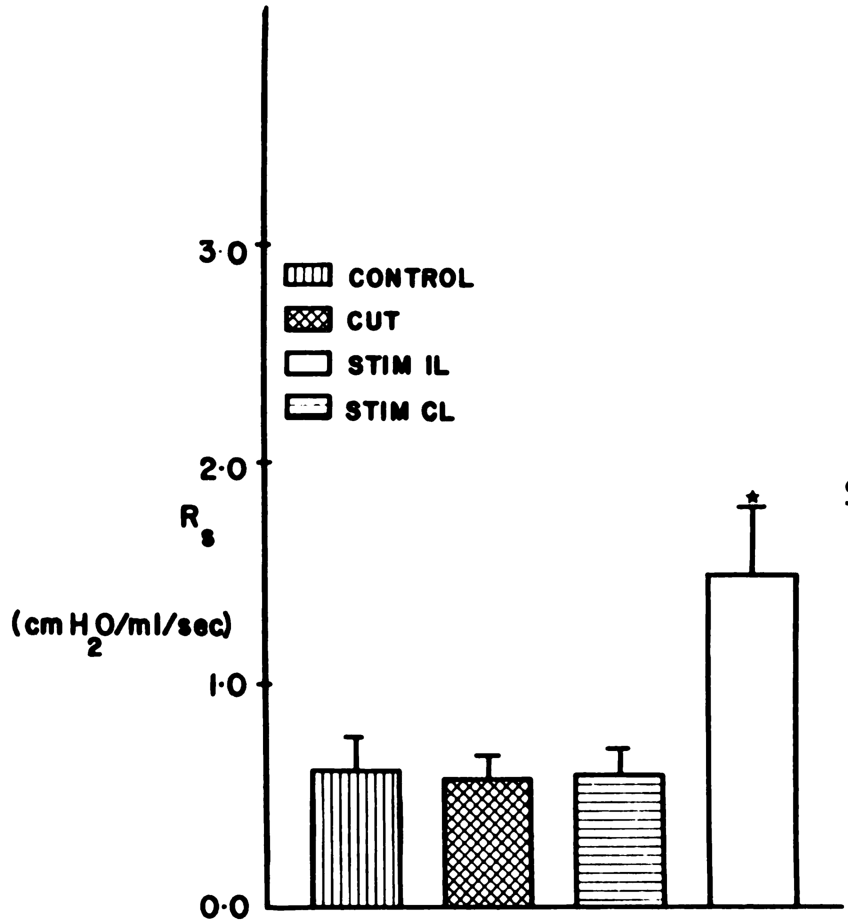

Figure 13

Figure 14. Time constant of the fast compartment (TC_f) in seconds with the vagi intact (control), vagi sectioned (cut), during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL). Data are from 10 dogs.

(mean $\pm$ SEM)

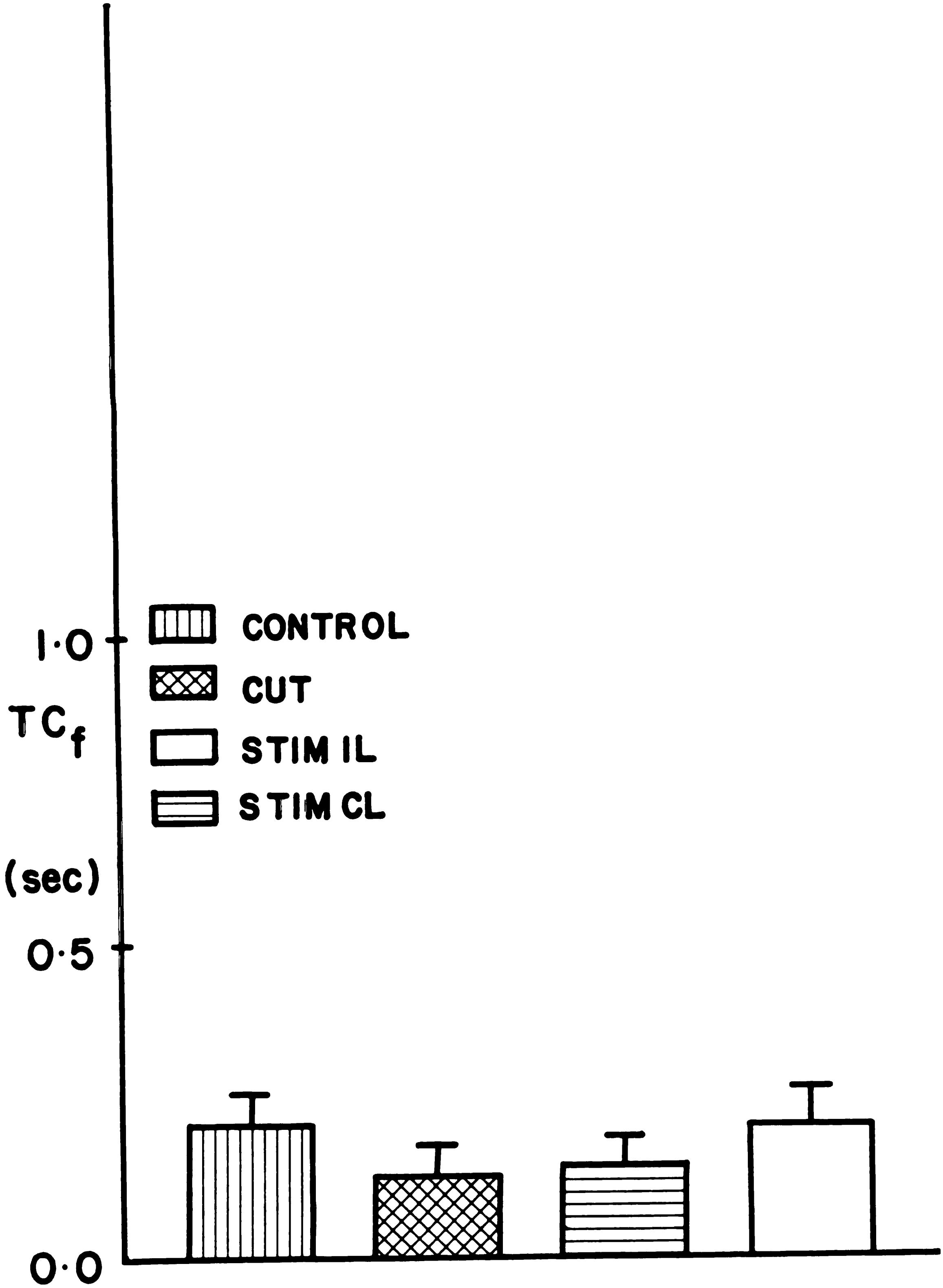

Figure 14

Figure 15. Time constant of the slow compartment (TC_S) in seconds with the vagi intact (control), vagi sectioned (cut), during ipsilateral vagal stimulation (Stim IL), and during contralateral vagal stimulation (Stim CL). Data are from 10 dogs.

(mean $\pm$ SEM)

* = significant at $P < .05$

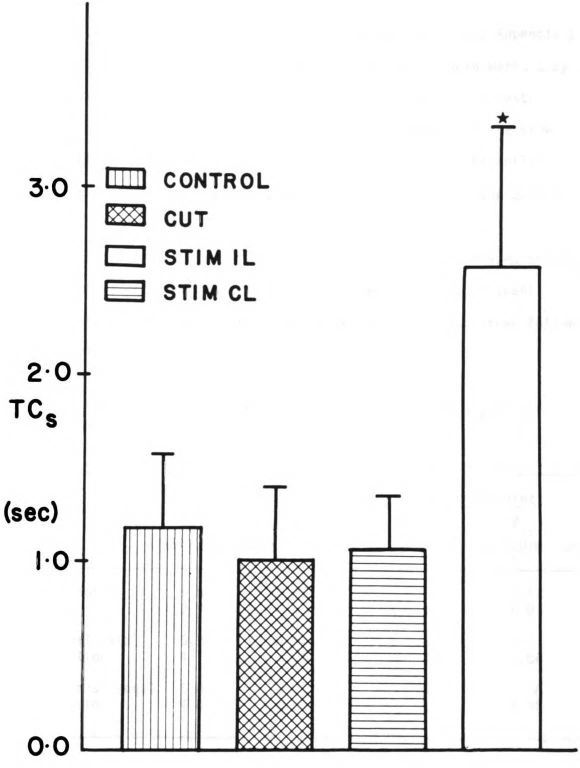

Figure 15

treatment groups were not found using the one-way ANOVA (see Appendix B). Since these results could not be normalized as the R_{ss} data were, they were analyzed using the non-parametric Wilcoxon's Two Sample Test. There was no treatment effect on TC_f. The time constant of the slow compartment during ipsilateral vagal stimulation was significantly greater than control. Sectioning the vagi and stimulating the contralateral vagus nerve had no effect on TC_s.

Results from one dog in which atropine sulfate was infused and R_{ss} determinations repeated are presented in Table 3. The significant increase in R_{ss} with ipsilateral vagal stimulation was abolished following cholinergic blockade with atropine.

Table 3. Steady State Resistance Data from One Dog Before and After Atropine Infusion

	Before Atropine		After Atropine	
	P_L (cm H_2O)	R_{ss} (cm H_2O/ml/sec)	P_L (cm H_2O)	R_{ss} (cm H_2O/ml/sec)
Vagi sectioned	6.6	0.62	6.4	0.57
	3.9	0.97	4.3	0.87
Ipsilateral vagal stimulation	6.2	1.54	6.2	0.61
	4.1	3.76	4.3	0.86
Contralateral vagal stimulation	5.6	0.70	6.0	0.58
	4.4	0.91	4.6	0.89

DISCUSSION

The results of this study indicate that collateral channels in the dog are responsive to vagal stimulation as evidenced by the increase in ΔR_{ss} during ipsilateral stimulation in all experimental groups (Figures 8, 9, and 11). Furthermore, the segment is interdependent with the surrounding lung tissue as indicated by the increase in R_{ss} with decreases in P_L and %VC (Figures 3 and 4).

Using Hilperts method (Hilpert, 1970), Shon and Batra (1978) demonstrated that infusing urecholine, a parasympathomimetic, increased R_{coll} 41% in closed chested dogs. They interpret their results as suggesting that collateral channels possess cholinergic receptors. While an attempt was made to separate the reported R_{coll} into a fast and slow component, the abstract is insufficient to determine the validity of the mathematical method used. While these investigators did not attempt to determine whether the results could be explained on the basis of a decrease in lung volume with cholinergic stimulation, their findings are consistent with results of vagal stimulation reported in the present study.

Using a two series compartment model, it was possible in the present study to identify a fast compartment and a slow compartment within the isolated segment. It is postulated that because the catheter is wedged in a bronchus of at least 5 mm diameter and that collateral pathways in the dog are thought to begin at the level of respiratory bronchioles, which are approximately 0.5 mm diameter, R_{ss} may be divided into an airway and collateral component using the model. The fast compartment may be due to a pressure drop occurring along airways distal to the catheter tip and proximal to the collateral pathways. The effective resistance of these airways is represented by R_f, and their compliance by C_f. The parameters of the slow compartment are believed to represent the mechanical properties of the collateral pathways and surrounding parenchyma. The effective resistance of the collateral pathways, through which gas leaves the segment, is R_s. The effective compliance of the pathways and parenchyma distal to the airways which comprise the fast compartment is C_s. This interpretation is consistent with Menkes and Traystman's (1977) demonstration that the introduction of methacholine, a potent parasympathomimetic, into the isolated segment results in a rapid drop in the pressure at the catheter tip followed by a slower pressure decay when flow is interrupted. These investigators also relate the initial rapid pressure drop to the resistance of airways between the wedged catheter tip and the collateral channels. If a sharp break point is not visually evidenced on the decay trace, however, they approximate the decay as a single exponential. These investigators further report this type of pressure decay trace in patients with emphysema, confirming the observation of Hogg et al. (1969) that airway resistance is greater than collateral resistance in emphysematous lungs.

It is important to recognize that R_s and R_f are effective resistances and therefore depend on the number and arrangement of the airways and collateral channels within the segment. This does not imply that R_f

represents the resistance of any one particular airway or R_s the resistance of one particular collateral channel. The same reasoning applies to the interpretation of C_s and C_f.

Another point to consider when evaluating the model is that a double exponential equation is the solution to many models having different arrangements of resistors and capacitors. Furthermore it was demonstrated that a single compartment model with a variable resistor yields a curve which the non-linear curve fitting routine indicates may be fit well as a double exponential (Appendix C). This suggests that the sensitivity of the fit is not sufficient to distinguish between exponential behavior due to a variable resistor, a simple two series compartment model, or an alternate arrangement of the various components.

The possibility that the observed double exponential behavior may be due to a variable resistance is supported by the bronchographic data of Hahn et al. (1976). There is a 3 cm H_2O pressure gradient between the isolated segment and the remainder of the lobe during the determination of R_{ss}. When flow is stopped, this pressure difference dissipates as gas leaves the segment via collateral pathways resulting in the recorded pressure decay. If the maneuver was performed at P_L = 5 cm H_2O, the pressure in the segment (P_s) would decay from 8-5 cm H_2O when flow was interrupted. Hahn et al. (1976) demonstrated that the diameter of 3-15 mm diameter airways is reduced by approximately 5% between P_L = 8 and P_L = 5 cm H_2O during vagal stimulation. As resistance is a function of cross sectional airway diameter, it would vary as P_S decayed from 8-5 cm H_2O. While this property would not affect the R_{ss} determination, the introduction of a variable resistor would alter the interpretation of the parameters of Equation 5. Because the two compartment fixed resistance model is simple and can be used to explain the observed results, it is a reasonable first approximation.

In a bronchographic examination of peripheral airways, Hahn et al. (1976) report a reduction in airway diameter with vagal stimulation. Data presented in Figures 12 and 13, indicate that R_f and R_s are both increased by ipsilateral vagal stimulation. It is not possible, however, to conclude whether this increase is due to a reduction in the diameter of compartmental pathways or a decrease in their number resulting in a decreased cross sectional area.

The effect of ipsilateral vagal stimulation on the compartmental time constants lends support to the anatomical interpretation of the simple two series compartment model used in this study. Ipsilateral vagal stimulation did not increase TC_f (Figure 14) although R_f was increased (Figure 12). As TC_f is the product of R_f and C_f, a concomitant decrease in airway compliance must have occurred. This observation is consistent with the report of Olsen et al. (1967) that adding acetylcholine to the solution bathing isolated tracheae and bronchi reduces their volume and their specific compliance.

In contrast, TC_s was increased by ipsilateral vagal stimulation (Figure 15). It is reasonable to assume that the effect of ipsilateral vagal stimulation on C_s would be the same as the effect of vagal stimulation on the compliance of the lungs as parenchymal elasticity and surface tension are the primary determinants of static compliance.

Results presented in Table 2 reveal that the index of compliance (α) is not altered by vagal stimulation. As these data represent static P-V curves, alpha is determined only by the elastic recoil of the lungs and not by their flow resistance. Computing a mean C_s from the average TC's and R's presented in Figures 13 and 15, also indicates no change in C_s with ipsilateral vagal stimulation. The increase in R_s with no change in C_s results in an increase in TC_s with ipsilateral vagal stimulation. This increase in TC_s confirms Woolcock and Macklem's (1971) observation in one dog that the increase in the collateral time constant with vagal stimulation was due to a large increase in resistance and such smaller decrease in compliance.

The effect of vagal stimulation on vascular parameters was considered when evaluating the results of the present study. Stimulating the vagus nerves separately or simultaneously always resulted in cardiac arrest and a rapid fall in mean arterial blood pressure. Presumably the vascular effects during contralateral vagal stimulation are the same as during ipsilateral stimulation as catheter placement was arbitrary. Since contralateral stimulation had no significant effect on ΔR_{ss}, R_f, R_s, TC_s, or TC_f, it is inferred that the effect of ipsilateral vagal stimulation on these variables is due to the specific action of the vagus on airways and collateral channels within the segment and not to vascular effects.

Stimulation of the contralateral vagus nerve had no effect on any of the variables studied. This finding confirms the report of Olsen et al. (1965) that in the dog and cat, the right vagus nerve provides the predominant parasympathetic innervation to the right lung and the left vagus to the left lung. They report some crossover of vagal fibers, however, the effectiveness of these fibers in increasing airway resistance was minimal.

Statistical analysis of the parameters describing the deflation limb of the P-V curves reveals that the maximum volume that can be added to the lung over residual volume as a percentage of vital capacity (%VC) is decreased by vagal stimulation while the compliance index (α) is unchanged. Results of the SNK analysis on $\%V_{max}$ indicate that no significant difference is demonstrable between $\%V_{max}$ with the vagi severed and $\%V_{max}$ with the vagi intact or during vagal stimulation. Figure 10 shows that $\%V_{max}$ apparently decreases after vagal sectioning although the data are inadequate to demonstrate that the decrease is statistically significant. It is difficult to understand how sectioning the nerves and stimulating the nerves could each result in a reduction in $\%V_{max}$. These results are consistent with the report of Hahn et al. (1976) that sectioning the vagus nerves has no effect on lung volume.

Because for any P_L, lung volume is reduced during vagal stimulation, results from Groups I and II must be interpreted with caution. The diameter of airways within the parenchyma is determined by surface forces and the transmission of distending pressure through the parenchyma. The parenchyma has been postulated to stabilize the airways in guy-wire fashion (Mead et al., 1970). It is therefore possible that although ΔR_{ss} was calculated at the same distending pressure in Groups I and II, the significant increase in ΔR_{ss} during ipsilateral vagal stimulation is merely the result of tension/relaxation adjustments within the parenchyma with vagal stimulation, resulting in significant reductions in the cross sectional area of segmental airways and collateral channels.

To assess the contribution of shifts in the locus of measurements along the P-V curve on ΔR_{ss} in Groups I and II, data presented in the report of Hahn et al. (1976) were used. On the portion of the P-V curve where most R_{ss} determinations were made, the reduction in %VC with vagal stimulation is approximately 4%. Appendix D presents a calculation demonstrating that 60% and 30% respectively of the increase in ΔR_{ss} with ipsilateral vagal stimulation in Groups I and II may be due to lung volume reduction with vagal stimulation. For this reason ΔR_{ss} was normalized to %VC for five dogs to eliminate this lung volume effect. As in Groups I and II, the only significant increase in ΔR_{ss} was during ipsilateral vagal stimulation when ΔR_{ss} was calculated at the same lung volume rather than the same distending pressure (Figure 11).

The difference between $\%V_{max}$ in the control state (vagi intact) and during stimulation of the peripheral ends of both vagi is 7.5% (Table 2). This agrees with the results of Hahn et al. (1976) who report a mean decrease in lung volume of 5% as determined plethysmographically. Woolcock et al. (1969B) report a mean decrease in %VC of 12% (range 5-17%) with vagal stimulation and 23% (range 5-47%) with vagal stimulation following propranolol, as determined from P-V curves. The larger decrease reported by Woolcock et al. (1969B) may be due to the fact that the reduction in %VC was calculated for each animal and the results averaged. In the present report and in the report of

Hahn et al. (1976), the data were combined and a mean decrease in %VC calculated.

Results obtained following atropine infusion in one animal indicate that parasympathetic blockade eliminates the effect of the ipsilateral vagus on R_{ss} (Table 3) supports the suggestion that the increase in R_{ss} is due to stimulation of cholinergic receptors in the segment. As the vagus nerve in the dog contains sympathetic fibers, the effect of vagal stimulation could have been masked by sympathetically mediated dilation of pathways within the segment in the event that beta adrenergic blockade with propranolol was not complete. The fact that at P_L = 6.2 cm H_2O TC_s was 0.47 sec in the control state, 1.11 sec during ipsilateral vagal stimulation and 0.33 sec during ipsilateral vagal stimulation following atropine suggests that collateral channels are directly responsive to vagal stimulation as the reduction in lung volume at P_L = 6 cm H_2O with vagal stimulation is minimal (Figure 10) and compliance is not altered (Table 2).

Thirty-one percent of the control pressure decay curves, 48% of the curves with the vagi sectioned, 50% of the curves during contralateral stimulation and 13% of the curves during ipsilateral stimulation were best described as single exponentials (Equation 4). This could be the results of two factors, the sensitivity of the curve fitting procedure, or interanimal variation. It was assumed that when the segment is best modelled as a single compartment (Equation 4), it is because the fast compartment is unable to be detected due to the resolution errors inherent in the graphic determination of curve points, the arrangement or number of airways present in the segment, or the distribution of cholinergic receptors within the segment. The high percentage of curves described by the two compartment model with ipsilateral vagal stimulation (Equation 5) supports this assumption as R_f is increased with ipsilateral vagal stimulation (Figure 12). Further evidence in support of this assumption is provided by results obtained in the dog in which data were collected before and after atropine infusion. Unlike curves obtained during ipsilateral stimulation prior to atropine infusion, which were best described as double exponentials, decay curves during ipsilateral vagal stimulation after parasympathetic blockade were best described as single exponentials indicating that the airways no longer contributed significantly to the segment resistance, or had the same time constant. This idea is supported by clinical findings in which atropine has been shown to mitigate antigen induced bronchoconstriction in asthmatic patients (Fish et al., 1977).

In summary, this investigation demonstrates that collateral channels like peripheral airways are responsive to vagal stimulation. This implies that collateral channels possess smooth muscle which is responsive to cholinergic input. While Pores of Kohn and Martin's channels are postulated to be the functional collateral pathways in the dog, only Martin's channels have been demonstrated to possess smooth muscle (Martin, 1966). It is not possible to determine if the Pores of Kohn are involved on the basis of these results. A more complete anatomical description of collateral channels is necessary before any further conclusions may be drawn regarding which structure represents collateral pathways in the dog.

A remaining question, which cannot be answered at this point, is the physiological significance of vagal innervation of collateral channels in the dog. What is critical to the animal is not merely the alteration in the resistance or compliance of the lung components, but how well perfusion is adjusted to the resulting change in ventilation. The matching of ventilation and perfusion ($\dot{V}/\dot{Q}$) by alterations in airway and vascular resistance determines the effectiveness of the lung as a gas exchanging system. While tonic vagal control of the pathways in the lung may be important in balancing dead space,and resistance and compliance of airways during tidal breathing, vagally mediated airway constriction is an important response to inhaled irritants and a debilitating reflex response in pathological states such as asthma or allergic diseases.

In a study using radiolabelled microspheres to measure regional blood flow, inert gases to measure $\dot{V}/\dot{Q}$ and a mass spectrometer to measure P_{O_2} and P_{CO_2}, Metcalf et al. (1978) demonstrated that the dog is able to reduce blood flow to an obstructed collaterally ventilating segment of lobe thereby preventing an increase in shunt blood fraction. When the whole lobe or entire left lung is obstructed, perfusion is not able to be decreased sufficiently to prevent an increase in shunt blood fraction. It would be interesting and informative to repeat this experiment in a species such as the cow or pig in which the lungs are very lobulated and determine whether the pulmonary vasculature is more efficient in regulating perfusion as collateral ventilation does not occur across the complete interlobular septa.

Flenley et al. (1972) compared the effect of bronchial obstruction with beads on $\dot{V}/\dot{Q}$ of the collaterally ventilating space, the difference in alveolar and arterial P_{O_2}, and percent shunt blood fraction in dogs and miniature pigs. No change in $\dot{V}/\dot{Q}$ in the lobe was found in either species following obstruction, while the pig showed a significant increase in shunt fraction. Their findings do not eliminate the possibility that porcine pulmonary vasculature is more responsive to alveolar hypoxia. It is possible that without a hyper-responsive pulmonary vasculature, the shunt fraction would have been much greater. A CO_2 computation method was used to evaluate $\dot{V}/\dot{Q}$ in the study of Flenley et al. (1972). This method yields only a mean $\dot{V}/\dot{Q}$ for the lobe in contrast to the inert gas technique which indicates a distribution of $\dot{V}/\dot{Q}$'s in addition to a mean value. Therefore, the negative findings regarding $\dot{V}/\dot{Q}$ alterations may be due to the CO_2 technique. If the pulmonary vasculature of the pig is more responsive to alveolar hypoxia or if the lack of collateral channels permits alveolar P_{O_2} to drop to levels which would stimulate hypoxic vasoconstruction, $\dot{V}/\dot{Q}$ should be maintained to prevent significant shunting, while the distribution of $\dot{V}/\dot{Q}$ in the lobe will be altered. Further studies are indicated to determine the effect of chronic lung obstruction in various species and the role that collateral ventilation plays in conjunction with vascular reactivity.

One final point to consider is that perhaps it is not the presence of collateral channels which is critical in these different species but rather the extent to which the lung is lobulated. Collateral channels may actually be no more than the normal arrangement of peripheral airways.

This idea is supported by Woolcock and Macklem's (1971) observation that collateral ventilation seemed to occur within a lobule but not across lobules in pig lungs. The observations that collateral pathways respond to changes in lung volume, vagal stimulation and P_{CO_2} as airways do suggests that either the techniques used are measuring changes in peripheral airways, or that collateral channels are peripheral airways. The answering of this question provides opportunities for study in the future.

SUMMARY AND CONCLUSIONS

The results of this investigation indicate that:

1) Steady state resistance (R_{ss}) of pathways within an isolated segment of dog lung is increased with vagal stimulation.

2) R_{ss} increases as lung volume decreases.

3) In the dog, the right vagus nerve has its predominant effect on the right lung and the left vagus nerve on the left lung.

4) The isolated segment of dog lobe may be modelled as two series compartments permitting the separation of R_{ss} into an airway and collateral component.

5) Vagal stimulation increases the resistance of airways within the isolated segment.

6) Vagal stimulation increases the resistance of collateral channels within the isolated segment.

7) Vagal stimulation has no effect on the compliance of the isolated segment.

8) Vagal stimulation decreases the compliance of airways within the isolated segment.

9) Part of the increase in the change in steady state resistance (ΔR_{ss}) from control with vagal stimulation may be due to a reduction in lung volume when ΔR_{ss} is normalized to transpulmonary pressure (P_L).

(10) Vagal stimulation causes a reduction in the maximum volume of air that can be added to the lungs over residual volume.

(11) Vagal stimulation does not alter the compliance of the lungs.

LIST OF REFERENCES

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Alley, R. D. and G. E. Lindskog. Pharmacologic factors influencing collateral respiration; possible relation to the etiology of pulmonary complication. Ann. Surg. 128:497-508, 1948.

Baarsma, P. R., M. N. J. Dirkin and E. Huizinga. Collateral ventilation in man. J. Thorac. Surg. 17:252-263, 1948.

Baker, W. Kirkes Handbook of Physiology. P. Blakiston, Son & Co., Philadelphia, Pa., 1893.

Batra, G., R. Traystman, H. Rudnick and H. Menkes. Collateral ventilation-effect of atropine and dibenzylene on responses to CO_2. Fed. Proc. 34:387, 1975A.

Batra, G., R. Traystman, H. Rudnick and H. A. Menkes. Collateral ventilation: effect of position on response to hypoxia and CO_2. Physiologist 18:132, 1975B.

Bevington, P. Data reduction and error analysis for the physical sciences. McGraw-Hill, New York, 1969.

Brown, R., A. J. Woolcock, N. J. Vincent and P. T. Macklem. Physiological effects of experimental airway obstruction with beads. J. Appl. Physiol. 27:328-335, 1969.

Chen, C., W. C. Sealy, and A. Seaber. The dynamic nature of collateral ventilation. J. Thorac. Cardiovasc. Surg. 59:518-529, 1970.

Fish, J. E., R. R. Rosenthal, W. R. Summer, H. Menkes, P. S. Norman and S. Permutt. The effect of atropine on acute antigen-mediated airway constriction in subjects with allergic asthma. Am. Rev. Resp. Dis. 115:371-379, 1977.

Flenley, D. C., J. Picken, L. Welchel, F. Ruff, P. M. Corry and P. T. Macklem. Blood gas transfer after small airway obstruction in the dog and minipig. Resp. Physiol. 15:39-51, 1972.

Hahn, H. L., P. D. Graf and J. A. Nadel. Effect of vagal tone on airway diameters and on lung volume in anesthetized dogs. J. Appl. Physiol. 41:581-589, 1976.

Henderson, R., K. Horsfield and G. Cumming. Intersegmental collateral ventilation in the human lung. Resp. Physiol. 6:128-134, 1968/1969.

Hilpert, P. Collaterale ventilation, Habilitationsschrift, University of Tuebingen, West Germany, 1970.

Hogg, J. C., P. T. Macklem and W. M. Thurlbeck. The resistance of collateral channels in excised human lungs. J. Clin. Invest. 48:421-431, 1969.

Hoppin, F. G., M. Green and M. S. Morgan. Relationship of central peripheral airway resistance to lung volume in dogs. J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 44:728-737, 1978.

Johnson, R. and G. Lindskog. Further studies on factors influencing collateral ventilation. J. Thorac. Cardiovasc. Surg. 62:321-329, 1971.

Lambert, M. N. Accessory bronchiole-alveolar communications. J. Pathol. Bacteriol. 70:311-314, 1955.

Macklem, P. T. Airway obstruction and collateral ventilation. Phys. Rev. 51:368-436, 1971.

Macklem, P. T. and J. Mead. Resistance of central and peripheral airways measured by a retrograde catheter. J. Appl. Physiol. 22:395-401, 1967.

Mead, J., T. Takishima and D. Leith. Stress distribution in lungs, a model of pulmonary elasticity. J. Appl. Physiol. 28:596-608, 1970.

Martin, J. B. The effect of aging on the alveolar Pores of Kohn in the dog. Am. Rev. Resp. Dis. 88:773-778, 1963.

Martin, H. B. Respiratory bronchioles as the pathway for collateral ventilation. J. Appl. Physiol. 21:1443-1447, 1966.

Menkes, J. A. and R. J. Traystman. State of the art: Collateral ventilation. Am. Rev. Resp. Dis. 116:287-309, 1977.

Menkes, J. H., R. J. Traystman, P. B. Terry, G. K. Batra, B. R. Pitt and J. T. O'Neill. The effects of changes in pulmonary vascular pressure and flow on collateral resistance. Fed. Proc. 35:395, 1976.

Metcalf, J. F., P. D. Wagner and J. B. West. Effect of local bronchial obstruction on gas exchange in the dog. Am. Rev. Resp. Dis. 1117:85-95, 1978.

Olsen, C. R., A. E. Stevens and M. B. McIlroy. Rigidity of tracheae and bronchi during muscular constriction. J. Appl. Physiol. 23:27-34, 1967.

Olsen, C. R., H. J. H. Colebatch, P. E. Mebel, J. A. Nadel and N. C. Staub. Motor control of pulmonary airways studied by nerve stimulation. J. Appl. Physiol. 20:202-208, 1965.

Ploy-Song-Sang, Y., R. P. Corbin and L. A. Engel. Effects of intravenous histamine on lung mechanics in man after beta-blockade. J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 44:690-695, 1978.

Raskin, S. P. and P. G. Herman. Interacinar pathways in the human lung. Am. Rev. Resp. Dis. 111:489-495, 1975.

Robinson, N. E. and P. R. Sorenson. Collateral flow resistance and time constants in dog and horse lungs. J. Appl. Physiol. Respirat. Environ. Exercise Physiol. 44:63-68, 1978.

Rohlf, F. J. and R. R. Sokal. Statistical Tables. W. H. Freeman and Co., San Francisco, Calif., 1969.

Salazar, E. and J. H. Knowles. An analysis of pressure-volume characteristics of the lungs. J. Appl. Physiol. 19:97-104, 1964.

Sealy, W. C. and A. Seaber. The action of carbon dioxide on the collateral pathways of pulmonary ventilation. J. Thorac. Cardiovasc. Surg. 69:533-538, 1975.

Shon, B. and G. K. Batra. Effects of urecholine on the mechanics of collateral ventilation. Fed. Proc. 37:871, 1978.

Sokal, R. R. and F. J. Rohlf. Biometry. W. J. Freeman and Co., San Francisco, Calif., 1969.

Traystman, R. J., G. K. Batra and H. A. Menkes. Local regulation of collateral ventilation by oxygen and carbon dioxide. J. Appl. Physiol. 40:819-823, 1976.

Van Allen, C. M., G. E. Lindskog and H. G. Richter. Gaseous interchange between adjacent lung lobules. Yale J. Biol. Med. 2:297-300, 1930.

Van Allen, C. M., G. E. Lindskog and H. G. Richter. Collateral respiration. Transfer of air collaterally between pulmonary lobules. J. Clin. Invest. 10:559-590, 1931.

Widdicombe, J. G. Regulation of tracheobronchial smooth muscle. Physiol. Rev. 43:1-37, 1963.

Woolcock, A. J. and P. T. Macklem. Mechanical factors influencing collateral ventilation in human, dog and pig lungs. J. Appl. Physiol. 30:99-115, 1971.

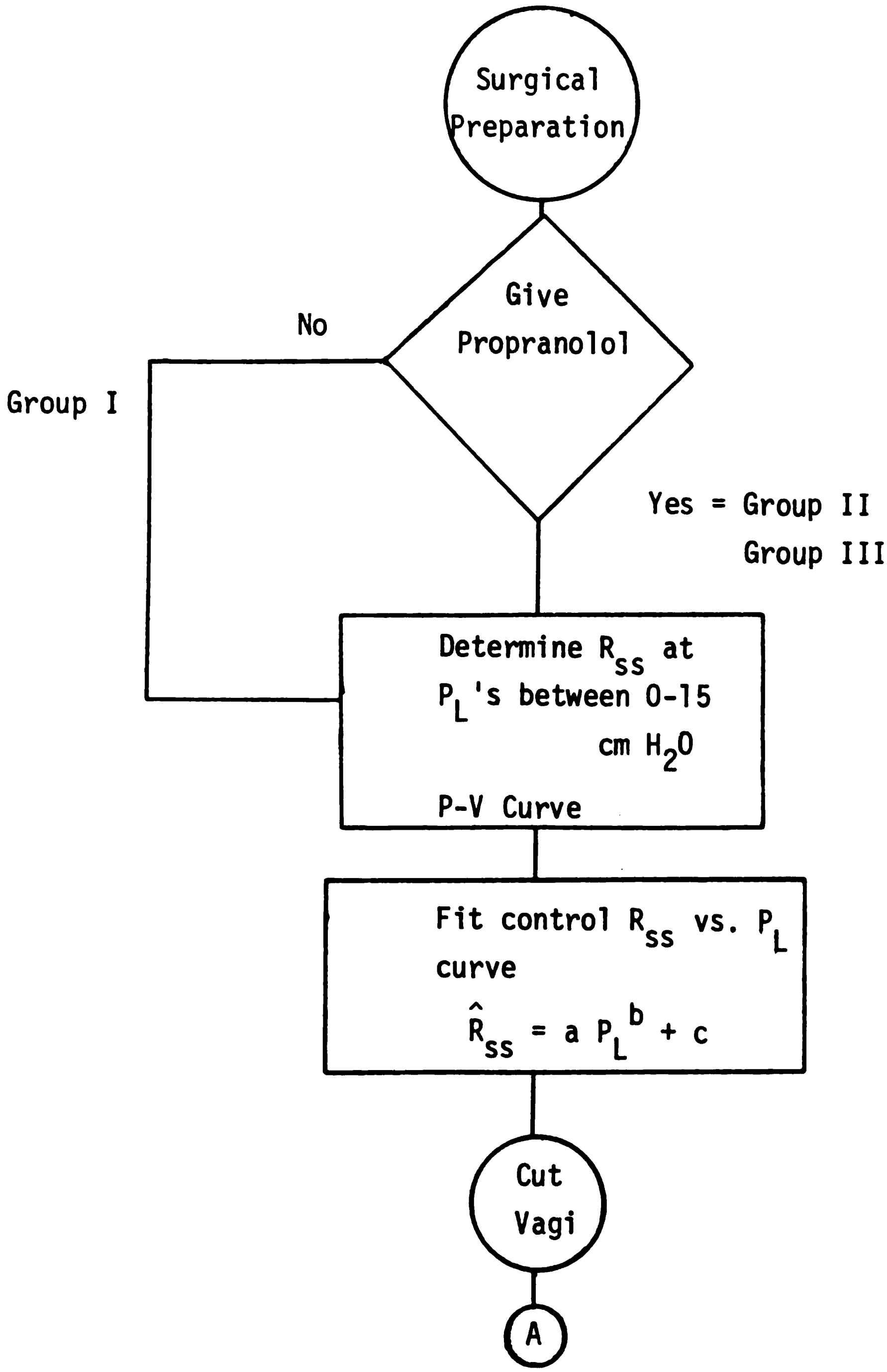
Woolcock, A. J., P. T. Macklem, J. C. Hogg, N. J. Wilson, J. A. Nadel, N. R. Frank and J. Brain. Effect of vagal stimulation on central and peripheral airways in dogs. J. Appl. Physiol. 26:806-813, 1969A.

Woolcock, A. J., P. T. Macklem, J. C. Hogg and N. J. Wilson. Influence of autonomic nervous system on airway resistance and elastic recoil. J. Appl. Physiol. 26:814-818, 1969B.

APPENDICES

APPENDIX A

FLOW DIAGRAM OF EXPERIMENTAL PROTOCOL



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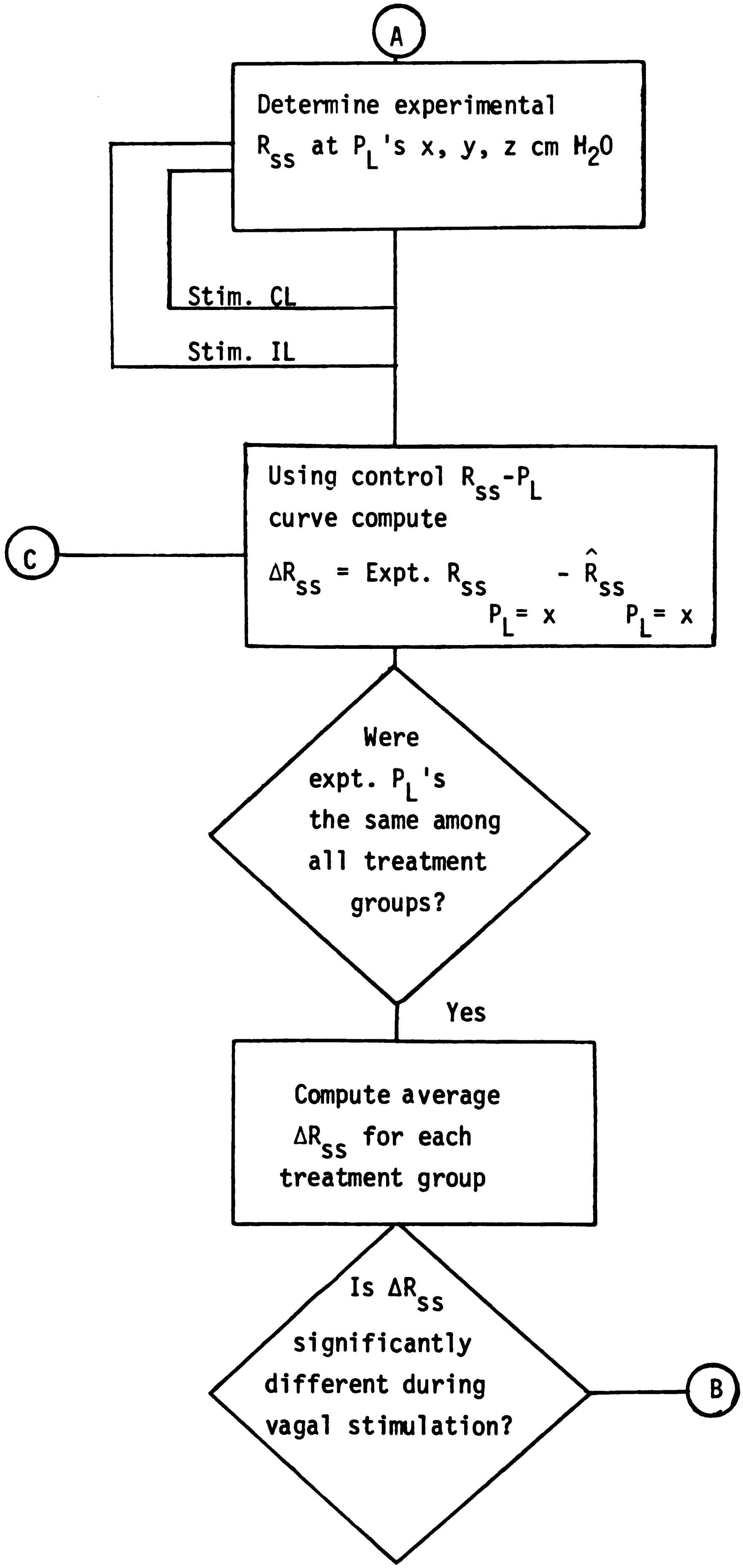
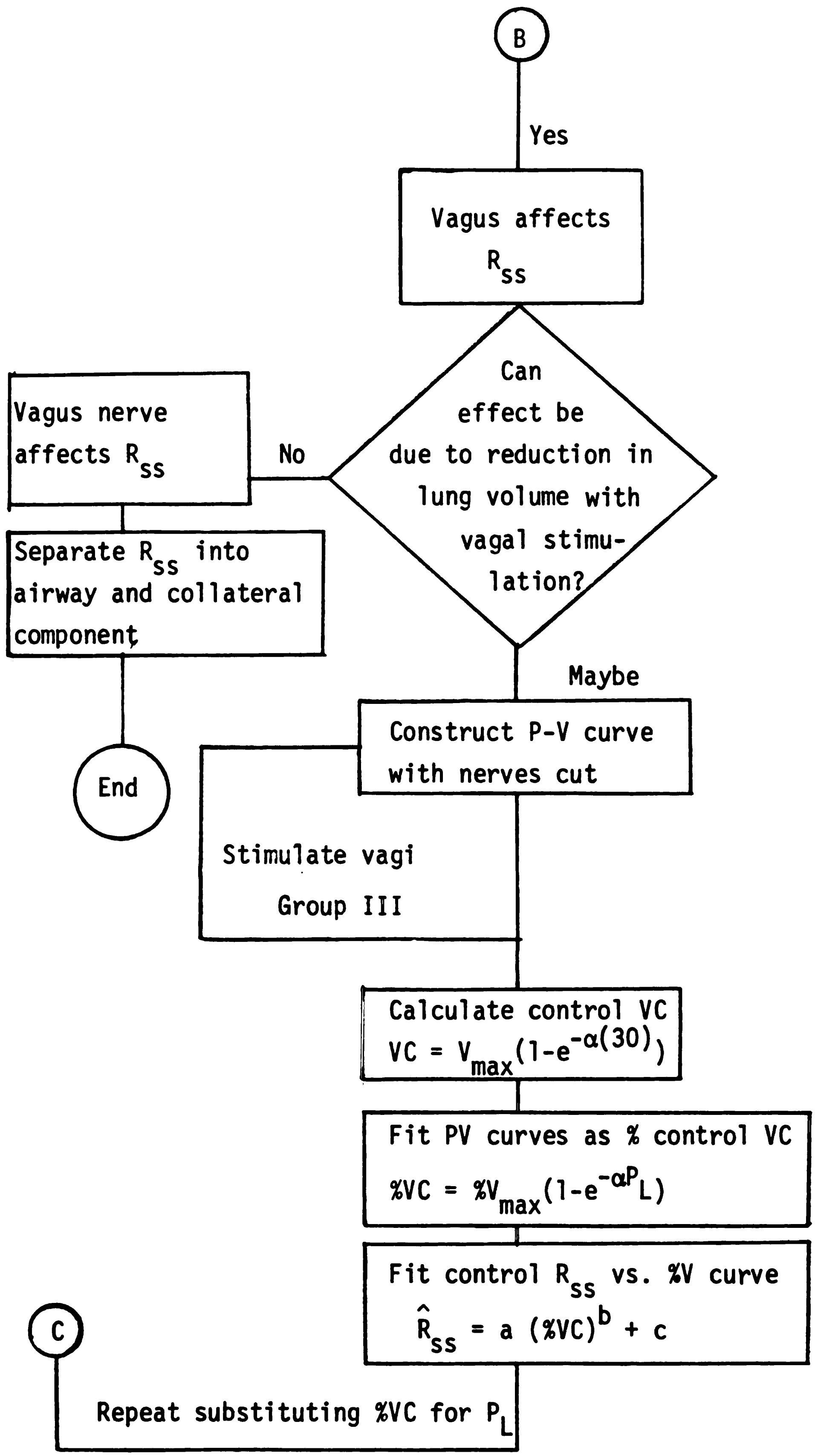

A
Determine experimental R_{ss} at P_L's x, y, z cm H_2O
Stim. CL
Stim. IL
Using control R_{ss}-P_L curve compute
ΔR_{ss} = Expt. R_{ss} $_{P_L = x}$ - $\hat{R}_{ss}$ $_{P_L = x}$
C
Were expt. P_L's the same among all treatment groups?
Yes
Compute average ΔR_{ss} for each treatment group
Is ΔR_{ss} significantly different during vagal stimulation?
B

continued


B
Yes
Vagus affects R_{ss}
Can effect be due to reduction in lung volume with vagal stimulation?
No
Vagus nerve affects R_{ss}
Separate R_{ss} into airway and collateral component
End
Maybe
Construct P-V curve with nerves cut
Stimulate vagi
Group III
Calculate control VC
$VC = V_{max}(1-e^{-\alpha(30)})$
Fit PV curves as % control VC
$\%VC = \%V_{max}(1-e^{-\alpha P_L})$
Fit control R_{ss} vs. %V curve
$\hat{R}_{ss} = a\ (\%VC)^b + c$
C
Repeat substituting %VC for P_L

APPENDIX B

ANOVA TABLES AND RESULTS OF WILCOXON'S TWO SAMPLE TEST ON TC DATA

Source of Variation	df	SS	MS	F
<u>Group I - 3 Dogs</u>				
ΔR_{ss}	2	0.80	0.40	5.71*
Error	44	3.24	0.07	
Total	46	4.04		
P_L	2	7.42	3.71	0.38
Error	44	424.2	9.64	
Total	46	431.7		
<u>Group II - 7 Dogs</u>				
ΔR_{ss}	2	1.68	0.84	7.64*
Error	98	10.32	0.11	
Total	100	12.0		
P_L	2	0.0461	0.023	0.0032
Error	98	714.06	7.29	
Total	100	714.1		
<u>Group III - 5 Dogs</u>				
ΔR_{ss}	2	0.54	0.27	6.75*
Error	70	2.83	0.04	
Total	72	3.37		
%VC	2	83.8	41.9	0.17
Error	70	16987.8	242.68	
Total	72	17071.6		

* = significant at $P < .05$

continued

ANOVA Tables--continued

Source of Variation	df	SS	MS	F
Groups I and II Combined - 10 Dogs				
R_s	3	13.38	4.46	5.79*
Error	85	65.04	0.77	
Total	88	78.42		
R_f	3	31.0	10.33	7.38*
Error	86	120.13	1.40	
Total	89	151.13		
TC_f	3	0.12	0.04	0.67
Error	85	5.01	0.06	
Total	88	5.13		
TC_s	3	36.72	12.24	2.31
Error	85	450.05	5.29	
Total	88	485.77		
5 Dogs from Group II plus 5 Additional Dogs				
α	2	.0014	.00068	1.65
Block (Dogs)	9	.0048	.00053	1.28
Error	18	.0075	.00042	
Total	29	.014		
$\%V_{max}$	2	300.7	150.3	5.33*
Block (Dogs)	9	549.1	61.0	2.16
Error	18	508.0	28.2	
Total	29	1357.8		

* = significant at $P < .05$

continued

Results of Wilcoxon's Two Sample Test on TC Data

Group I + Group II (10 dogs)

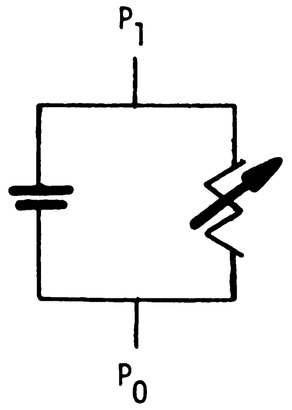
	t'_{TC_s}	t'_{TC_f}
Vagi intact vs. vagi sectioned	0.033	0.942
Vagi intact vs. contralateral vagal stimulation	0.182	0.810
Vagi intact vs. ipsilateral vagal stimulation	2.47*	0.352

t' compared to $t_{.05, \infty}$

* = significant at $P < .05$

APPENDIX C

SINGLE COMPARTMENT VARIABLE RESISTOR MODEL



$$i_{in} = C\frac{d(P_1-P_0)}{dt} + \frac{P_1-P_2}{R}$$

let $R = f(P)$

i.e. $R \alpha 1/P(t)$

$\therefore R = K/P(t)$

when $i_{in} = 0$

$$\frac{dp}{dt} = -\frac{P}{RC}$$

$$\int 1/P \; dP = \int -\frac{1}{RC} dt$$

$$P(t) = P_{(o)} e^{-(1/RC)t}$$

but $R = k/R(t)$

$$\therefore \frac{dP}{dt} = -K \frac{P^2_{(t)}}{C}$$

by Euler Integration

$$\frac{\Delta P}{\Delta t} = \frac{-K}{C} P^2(t) = \frac{P(t+\Delta t) - P(t)}{\Delta t}$$

$$P(t+\Delta t) = P(t) - \left[\frac{K}{C} P^2(t)\right]\Delta t$$

let $\Delta t = 0.05$ sec, $R = 1$, $C = 0.47$ ml/cm H_2O

and by an iterative procedure generate Table 4.

APPENDIX C - continued

Table 4. Hypothetical Data Generated Using a Single Compartment Variable Resistor Model

$P_{(t)}$ (cm H_2O)	(t) (sec)
3.14	0.00
2.09	0.05
1.62	0.10
1.35	0.15
1.16	0.20
1.02	0.25
0.91	0.30
0.82	0.35

Using the nonlinear least squares curve fitting routine performed by digital computer, the above data may be fit as a declining double exponential with a residual variance of 0.65×10^{-6}(cm H_2O)^2.

APPENDIX D

ESTIMATION OF $\%\Delta R_{ss}$ WITH IPSILATERAL VAGAL STIMULATION DUE TO A DECREASE IN LUNG VOLUME AT THE SAME P_L

In the region of the P-V curve in which most R_{ss} determinations were made, %VC decreases by 4% with vagal stimulation (Hahn et al., 1976). On the steepest portion of the P-V curve a 4% decrease in %VC represents a change in P_L of 2 cm H_2O. Upon examining Figure 3 it will be noted that a decrease in P_L of 2 cm H_2O on the steepest portion of the curve (i.e., between $P_L = 4$ and $P_L = 2$ cm H_2O) is equivalent to an increase in R_{ss} of 0.024 cm H_2O/ml/sec. Performing this calculation for all dogs in Groups I and II reveals a mean increase in R_{ss} when P_L is decreased from 4 cm H_2O to 2 cm H_2O of 0.583 cm H_2O/ml/sec and 1.26 cm H_2O/ml/sec respectively.

As mean ΔR_{ss} with ipsilateral vagal stimulation is 2.08 cm H_2O/ml/sec in Group II and 2.01 cm H_2O/ml/sec in Group I (Figures 8 and 9), 60% and 30% of this increase in ΔR_{ss} may be due to a decrease in lung volume with vagal stimulation rather than a direct cholinergic effect on pathways within the segment.