THE EFFECT OF PULMONARY VENOUS PRESSURE ON COLLATERAL VENTILATION IN DOGS

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ABSTRACT

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Steady state collateral resistance (Rcoll), residual volume (RV) and lung compliance (C) was measured in an isolated perfused dog lung (IPL) perfused with blood from a donor dog. A double lumen catheter was inserted through the mainstem bronchus and wedged in a peripheral airway, isolating a segment of lung. Rcoll was calculated as:

$$Rcoll = \frac{P_S - P_L}{\dot{V}coll}$$

where P_S is pressure at the catheter tip as measured by the inner lumen, P_L is lung inflation pressure and $\dot{V}coll$ is the flow of 95% O_2 and 5% CO_2 (95/5), room air (21/0) or 100% O_2 (100/0) through the outer lumen and into the isolated segment. When compared to 21/0, 95/5 decreased Rcoll while Rcoll with 100/0 was not consistently different. Elevating pulmonary venous pressure when both the lung and segment were ventilated with 95/5 decreased Rcoll, increased RV, did not affect C at 50% total lung capacity (TLC) and decreased C at 90% TLC.

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LIST OF ABBREVIATIONS

ESGV	Exhaled segmental gas volume
FRC	Functional residual capacity
VC	Vital capacity
RV	Residual volume
TLC	Total lung capacity
P_{aCO_2}	Arterial CO_2 tension
P_{ACO_2}	Alveolar CO_2 tension
P_{aO_2}	Arterial O_2 tension
P_{AO_2}	Alveolar O_2 tension
IPL	Isolated perfused lung
Ppv	Pulmonary venous pressure
Ppa	Pulmonary arterial pressure
P_{syst}	Systemic arterial pressure
PEEP	Positive end expiratory pressure
Rcoll	Steady state collateral resistance
P_S	Pressure in an isolated lung segment measured at the tip of the wedged catheter
P_L	Lung inflation pressure measured at the mainstem bronchus
$\dot{V}coll$	Flow of gas through the wedged catheter and into the isolated segment
95/5	95% O_2 and 5% O_2
21/0	room air
100/0	100% O_2

LIST OF ABBREVIATIONS--continued

C_L	Lung compliance between forty and fifty percent vital capacity
C_H	Lung compliance between ninety and one hundred percent vital capacity
$\dot{Q}$	Blood perfusion rate of the isolated perfused lung
Rvas	Pulmonary vascular resistance

I. INTRODUCTION AND LITERATURE REVIEW

Prior to 1930 the lung was thought to consist of a series of dichotomously branching airways terminating in alveoli with no anastomoses between adjacent lung lobules. This anatomical arrangement was considered to explain atelectasis produced by bronchial obstruction (61). Beginning in 1930 VanAllen, Lindskog and associates demonstrated anatomic connections between adjacent lung lobules within the same lobe of human, cat, dog and rabbit lungs. Their conclusions were based on three observations: 1) atelectasis occurred following lobar but not lobular obstruction (62), 2) an atelectatic lobe could be reinflated via a cannula wedged in a lobular airway (59, 63, 64, 65, 66) and 3) emphysema could be produced on the lobar but not the lobular scale by allowing gas flow into the lobe on inflation but not out on deflation (60). The findings of these investigators caused rejection of the older theory of the lung as a series of dead-end pathways. Their experiments are the foundation of today's research involving collateral ventilation.

A. Pathways for Collateral Ventilation

1. Pores of Kohn

Pores of Kohn occur in alveolar walls, have a diameter of 2-10 μ and have been described in virtually all mammalian species (32). In early life they are uniformly distributed over the lung. In middle and later life they are present in largest numbers in the borders and apices of the upper and lower lobes (35). Interalveolar pores were described as early as 1847 (1), but their existence in the normal lung was debated for the next 100 years. Miller (1, 41) denied their presence in the normal lung and believed the shedding of alveolar epithelium explained the findings of Kohn (1) who traced fibrin threads through alveolar pores in cases of pneumonia.

Martin (36) suggested that pores might be sites in alveolar walls previously occupied by inactive phagocytes which migrate during disease, leaving a pore. There are three points against this argument: 1) phagocytes may simply be passing through a pore rather than causing its formation. 2) In the manatee the pores are approximately 50 μ in diameter (33), much larger than an alveolar phagocyte which is approximately 10 μ in diameter. 3) Loosli (32) infected monkeys and dogs intratracheally with type I pneomococci and found that lung septa of recovered animals have the same appearance as in non-infected lungs.

Caradonna, according to Loosli (32), obtained two groups of guinea pigs: the first group was kept in a quiet environment while the second group was violently agitated several times per day. Pores appeared in the former group at 14-15 months of age while in the latter group pores appeared at 3-4 months of age and increased in number thereafter. Caradonna concluded that pores are a result of the "excessive effort and dilatation of alveolar walls during the act of respiration."

Because of the regularity of pore shape, Ogawa (44) believed pores are normally found in the lung and are not the result of histological fixation. Loosli (32) further suggests the pores to be avenues through which disease organisms may pass between adjacent lung lobules.

VanAllen, Lindskog and colleagues were the first to demonstrate some type of anatomical connection between adjacent lung lobules. Because the Pores of Kohn were the only pathways of this type known at that time, they were implicated as being the sole route for collateral ventilation. It is likely, however, these investigators were measuring gas flow through other collateral channels more so than through the pores because the resistance of the pores would require much greater driving pressures than those measured to initiate and maintain gas flow. In their early experiments, VanAllen et al. (64) placed a freshly excised lung lobe from a dog in an airtight chamber and

connected the lobar bronchus and the first side branch of this bronchus to the outside with tubes. Air was withdrawn from the chamber just to the point where the lung was uniformly expanded. The tip of one tube was submerged in water while air was run into the other tube. When pressures in the latter reached 1.0 cm H_2O, there was bubbling in the water at the tip of the submerged tube. When the lung was completely deflated, 6.0 cm H_2O was required to initiate air passage and 2.0 cm H_2O to maintain it. It is quite likely in these experiments that the bubbling which occurred at the tip of the submerged tube was from air which passed through other collateral channels and very little, if any, from air passing through the pores. This is suggested by the the following evidence: the proximal tip of the submerged catheter was 0.5 cm beneath the surface of the water (31), so the effective driving pressure needed to maintain the bubbling was really not 1.0 cm H_2O but rather 0.5 cm H_2O: likewise, when the lung was deflated the effective driving pressure would actually be 1.5 cm H_2O. This suggests the pores provide a very minimal resistance to air flow. The following evidence, however, indicates this may not be true: 1) the pores are probably closed at very low lung volumes. This may be the reason why some of the early investigators were not able to find pores in the normal lung since their fixations were performed with the lungs in the collapsed state (28, 35). Also, Kuno and Staub (28) found

that artificial microholes (25 and 51 μ in diameter) produced in cat lungs are closed at zero transpulmonary pressure. 2) Martin (37) calculated the opening pressure of an alveolar pore with a surface tension of 47 dynes/cm to be extremely high. The driving pressures in VanAllen's experiments (64) were much too low to be attributed solely to the Pores of Kohn. Since, according to LaPlace's law ($P = 2ST/r$, where ST is the surface tension and r is the cross-sectional radius of the pore), the calculated opening pressures become much smaller with a larger radius, larger collateral pathways must have been involved.

2. Canals of Lambert (bronchiole-alveolar communications)

In 1953 Lambert (29) and later Duguid and Lambert (14) described occasional interruptions in the walls of terminal and respiratory bronchioles in which the lumen of the bronchiole communicated directly with the surrounding alveoli. These bronchiole-alveolar communications are up to 30 μ in diameter and have been found in cats, rats, humans and sheep (27). They become more prominent in certain pathologic conditions and may not be affected by lung volume (29).

It is difficult from Lambert's original paper to ascertain how frequently these pathways occur. However, she made a tracing of several bronchioles taken from 500 serial sections in human lung and found 32 canals in a 1.0 x 1.5 mm area.

3. Martin's Channels (interbronchiolar respiratory bronchioles)

The third collateral channel was described by Martin (37) in 1966. He excised the left upper lobe from four dog lungs and cannulated the first two bronchial branches. By perfusing polystyrene spheres 60-710 μ in diameter suspended in saline into one of the cannulae and collecting the outflow through the other cannula, it was possible to pass spheres as large as 120 μ in diameter through collateral pathways. Next, he passed India ink aerosol through the catheter system and noted ink deposits on respiratory bronchioles which connected two terminal bronchioles. From these studies he suggested that collateral flow may occur through these respiratory bronchioles.

Martin's results raise the following question: are the channels through which the spheres pass the same connecting channels in which the ink was deposited? The respective sizes of the respiratory bronchioles and the spheres suggest the answer is no. The diameter of the respiratory bronchioles is normally in the range of 470-540 μ (in human lungs fixed at about 75% total lung capacity) (10), so why were spheres no larger than 120 μ found in the outflow of Martin's experiments? Raskin and Herman (48) describe interacinar communications 200 μ in diameter in the human lung fixed at a transpulmonary pressure of 25 cm H_2O. If these lungs were fixed at a somewhat lower transpulmonary

pressure, the diameter of the channels would decrease and may approach the size of the spheres in Martin's outflow.

The distribution of Martin's interbronchiolar respiratory bronchioles throughout the lung is unknown since he only studied upper lobes. But in this region, using serially sectioned lung samples, he traced a collateral channel from a terminal bronchiole in one segment to an adjacent segment and found it 1.56 mm in length. In the 1600 serial sections which he examined, he found twenty-two collateral respiratory bronchioles.

B. Some Factors Affecting Collateral Ventilation

1. Lung Volume and Volume History

The effect of lung volume on collateral flow was first indicated by VanAllen et al. (64) in which a driving pressure of 1.0 cm H_2O was needed to pass air collaterally in slightly inflated lungs whereas a driving pressure of 2.0 cm H_2O was needed in lungs which were collapsed. Lindskog and Bradshaw (31) passed a cannula with a dilatable tip through a tracheostomy of an anesthetized dog and wedged it in a bronchus of a lower lobe. The proximal end of the cannula was attached to one of two openings of a water bottle. The other end of this opening was attached to a tube which opened 0.5 cm beneath the surface of the water. The second opening of the bottle was attached to a delicately

balanced Krogh spirometer. When the dog breathed, gas passed from the surrounding lung through collateral channels and into the isolated segment. During exhalation, the volume of gas exhaled from the segment passed into the Krogh spirometer and was recorded on a kymograph. Exhaled gas from the rest of the lung was collected in a Roth-Benedict spirometer. Measurements were made under three conditions: 1) initial measurements were taken during normal tidal breathing at functional residual capacity (FRC). 2) Lindskog then placed several small weights on top of the Roth-Benedict spirometer which raised FRC and caused the dog to breathe at a higher end-expired lung volume. This increased exhaled segmental gas volume (ESGV). 3) When the dog increased its tidal volume (but maintained a normal FRC) by rebreathing its own expired gas, ESGV again increased. In more recent experiments using slightly different methods, Hogg et al. (20), Woolcock and Macklem (67), Menkes et al. (39), Inners et al. (22) and Robinson and Sorenson (49) have all reported collateral flow resistance to be inversely proportional to lung volume, thus confirming Lindskog's original findings.

An issue on which there is no agreement is the effect of volume history on collateral resistance. Some laboratories report that collateral resistance is greater on inflation than on deflation (20, 49) while others report the converse (67). Hogg et al. (20) isolated a lower lobe

segment in excised human lungs by wedging a catheter in a bronchus beyond the first branch to the superior segment. Polyethylene catheters (3 mm o.d.) were inserted through the pleural surface on either side of the interlobar fissure of the segment. When flow was introduced into the segment, collateral resistance was calculated as:

$$Rcoll = \frac{Palv_{(LL)} - Palv_{(UL)}}{\dot{V}} \qquad (1)$$

where Rcoll is collateral resistance, $Palv_{(LL)}$ is the alveolar pressure in the isolated segment, $Palv_{(UL)}$ is the alveolar pressure in the apical segment of the same lobe and $\dot{V}$ is the flow of gas into the segment. After suspending the lungs in a volume displacement plethysmograph, the cannulated segment was quasistatically inflated to a distending pressure of 30 cm H_2O and deflated to 0 cm H_2O. When flow was plotted against the pressure drop across the collateral channels, Rcoll was greater on inflation than on deflation at the same lung volume. They suggest this is due to the effect of surface tension on collateral channels since tissue forces would be the same during both inflation and deflation.

Robinson and Sorenson (49), using Hilpert's technique (33), inserted a double lumen catheter (2.5 mm o.d.) through the lobar bronchus of a lower lobe of excised dog lungs and wedged it in a peripheral airway, thus isolating a lung

segment. Steady state collateral resistance (Rcoll) was calculated as:

$$Rcoll = \frac{P_S - P_L}{\dot{V}} \qquad (2)$$

where $\dot{V}$ is the flow of air introduced into the outer lumen of the catheter, P_S is the pressure at the catheter tip as measured by the inner lumen and P_L is the lobar inflation pressure. These workers found inflation Rcoll to be significantly greater than deflation Rcoll at equal transpulmonary pressures. Using pressure-volume curves of the lobe, they plotted Rcoll against percent vital capacity of the lobe. At a given lobar volume, inflation Rcoll was less than deflation Rcoll below forty percent total lobe capacity, and no significant difference existed between the two values above forty percent total lobe capacity. The former result is easily explained on the basis that at equal transpulmonary pressures lung hysteresis causes deflation lobar volume to be greater than inflation lobar volume. The collateral channels have a greater diameter at higher volumes and thus have less resistance to flow of gas. The latter finding is difficult to explain. Both Hogg et al. (20) and Robinson and Sorenson (49) calculated lobar volume from pressure-volume curves. Hogg et al. (20), however, obtained their pressure-volume curves at the same time they made their measurements of Rcoll, whereas Robinson and Sorenson (49)

obtained their pressure-volume curves before or after the measurements of Rcoll. Perhaps in the latter case, lobar compliance changed over time so that a transpulmonary pressure of 10 cm H_2O, for example, did not produce the same lobar volume when plotting the pressure-volume curve as it did when making Rcoll measurements.

In contrast with Hogg et al. (20) but in agreement with Robinson and Sorenson (49), Woolcock and Macklem (67) found inflation Rcoll to be less than deflation Rcoll in experiments in which collateral ventilation was studied using two different methods. In the first method a segment of an excised lobe of lung was isolated with a double lumen cathether inserted through the lobar bronchus. One lumen measured pressure at the catheter tip when a small quantity of air was rapidly injected with a syringe through the other lumen. The effective compliance of the segment (C_{eff}) was calculated as the change in volume of the segment divided by the change in the pressure difference (P_c) between the catheter tip and the pleural surface.

The second method involved the same experimental preparation as the first method but only a single lumen catheter was used. After subjecting the lobe to a particular volume history, it was held at a given lung volume and oscillated by applying a quasi-sinusoidally varying pressure to the bronchial or tracheal cannula at frequencies of 0.3, 0.5, 1.0 and 1.5 cycles per second using a loud speaker powered

by a variable frequency sine wave generator. Lung volume (V_l) was plotted against P_c on a storage oscilloscope, and the following calculations were made:

$$\Theta = \tan^{-1} 2\pi fRC \qquad (3)$$

where Θ is the phase angle by which P_c lags V_l and is determined by the time constant (T) for ventilation of the isolated segment. R was assumed to be the resistance through the collateral channels since resistance through larger airways would probably be much smaller in comparison. C is the compliance of the lung (assumed to be equal to the compliance of the isolated segment), and f is the frequency of oscillations. T could be solved for by rearranging the equation:

$$RC = T = \frac{\tan\Theta}{2\pi f} . \qquad (4)$$

In this manner, collateral resistance (Rcoll) could be calculated by dividing T by the effective compliance (determined as described previously):

$$Rcoll = \frac{T}{C_{eff}} . \qquad (5)$$

There are several points of criticism to the methods of Woolcock and Macklem. Concerning their first method: 1) they state that "... volumes of air were rapidly injected until peak pressure registered by the catheter was about 30 cm H_2O and not more than 40 cm H_2O. The quantity of

injected air depended on the position of the catheter. When it was wedged in a small bronchus, less than 0.5 ml was needed to distend the lung distal to the catheter to a P_c of 30 cm H_2O, but when the catheter was wedged in a large bronchus as much as 15 ml was needed." They calculated their segment volumes (based on lobe volume fixed at 30 cm H_2O) to be 14, 34, 60, 140 and 225 ml. In all cases, the volume of air required to produce a peak pressure of 30 cm H_2O was much less than 1/10th the segment volume. It is generally accepted that a static distending pressure of 30 cm H_2O causes a lung inflation to total lung capacity, and yet these investigators reached such a distending pressure in the segment with an injection of air less than 1/10th the segment capacity. Because of this and because the air was injected rapidly, it is possible that most of the pressure recorded after the injection may have been needed to overcome the resistance of small airways distal to the tip of the catheter while only a small portion of the pressure was applied toward overcoming the elastic and surface tension forces in distending the segment. Even if the segment was considered as a closed compartment without collateral channels, placing a volume of gas in the segment equivalent to less than 1/10th its total capacity would cause only a minimal change in pressure. 2) Some of the air injected would leak out through collateral channels resulting in an underestimation of P_c. It is known that Rcoll varies

inversely with lung volume (20, 22, 39, 49, 67). Because their determinations were made at different lung volumes, Rcoll would vary and thus the amount of air leaking out during rapid injection would increase as lung volume increased. This causes a greater experimental error at higher lung volumes; that is, P_c is underestimated to a greater extent at higher lung volumes causing an overestimation of C_{eff} and an underestimation of Rcoll.

Concerning the second method, accurate measurement of the phase angle is possible only when the tracing is a perfect ellipse. Any deviation from this shape would mean arbitrary placement of the axes and a corresponding error. Also, the calculation of Rcoll contains the error introduced by inaccurate measurement of C_{eff}.

2. Pharmacologic Agents

Airways respond to many pharmacologic agents, and generally one would predict collateral channels to respond in qualitatively the same manner since both are surrounded by smooth muscle. Only four drugs have been tested for their effect on collateral ventilation: histamine, acetylcholine, epinephrine and isoproterenol.

a. Histamine

Histamine constricts airways (9, 12, 13, 46). This effect may be size and species dependent since Persson and Eckman (46) have reported that *in vitro* preparations of cat

bronchioles (1 mm) were constricted in a histamine bath (0.08-10.0 μg/ml) but larger airways (> 3 mm) were unaffected, whereas both large and small airways from dog, guinea pig and human constricted in response to histamine.

Lung volume history may also affect the response to histamine. Drazen et al. (13) report that histamine-induced increases in peripheral airway resistance were mostly reversed by an inflation to total lung capacity. Likewise, Colebatch et al. (9) found that all changes in lung compliance and resistance caused by the intravenous administration of histamine to cats were completely reversed by a temporary inflation of the lungs to a transpulmonary pressure of 20 cm H_2O.

Constriction of collateral channels by histamine was first demonstrated by Ally and Lindskog (2) who wedged a cannula with a dilatable tip in a subsegmental bronchus of a lower lobe in anesthetized dogs. As the dog inhaled through a tracheostomy, air which entered the surrounding lung passed through collateral channels and into the isolated segment. During exhalation, a portion of the gas volume passed through the wedged cannula and was recorded with a Krogh spirometer while the remaining gas may have passed back through collateral channels and into the surrounding lung. Histamine given intravenously in doses of 0.02-2.0 mg resulted in a marked diminution or elimination of ESGV. There was a gradual return to the preinjection

rate in a period of minutes. Benadryl, an antihistamine, completely eliminated this effect. In more recent experiments with a similar method, Johnson and Lindskog (25) also noted ESGV is sharply reduced or obliterated in anesthetized dogs given 0.01 mg/kg histamine intravenously.

b. Acetylcholine

Acetylcholine given intravenously (8-800 µg) increases pulmonary resistance and decreases lung compliance in anesthetized cats (9). Isolated airways of cats, dogs, guinea pigs and man all constrict in response to acetylcholine (0.05-10.0 µg/ml media) regardless of their size (46).

Shon and Batra (52) noted an increase in collateral resistance in anesthetized dogs caused by Urecholine. Their results as well as those of Colebatch et al. (9) were reversed by atropine. Chen et al. (8) used a method similar to that of Johnson and Lindskog (25) in anesthetized dogs and found that ESGV completely stopped in response to 0.1 mg/kg mecholyl iv.

c. Epinephrine and Isoproterenol

ESGV increased 66-160 percent of the control level within 2 minutes after iv injection of epinephrine (0.01 mg/kg) in anesthetized dogs (8). In similar experiments, ESGV increased 14.4-64.0 percent in anesthetized dogs given 1.0-13.4 µg/kg isoproterenol iv (25).

3. Alveolar and Blood Gas Tensions

a. Carbon Dioxide

Peters (47) ventilated anesthetized dogs with 5.0, 7.5, 10.0, 15.0, 20.0 and 25.0 percent CO_2 in O_2. Bronchoconstriction occurred with arterial CO_2 tensions (P_{aCO_2}) from 56-84 mm Hg and was reversed when P_{aCO_2} dropped to 38-40 mm Hg. These effects were abolished by either atropine or vagotomy. Green and Widdicombe (19) demonstrated a decrease in dead space, lung compliance, tracheal volume and an increase in lung resistance in anesthetized dogs ventilated with 4% and 8% CO_2. Similar effects, but to a less magnitude, were seen with vagal stimulation. In the latter studies, control end-expired CO_2 tension ranged from 20-30 mm Hg, and administration of 4% CO_2 increased end-expired CO_2 tension to a mean of 42 mm Hg, and 8% CO_2 increased the mean value to 56 mm Hg. Bilateral cervical vagotomy reduced the changes in all parameters. It appears, therefore, that the constricting effect of systemic hypercapnea may be caused by a vagally mediated mechanism, since: 1) elevated P_{aCO_2} is needed for the changes to occur, and 2) the effects are reduced or abolished by vagotomy.

Ingram (21) performed experiments with anesthetized dogs which were tracheotomized and cannulated with a Carlens tracheal divider so that each lung could be ventilated independently. A balloon tip catheter was passed through the femoral vein and into the left pulmonary artery so that

the artery was occluded by baloon inflation. The right lung was used for gas exchange while measurements of lung compliance and resistance were made in the left lung. This experimental design allowed independent variations in both systemic and alveolar gas tensions and a determination of their effects on the airways. Increasing P_{aCO_2} to 70 mm Hg while holding alveolar CO_2 tension (P_{ACO_2}) to 35 mm Hg decreased lung compliance and increased lung resistance. This effect was abolished by vagotomy, thus demonstrating its reflex origin. Increasing P_{ACO_2} to 72 mm Hg while holding P_{aCO_2} to 37 mm Hg had no effect. It may be that the direct dilating effect of CO_2 on the airway was not strong enough to overcome the constricting effect of tonic vagal tone. When, however, P_{ACO_2} was lowered to 2 mm Hg and P_{aCO_2} was kept at 35 mm Hg, compliance decreased and resistance increased. This shows the direct constrictor effect of hypocapnea on the airways. The greatest changes in compliance and resistance were seen when arterial hypercapnea (P_{aCO_2} = 68 mm Hg) was coupled with alveolar hypocapnea (P_{ACO_2} = 2 mm Hg). This response was only attenuated, not abolished, by vagotomy, probably because alveolar hypocapnea caused constriction while the reflex constriction from arterial hypercapnea was removed.

Severinghaus et al. (51) produced unilateral pulmonary artery occlusion in close-chested anesthetized dogs by inserting a balloon tip catheter into either the left or

right pulmonary artery. When either pulmonary artery was occluded by balloon inflation, there was a shift of ventilation away from the unperfused lung due to bronchoconstriction. This effect was prevented by inhalation of 6% CO_2 into that side, but not by atropine or vagotomy. They attribute their results to hypocapnea directly constricting airway smooth muscle.

Daly et al. (11) reported evidence of the possible role of the central chemoreceptors and vagus nerve in the regulation of airway caliber. The brain of anesthetized dogs were perfused with blood containing various mixtures of O_2 and CO_2 while these gas tensions were held to within a normal range in the blood perfusing the rest of the body. Passing anoxic blood through the brain caused bronchoconstriction, and hypocapnic blood caused bronchodilation. These effects were abolished by either atropine or vagotomy.

In denervated lung preparations, CO_2 directly dilates the airways. Nisell (43) found that isolated perfused cat lungs previously constricted with carbaminoylcholine, muscarine or histamine dilated when the lungs were ventilated with 10-14 percent CO_2. This correlated with his studies in which a decrease in the pH of the perfusing blood caused dilation whereas an increase in the pH of the perfusate caused constriction of the airways.

Since collateral channels may be small airways surrounded by smooth muscle, they should be affected by CO_2 in

qualitatively the same manner as small airways. Most studies (8, 25, 50, 57) involve administration of inspired hypercapnic gas mixtures to anesthetized dogs, and the results indicate that CO_2 dilates collateral channels. Chen et al. (8) found that 15% CO_2 caused an increase in ESGV compared to room air or 100% O_2. P_{aCO_2} was usually in the range of 35-43 mm Hg, considerably lower than that needed to induce reflex bronchoconstriction. Johnson and Lindskog (25) noted varying increases in ESGV from 31-198 percent caused by adding 5% CO_2 to the inspired gas. In this case, control arterial pH was approximately 7.54 and decreased to 7.50 with 5% CO_2. Sealy and Seaber (50) varied inspired CO_2 concentrations from 2.5-15 percent and noted that the peak increase in ESGV occurred with 6% CO_2. No further increase was seen with 15% CO_2, perhaps because the smooth muscle of the airways and collateral channels was maximally dilated. In excised lungs, 15% CO_2 increased ESGV by as much as 150%. Traystman et al. (57), using Hilpert's method (33), isolated a segment of lung by wedging a double lumen catheter in a peripheral airway of an anesthetized dog. The dog was ventilated with room air with a tidal volume adjusted to give an end-expired CO_2 concentration of 4%. Collateral resistance was calculated as:

$$Rcoll = \frac{P_S}{\dot{V}} \qquad (6)$$

where Rcoll is collateral resistance, P_S is pressure at the catheter tip measured by the inner lumen and $\dot{V}$ is the flow of air, 5% CO_2 or 10% CO_2 into the segment through the outer lumen. When air flowing through the segment was replaced by 5% CO_2, Rcoll fell by 46%. When CO_2 concentration was increased from 5% to 10%, Rcoll fell an additional 9%. These studies indicate that CO_2 may act directly on smooth muscle to produce a decrease in collateral resistance.

b. Oxygen

Nisell (43) reports that previously constricted airways of isolated perfused cat lungs dilate when ventilated with pure nitrogen and constrict when exposed to 100% O_2. Pulmonary vessels respond in the reverse manner. Since a hypoxic condition would cause bronchodilation and pulmonary vascular constriction (while the opposite would be true for a hyperoxic condition), he suggests O_2 plays a major role in the regulation of ventilation and perfusion of the lung. In agreement with Nisell are the results of Severinghaus et al. (51) who reported that unilateral bronchoconstriction caused by occlusion of the pulmonary artery to the same lung was prevented by the inhalation of 100% nitrogen into that lung.

Nisell did not consider, however, the reflex effect of altered arterial O_2 tension on the lung. Green and Widdicombe (19) reported that 10% O_2 in N_2 decreased dead space, lung compliance and tracheal volume, and increased

total lung resistance in anesthetized dogs. Small changes occurred with 100% O_2 generally in the opposite direction. They report that hypoxia increases tracheobronchial smooth muscle tone by a reflex effect from the carotid body chemoreceptor. Also, Nadel and Widdicombe (42) report that inhalation of 10-15 percent O_2 in N_2 resulted in constriction of both upper and lower airways which was prevented by tying the glossopharyngeal nerves or cooling the vagus. This demonstrates the reflex effect of arterial hypoxemia (causing constriction) was stronger than the local effect of airway hypoxia (causing dilation).

In regards to collateral channels, Traystman et al. (57) reported that collateral resistance rose 37% when air ventilating an isolated segment was replaced by 5% O_2 in N_2. However, 5% O_2 and 5% CO_2 in N_2 caused a slight reduction in Rcoll, suggesting that CO_2 had the dominant effect. Arterial blood gases were not measured, so it is not known if central or peripheral chemoreceptors were activated.

4. Pulmonary Vessels and Vascular Pressures

Recent anatomical studies (4, 16, 24) indicate that capillaries and other small vessels are directly attached to the terminal airways and can influence airway behavior. Kapanci et al. (26) and Assimacopolous et al. (4) using rats, lambs, humans and monkeys found interstitial cells and fibers which are possibly attached to the capillary and

alveolar basement membranes as well as being found in the pillars of alveolar capillaries (53). In the human lung, Gehr et al. (16) have shown that capillaries are embedded in a network of connective tissue fibers intercalated between endothelium and epithelium. They have also found that in the thin portion of the alveolar septum the endothelial and epithelial basement membranes are fused. These studies indicate that the terminal airways and the vessels which surround them are connected to each other and therefore are interdependent with each other. Thus, pulmonary vessels potentially influence the mechanical behavior of the lung.

A possible role for the vascular influence on terminal airways may be seen in the lung of the newborn. Jaykka (23, 24) studied the effect of vascular distention in fetal and newborn lambs. Unperfused lungs inflated to an airway pressure of at least 20 cm H_2O were not uniformly expanded, whereas when India ink was injected into the pulmonary artery under a pressure of 80 mm Hg, the microscopic picture resembled that of a normally aerated lung. He suggests the capillary system was rendered rigid by the liquid and formed a framework that supported the terminal airspaces, so that in the fetus capillary erection would cause amniotic fluid to enter the potential airspaces.

The results of airway distention caused by pulmonary vascular congestion may depend on whether the lungs are

excised or intact within a close-chested animal. Avery et al. (5) performed studies on the gas-free excised lungs of cats, dogs and human stillborn infants. After cannulating the pulmonary artery and left auricle, vascular pressures were elevated by infusing Dextran in Ringer's-lactate into the system. An intratracheal cannula was used to record simultaneous pressure changes in the airways. At vascular pressures of 20-30 cm H_2O, the pressure in the airways was 1.0-1.5 cm H_2O subatmospheric. At vascular pressures of 70 cm H_2O, the pressure in the airways was 5.0 cm H_2O subatmospheric. They concluded, however, that these airway pressures resulting from capillary distention alone would not approximate the pressures required for inflation of the lung from the degassed state.

Frank et al. (15) reported that the effect of pulmonary vascular congestion on the elastic recoil of excised cats' lungs may be dependent on lung volume. At large lung volumes (airway pressures of 5 cm H_2O or more) recoiling force was increased by pulmonary vascular congestion; at intermediate lung volumes (airway pressures of 2.5-3.0 cm H_2O, approximately equal to FRC) the change was negligible and, at smaller volumes recoiling force was reduced. Thus, at low lung volumes pulmonary vascular congestion exerts an erectile effect on the airways, whereas at high lung volumes vascular congestion has a compressing effect by increasing lung recoil. These studies indicate that pulmonary vascular

congestion tends to return the lung to a resting volume which is approximately FRC. In this condition, a change in lung volume in either direction will require a greater force than if the pulmonary vessels are not filled. Similar effects have been shown in the intact lungs of normal human subjects (17). In contrast, other studies (18, 30) of intact lungs of close-chested animals have indicated a decreased FRC, decreased compliance and a decreased end-expiratory transpulmonary pressure in response to pulmonary vascular engorgement.

At this point there is no agreement regarding the effect of pulmonary vascular pressures on collateral ventilation. Ankeney et al. (3) found that ESGV decreased in anesthetized dogs in response to increased vascular pressures caused by pulmonary venous obstruction, myocardial infarction or pulmonary venous stasis. Close examination of their methods, however, would allow the reader to support the opposite conclusion. They obstructed a secondary bronchus in the right lower lobe with a cannula similar to the one used by VanAllen (59). The proximal end of the cannula was attached to glass tubing, the other end of which was placed just below the water level in a trap bottle. Another piece of glass tubing whose tip was above the water level in the trap bottle was connected to a volume recorder. Gas from the obstructed segment bubbled through the water, and the volume was recorded. With this method, gas passes from

the surrounding lung into the isolated segment during inspiration. During expiration, however, the gas may leave the segment via two routes: 1) through the cannula to the trap bottle, or 2) back out through collateral channels and into the surrounding lung. Their conclusion that increased pulmonary vascular pressures decreased collateral ventilation was made on the reduced volume of gas collected, and they assumed that elevated pressures distended alveolar capillaries which then encroached upon the Pores of Kohn and thus decreased the volume of gas passing through them; less gas would be allowed to enter the segment, causing a smaller collateral volume to be recorded. This assumption may be erroneous for three reasons: 1) these workers did not consider that there may be pathways other than alveolar pores which provide for collateral flow. 2) It has been shown that capillary distention does not have a measureable effect on pulmonary blood volume (38). This indicates that capillaries change their size only minimally in response to high vascular pressures and therefore should not occlude the pores any more than they would at low vascular pressures. 3) The capillaries are interdependent with the terminal airways they surround (4, 16, 53) and may act as a supportive structure to them (23, 24). If this is true, vascular engorgement would have the effect of making capillaries and small vessels more rigid. This would add increased support to the small airways and collateral channels and tend to

prevent their closure during expiration. The decreased ESGV seen by these workers may thus be explained as follows: at low vascular pressures, most of the air leaving the segment during expiration passes through the obstructing cannula because its resistance is much lower than the resistance through collateral channels. High vascular pressures, however, stabilize collateral channels and causes them to remain more dilated. The resulting decrease in resistance through these pathways causes a greater proportion of the expired gas to leave the segment via this route, causing less collateral volume to be recorded. The conclusions of Ankeney et al. may therefore be in exact contradiction to their data.

Other experiments dealing with the effect of vascular pressure on collateral ventilation were performed by Johnson and Lindskog (25) who clamped the left pulmonary artery in dogs and noted a 16.6-53.0 percent decrease in ESGV which then rose after the clamp was released. They were not able to explain this finding.

Menkes et al. (40) and Traytsman et al. (58) used a stop-flow technique in which pulmonary artery pressures of anesthetized dogs on right heart bypass were elevated by as much as 20 mm Hg. Lung perfusion was then abruptly stopped so that pulmonary vascular pressures declined to 0 mm Hg within 12-15 seconds. Rcoll increased as pulmonary vascular pressures decreased, and this was attributed to the effect

of local hypocapnea, since: 1) when air was continually introduced into the segment under conditions of no blood flow, the resultant local hypocapnea caused constriction of collateral channels. 2) The effect of vascular pressure on Rcoll was greatly attenuated when 10% CO_2 was introduced into the segment instead of room air. They conclude that the change in Rcoll is not directly related to the changes in intravascular pressure since the fall in vascular pressures preceded the increase in Rcoll. This conclusion may be in error, however, because Rcoll was not measured until three seconds after lung perfusion was stopped. Their figures indicate that the greatest changes in pulmonary vascular pressures occurred during this time, so the mechanical effect of the pulmonary vessels on the airways may have occurred prior to the time their measurements were taken. Also, they did not measure P_{aCO_2}, so it is unknown if reflexes influenced their results.

The local hypocapnea produced in this method may have influenced these workers' results but, in contrast to their conclusion, the change in vascular pressures may be an important factor. Their data indicate that the increase in Rcoll occurred after pulmonary vascular pressures had declined to low levels. This may be explained as follows: high vascular pressures may tend to hold collateral pathways open. When vascular volume is suddenly and rapidly depleted (as with stop-flow), these pathways will tend to narrow but

at a rate which may be slower than the rate of vascular volume depletion. This is because the smooth muscle surrounding the collateral pathways as well as other elastic elements attached to them may continue to contract several seconds after the distending force has disappeared. In fact, this is a major cause of the time-dependent increase in Rcoll in unventilated lungs statically held at a given transpulmonary pressure (49).

Because there is no conclusive evidence which demonstrates the mechanical effect of pulmonary vessels on collateral pathways, the following studies measure the effect of pulmonary venous pressure on steady state collateral resistance. If pulmonary vascular congestion exerts an erectile effect on the lung, the resultant changes in lung volume may account for the change in collateral resistance. To determine this, residual volume is also measured. Since measurements were made at different lung inflation pressures, changes in lung compliance may affect the lung volume at which measurements were made. Pressure-volume curves are therefore plotted at various pulmonary venous pressures. An isolated perfused lung was chosen as the model for the experiments so that alveolar and blood gas tensions could be controlled during alterations in pulmonary venous pressure. The viability of the isolated perfused lung was tested by measuring its response to inspired hypocapnic and hyperoxic gas mixtures.

II. MATERIALS AND METHODS

A. Isolated Perfused Lung Preparation (IPL)

Two mongrel dogs were used in each experiment. The larger dog (16-18 kg, subsequently referred to as the donor dog) was anesthetized with sodium pentobarbitol 33 mm/kg (Abbott Laboratories, North Chicago, IL) and intubated. Ventilation was controlled with a Harvard pump (Model 607, Harvard Apparatus, Dover, MA) to maintain an end-expired CO_2 concentration of 5% as measured by an infra-red CO_2 analyzer (LB-2, Beckman Instruments, Schiller Park, IL) which was calibrated before each experiment with a known concentration of CO_2. After injecting heparin (Sigma Chemical Co., St. Louis, MO) for anticoagulation (10,000 units intravenously), the left femoral artery was cannulated and connected to a pressure transducer (4710, Bell and Howell, Pasedena, CA) in order to monitor systemic arterial pressure (P_{syst}). A fall in P_{syst} may cause the release of broncho-active substances (catecholamines, etc.) from the donor dog which affects the mechanical behavior of the isolated lung. Therefore, care was taken (such as the regulation of depth of anesthesia) to prevent this from occurring. The left cephalic vein was cannulated for infusion of supplemental

anesthetic. The right femoral artery and vein were cannulated to provide and receive blood for subsequent perfusion of the isolated lung. The animal was kept warm with a heating pad.

A second dog (9-12 kg) was euthanized with 20 ml of 5% sodium pentobarbitol containing 5000 units of heparin. A thoracotomy was performed at the sixth intercostal space on the left side. After carefully wrapping the left lung with a gauze pad, it was gently held to prevent damage while the left mainstem bronchus was cut at the bifurcation with the trachea. In order to expose the heart, the pericardium was opened and cut around the heart at the level of the atrioventricular valves. After ligation, all pulmonary veins of the right lung as well as the posterior vena cava were sectioned, and the right lung was discarded. The heart was divided in the lower third midway between the apex and the atrioventricular valves, and the apex was discarded. The left pulmonary artery was severed at the bifurcation with the right pulmonary artery. After cutting all remaining tissue attachments, the left lung and remaining portion of the heart were removed as a unit and weighed. At the termination of the experiment, the heart and lung unit were again weighed to determine total weight gain as an estimation of fluid gain of the preparation. At this time, the airways were checked for gross edema by dissecting several airways as distally as possible with a scissors.

A "T-tube" was tied into the left mainstem bronchus of the isolated lung and attached via a sidearm to a tripod so that the heart and lung unit were suspended. The outer surface of the lung was kept moist with a saline spray. Lung inflation pressure (P_L) was measured at the mainstem bronchus with a cannula attached to a transducer (PM 131, Statham Instruments, Hato Rey, PR), and under static conditions was assumed to be equal to alveolar pressure in the surrounding lung. The lung was inflated several times with a blower to P_L = 30 cm H_2O in order to remove atelectasis. In the studies which measured the effect of gas composition on collateral resistance, the lung was ventilated with three different gas mixtures: room air (21/0), 95% O_2 and 5% CO_2 (95/5) and 100% O_2 (100/0). In the studies which measured the effect of pulmonary venous pressure on collateral resistance, the lung was ventilated with 95/5 only. The tidal volume was 250-300 ml with a respiratory rate of 10 breaths per minute, and the lung was regularly given deep breaths to P_L = 30 cm H_2O. A cannula (9 mm o.d.) was inserted into the left pulmonary artery so that blood from the donor dog's right femoral artery could be pumped into the lung at a constant flow rate using a roller pump (designated as the inflow pump) (Masterflex, Cole Palmer, Chicago, IL). Another cannula attached 10 cm upstream from the pulmonary artery was connected to a transducer (P23 Db, Statham Instruments, Hato Rey, PR) and measured pulmonary arterial pressure (Ppa).

Blood flow ($\dot{Q}$), as measured with a stopwatch and graduated cylinder, was initially adjusted to produce a mean Ppa in the low to normal range (approximately 10 mm Hg), and $\dot{Q}$ was maintained constant thereafter.

The left atrium was cannulated with a rigid large bore tube with a flared end (29 mm o.d.). Pulmonary venous pressure (Ppv) was measured with a transducer (P23 Gb, Statham Instruments, Hato Rey, PR) connected to a cannula whose tip rested at the opening of the large bore tube. Ppa and Ppv were recorded with a multipen recorder (Model 60297, Soltec Corp., Sun Valley, CA). Blood leaving the lung passed through the left atrium and was pumped with a second roller pump (designated as the outflow pump) (Masterflex, Cole Palmer, Chicago, IL) into the right femoral vein of the donor dog. Blood therefore passed through the following circuit: donor dog, inflow pump, excised lung, left atrium, outflow pump, donor dog (Figure 1). The total time of ischemia of the isolated lung was approximately 25 minutes.

A feedback control system regulated Ppv. A proportional gain current output controller (Leeds and Northrup, North Wales, PA) received a signal from the Ppv amplifier, compared this to a predetermined Ppv set point and adjusted the speed of the outflow pump appropriately to maintain a constant Ppv. The response time of the system was such that only small changes in Ppv ($\pm$ ½ mm Hg) occurred with lung inflation and deflation.

Figure 1

A diagram of the isolated perfused lung preparation (IPL).

PEEP = positive and expiratory pressure.

P_L = lung inflation pressure measured at the mainstem bronchus.

P_S = pressure in the isolated segment as measured by the inner lumen of the wedged catheter.

$\dot{V}coll$ is the flow of gas through the outer lumen of the wedged catheter into the isolated segment.

Ppa = pulmonary arterial pressure.

Ppv = pulmonary venous pressure.

P_{syst} = systemic arterial pressure.

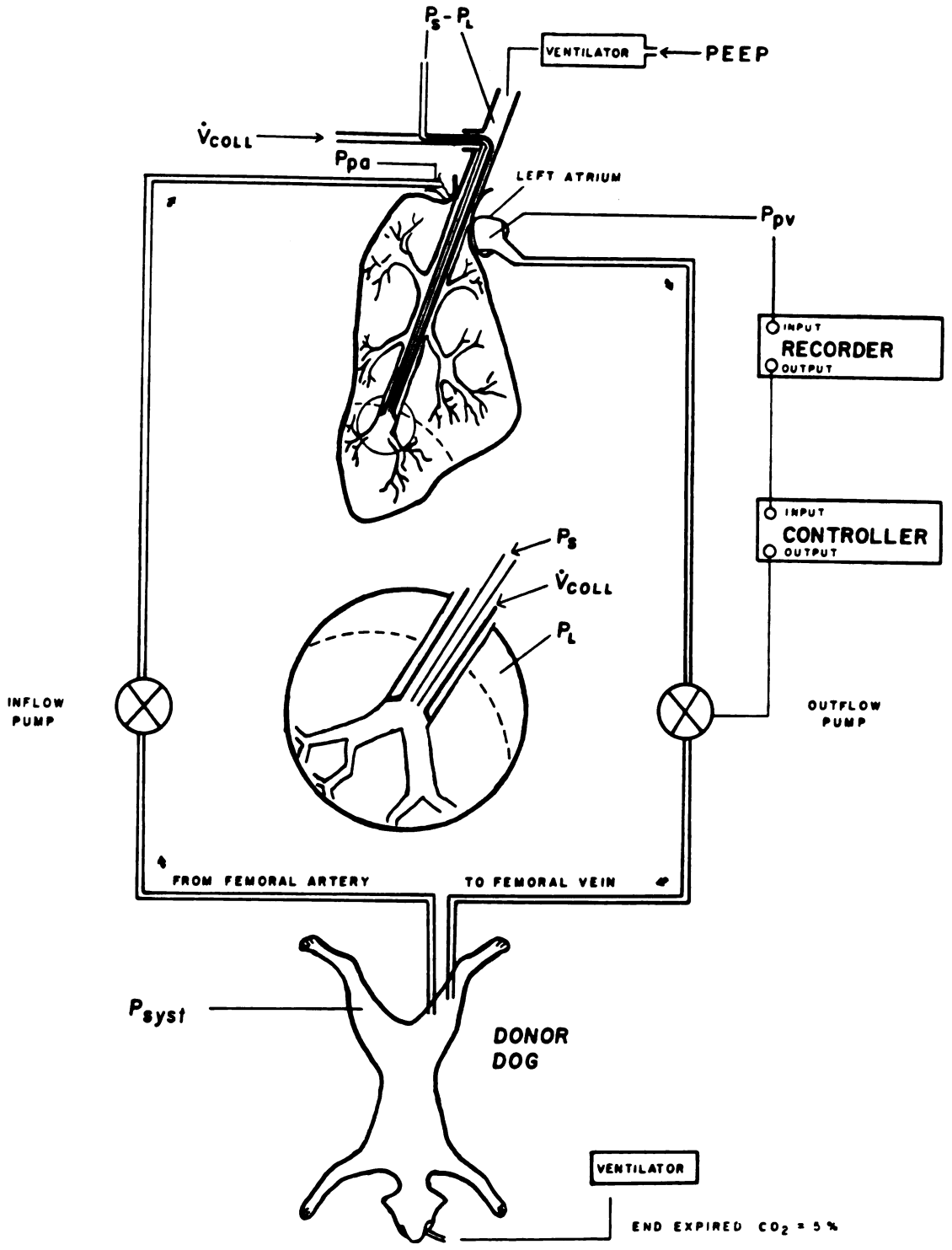
$P_s - P_L$
VENTILATOR
PEEP
$\dot{V}_{COLL}$
P_{pa}
LEFT ATRIUM
P_{pv}
INPUT
RECORDER
OUTPUT
INPUT
CONTROLLER
OUTPUT
P_s
$\dot{V}_{COLL}$
P_L
INFLOW PUMP
OUTFLOW PUMP
FROM FEMORAL ARTERY
TO FEMORAL VEIN
P_{syst}
DONOR DOG
VENTILATOR
END EXPIRED CO_2 = 5 %

Figure 1

Pulmonary vascular resistance (Rvas) of the IPL was calculated as:

$$Rvas = \frac{Ppa - Ppv}{\dot{Q}} \qquad (7)$$

where Ppa is pulmonary arterial pressure, Ppv is pulmonary venous pressure and $\dot{Q}$ is the rate of blood flow through the IPL.

B. Measurement of Steady State Collateral Resistance

Steady state collateral resistance (Rcoll) was measured according to the method of Hilpert (described by Macklem (33)). With the lung inflated to 30 cm H_2O, a double lumen catheter with a flared tip (4 mm o.d.) was inserted into the mainstem bronchus and wedged in a peripheral airway of the lower lobe, thus isolating a segment of lung. The inner lumen was connected to a transducer which measured pressure at the catheter tip (P_S). Gas flowed through the outer lumen and into the isolated segment from a compressed gas source and through a rotameter (Model 7431T, Matheson Gas Products, Joliet, IL) which measured collateral flow ($\dot{V}coll$), and it leaked out of the segment through collateral channels and into the surrounding lung. To measure the pressure gradient between the segment and the lung, P_S and P_L were

recorded on opposing ends of a differential transducer (PM 131, Statham Instruments, Hato Rey, PR).

Rcoll was measured at P_L = 0, 2 and 4 cm H_2O while P_L was maintained by adjusting a blower attached to the exhaust port of the ventilator. When $\dot{V}coll$ was adjusted with the rotameter to maintain $P_S - P_L$ = 3 cm H_2O, Rcoll was calculated as:

$$Rcoll = \frac{P_S - P_L}{\dot{V}coll} . \qquad (8)$$

The tracing of P_L and $P_S - P_L$ were recorded on a photo recording oscilloscope (Electronic for Medicine, White Plains, NY).

It may be possible that some of $\dot{V}coll$ leaks around the tip of the wedged catheter and leaves the segment through more proximal airways rather than through collateral channels. However, the following evidence suggests that this probably does not occur: 1) the catheter is wedged in the segment while the left lung is inflated to total lung capacity. The lung is then deflated so that the airway collapses around the tip of the catheter such that removal of the catheter with the lung collapsed may only be done at the expense of damaging the lung. 2) The tip of the catheter is flared, contributing to a more secure wedge. 3) Rcoll measurements were made at low lung volumes (residual volume to functional residual capacity). The airways

are thus more constricted than when the catheter is inserted and tend to retain the catheter in its place. 4) In an animal with poor collateral ventilation (such as the horse), air injected through the outer lumen of the wedged catheter distends the segment and remains trapped when the catheter is clamped (unpublished observations, Robinson and Sorenson, 1975). 5) When recording P_S and P_L on two different channels of a recorder, during early inflation of the IPL (when collateral channels have not yet opened) the two pressures are out of phase with each other, such that as the lung expands around the isolated segment, P_L becomes positive and P_S becomes negative.

C. Response of the Isolated Perfused Lung to Hypocapnea and Hyperoxia

Since the IPL model clearly differs from an intact preparation, it was decided to verify its use for measurements of Rcoll and its viability by determining the response to inspired hypocapnea and hyperoxia. Lungs were ventilated with 21/0 (hypocapnea), 95/5 (normocapnea) and 100/0 (hyperoxia). Blood samples were taken from the pulmonary arterial and pulmonary venous sides of the IPL and analyzed for CO_2 tensions with a blood gas machine which was calibrated before each measurement (Model BM3, Mark 2, Radiometer Co., Copenhagen, Denmark). A comparison of P_{paCO_2}

and P_{pvCO_2} was an indication of the gas exchange function of the IPL. Because the sequence in which the gases are administered may influence the lung's response (8), each gas mixture was administered three times in random order (latin square design) to determine the effect of sequence on the repeatability of measurements.

Four experiments were performed in which both the isolated segment and surrounding lung were ventilated with the same gas mixture. When changing gas mixtures, 5 minutes were allowed for equilibration. A minimum of three Rcoll measurements were taken at P_L = 2 and P_L = 4 cm H_2O in each experiment. A typical data sheet is shown in Appendix A.

D. The Effect of Pulmonary Venous Pressure on Steady State Collateral Resistance, Residual Volume and Lung Compliance

Rcoll, lung pressure-volume curves and residual volume (RV) were measured as a function of Ppv. Both the lung and the isolated segment were ventilated with 95/5. In each of eleven experiments, Ppv was varied in the following sequence: Ppv = $5_{(1)}$, 10, $5_{(2)}$, 15, $5_{(3)}$, 20, $5_{(4)}$, 25, $5_{(5)}$, 30 $5_{(6)}$ mm Hg*. A minimum of three Rcoll measurements were made at P_L = 4, P_L = 2 cm H_2O in eleven experiments and at P_L = 0 cm H_2O in 6 experiments so that the mean values between

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*Ppv = $5_{(1)}$, $5_{(2)}$, etc. are the first, second, etc. times that Ppv of 5 mm Hg appeared in the protocol sequence.

adjacent Ppv's could be compared. A typical data sheet is shown in Appendix A.

At each Ppv, RV was measured in nine of eleven experiments by equilibrating the gas in the IPL at P_L = 0 cm H_2O with a known volume of room air and analyzing the nitrogen concentration of the mixture with a rapidly responding nitrogen analyzer (Model 410, Cardio-pulmonary Instruments Corp., Houston, TX). Known volumes of gas were injected into the lung through the mainstem bronchus in stepwise fashion while P_L was recorded, and pressure-volume curves were plotted. Total lung capacity (TLC) was defined as the volume of gas contained in the IPL at P_L = 20 cm H_2O.

E. Analysis of Data

Unless otherwise stated, all data were analyzed with a randomized complete block analysis of variance (55) and the means compared using the indicated tests with a type I error probability set at 5%.

1. Response of the Isolated Perfused Lung to Inspired Hypocapnea and Hyperoxia

At each P_L the treatments were divided into three groups with each gas administered once per group. This is shown as follows:

GROUP I			GROUP II			GROUP III		
95/5	21/0	100/0	21/0	100/0	95/5	100/0	95/5	21/0
1	1	1	2	2	2	3	3	3

At least three Rcoll measurements were made per treatment for each dog; when more than three treatments were made, the excess values furthest from the mean were discarded. In this manner, each treatment contained three measurements of Rcoll at each P_L. The groups were analyzed with a randomized complete block analysis of variance with replicates (54) and the means compared using Tukey's w-procedure.

To analyze the effect of time on Rcoll, the gas mixtures of Groups I, II and III were regrouped as follows:

GROUP A			GROUP B			GROUP C		
21/0	21/0	21/0	95/5	95/5	95/5	100/0	100/0	100/0
1	2	3	1	2	3	1	2	3

The means of each group were compared using Tukey's w-procedure or the least significant difference (lsd) test.

2. The Effect of Pulmonary Venous Pressure on Steady State Collateral Resistance

The effect of Ppv on Rcoll was analyzed in two ways: 1) the mean Rcoll at each P_L of adjacent Ppv's were compared using the lsd test, and 2) Rcoll values at the different P_L's were grouped at each Ppv, and the resulting average

Rcoll at adjacent Ppv's were compared using the paired Student t test.

To analyze the effect of time and sequence on Rcoll, the means of the grouped P_L's at all Ppv's = 5 mm Hg were compared using the lsd test.

3. The Effect of Pulmonary Venous Pressure on Residual Volume

The effect of Ppv on RV was analyzed by comparing the means of adjacent Ppv's using the lsd test. One experiment terminated prematurely because the IPL developed pulmonary edema indicated by large amounts of frothy edema fluid in the airways. Therefore, the data were divided into two groups:

	GROUP I						GROUP II				
Ppv	$5_{(1)}$	10	$5_{(2)}$	15	$5_{(3)}$	20	$5_{(4)}$	25	$5_{(5)}$	30	$5_{(6)}$
	n = 9						n = 8				

A separate analysis of variance was performed on each group.

4. The Effect of Pulmonary Venous Pressure on Lung Compliance

Pressure-volume curves were plotted in ten experiments. The curves were analyzed by calculating the compliance on two different portions of the curve. The compliance on the low portion of the curve, C_L, was calculated as:

$$C_L = \frac{50\% - 40\% \text{ TLC}}{\Delta P_L} \qquad (9)$$

and the compliance on the upper portion of the curve was calculated as:

$$C_H = \frac{100\% - 90\% \text{ TLC}}{\Delta P_L} \qquad (10)$$

The effect of Ppv on C_L and C_H were analyzed by comparing the means at adjacent Ppv's using Tukey's w-procedure.

In two of the ten dogs, pressure-volume curves were not plotted at every Ppv. One IPL developed pulmonary edema and the other IPL developed a tear in the parenchyma, both at Ppv = 20 mm Hg. Therefore, the data were divided into two groups:

	GROUP I						GROUP II				
Ppv	$5_{(1)}$	10	$5_{(2)}$	15	$5_{(3)}$	20	$5_{(4)}$	25	$5_{(5)}$	30	$5_{(6)}$
	n = 10						n = 8				

A separate analysis of variance was performed on each group.

5. The Effect of Pulmonary Venous Pressure on Pulmonary Vascular Resistance

The change in Rvas between the following adjacent Ppv's were compared:

Ppv $5_{(1)}$ - 10, $5_{(2)}$ - 15, $5_{(3)}$ - 20, $5_{(4)}$ - 25, $5_{(5)}$ - 30 mm Hg.

The means were compared using a Student-Newman-Keuls' (SNK) test.

III. RESULTS

A. Response of the Isolated Perfused Lung to Hypocapnea and Hyperoxia

Figure 2 shows the effect of changing alveolar gas composition on Rcoll during repetitions of the various gas mixtures. In all Groups, Rcoll with 21/0 was significantly higher than with 95/5. The following differences occurred between Groups II and III and Group I: 1) in Groups II and III, Rcoll with 21/0 was not significantly different than Rcoll with 100/0, but in Group I this difference was significant. 2) In Groups II and III there was a significant difference in Rcoll with 95/5 and 100/0, but in Group I this difference was not significant at P_L = 2 cm H_2O. 3) In Group I at P_L = 4 cm H_2O, there were no significant differences between any of the means when using Tukey's w-procedure (the same statistical test used for comparison of the other means). However, when using a more liberal test (the lsd test), all three means were significantly different.

The effect of time on the IPL is indicated in Figure 3. The data in Figure 2 have been regrouped so that each section of Figure 3 shows the repetition of the same gas mixture with each mixture administered once near the beginning, middle and end of the experiment, and each experiment

Figure 2

The effect of 95% O_2 and 5% CO_2 (95/5), room air (21/0) and 100% O_2 (100/0) on steady state collateral resistance (Rcoll) at two lung inflation pressures (P_L = 2 and 4 cm H_2O). Each gas mixture was administered three times in random sequence (latin square design) so that Groups I, II and III contain the first, second and third administrations, respectively, of each mixture. In the figure, however, the sequence within each group is the same for the sake of clarity. All differences not marked NS (not significant) are significant at $P < .05$. n = 4 for each Group.

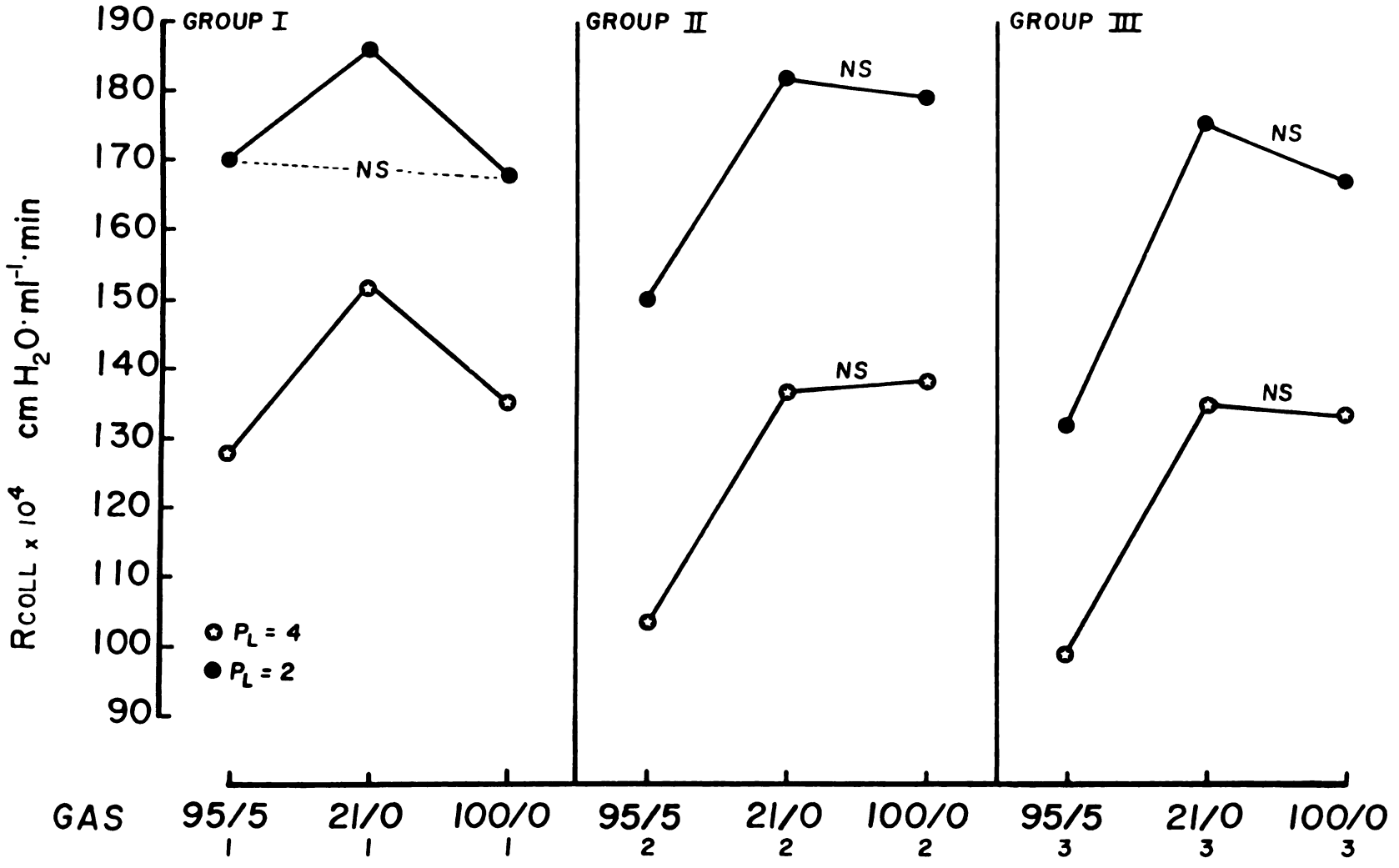

GROUP I
GROUP II
GROUP III
NS
NS
NS
NS
NS
190
180
170
160
150
140
130
120
110
100
90
$R_{COLL} \times 10^4$ cm $H_2O \cdot ml^{-1} \cdot min$
$P_L = 4$
$P_L = 2$
GAS
95/5 1
21/0 1
100/0 1
95/5 2
21/0 2
100/0 2
95/5 3
21/0 3
100/0 3

Figure 2

Figure 3

Data from Figure 2 is regrouped to show the effect of time on steady state collateral resistance (Rcoll) in the isolated perfused lung (IPL). Groups A, B and C contain the first (1), second (2), and third (3) administrations of the same gas mixture. Since each gas mixture was administered once near the beginning, middle and end of the experiment, any change in Rcoll within the Groups may be due to time. All differences not marked by NS (not significant) are significant at $P < .05$.
$n = 4$ for each Group.

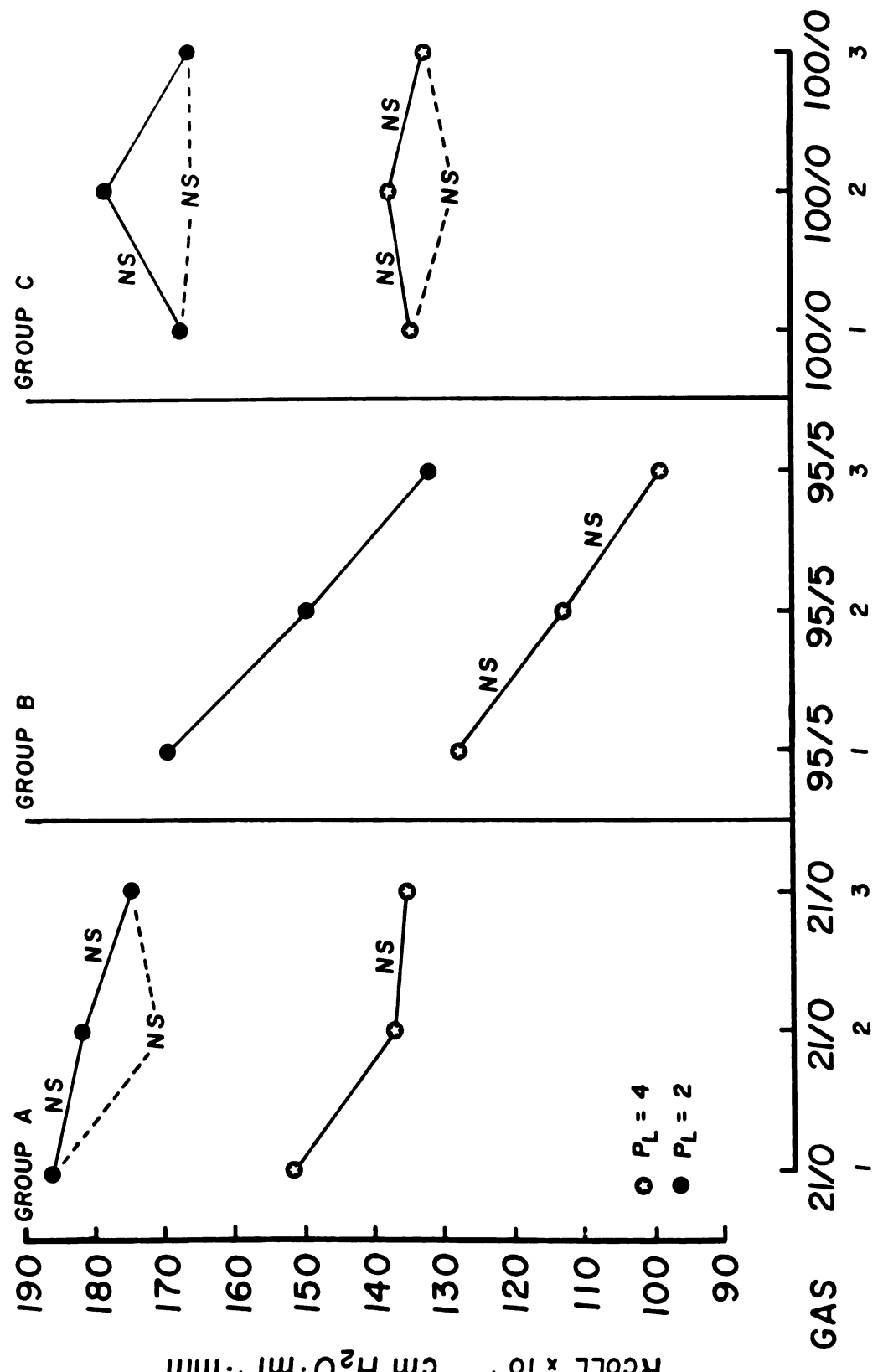

GROUP A
GROUP B
GROUP C
NS
NS
NS
NS
NS
NS
NS
NS
NS
$P_L = 4$
$P_L = 2$
$R_{COLL} \times 10^4$ cm $H_2O \cdot ml^{-1} \cdot min$
190
180
170
160
150
140
130
120
110
100
90
GAS
21/0
21/0
21/0
95/5
95/5
95/5
100/0
100/0
100/0
1
2
3
1
2
3
1
2
3

Figure 3

lasting approximately 4 hours. In some cases, there is a significant decrease in Rcoll over time, with the greatest changes occurring with 95/5. With 21/0 at P_L = 2 cm H_2O and with 100/0 at P_L = 4 cm H_2O, there were no significant changes over time. With 21/0 at P_L = 4 cm H_2O and with 100/0 at P_L = 2 cm H_2O, there were no significant differences using Tukey's w-procedure (the same statistical test used for comparison of the other means); however, when using a more liberal test (the lsd test), significant differences were found as indicated in the Figure.

Table 1 shows the mean P_{paCO_2} and P_{pvCO_2} for Group I in three of the four experiments. When using 95/5, blood is normocapnic in both the IPL's artery and vein. When using 21/0 or 100/0, however, the IPL receives normocapnic blood in its arterial side, and hypocapnic blood drains from the pulmonary veins.

Table 1. Mean pulmonary arterial and pulmonary venous CO_2 tensions for Group I in three of the four experiments.

	95/5		21/0		100/0	
	P_{paCO_2}	P_{pvCO_2}	P_{paCO_2}	P_{pvCO_2}	P_{paCO_2}	P_{pvCO_2}
$\bar{x}$	40.0	40.3	41.1	18.2	36.7	15.4
$\pm$ SE	1.5	2.7	2.5	1.3	4.2	0.8
n = 3						

Table 2 indicates the average IPL weights before and after the experiments, the average weight gain and average flow rate.

Table 2. Average isolated perfused lung weight before and after the experiments, weight gain and flow rate.

	Beginning lung weight (gms)	End lung weight (gms)	Weight gain (gms)	$\dot{Q}$ ($ml \cdot min^{-1}$)
$\bar{x}$	127.8	150.2	22.4	169
$\pm$ SD	22.8	30.0	----	16
n = 10				

B The Effect of Pulmonary Venous Pressure on Steady State Collateral Resistance

Figure 4 shows the effect of Ppv on Rcoll in two dogs. An increase in Ppv is associated with a decrease in Rcoll and vice versa. Because the change in Rcoll with changes in Ppv began at different Ppv's in each animal, it was only possible to demonstrate a statistically significant difference in Rcoll between Ppv = 25 and $5_{(5)}$ mm Hg, Ppv 30 and $5_{(5)}$ mm Hg and Ppv = 30 and $5_{(6)}$ mm Hg at P_L = 0 cm H_2O using the analysis of variance. However, when all P_L's are grouped together, there is a significant difference in Rcoll between Ppv = 15 and $5_{(2)}$ mm Hg, Ppv = 20 and $5_{(3)}$ mm Hg,

Figure 4

The effect of pulmonary venous pressure (Ppv) on steady state collateral resistance (Rcoll) in two representative dogs (each graph designates a single dog). In general, elevated Ppv's decrease Rcoll while low Ppv's increase Rcoll. Due to interanimal variation, this response begins early in the protocol in 4A and later in the protocol in 4B.

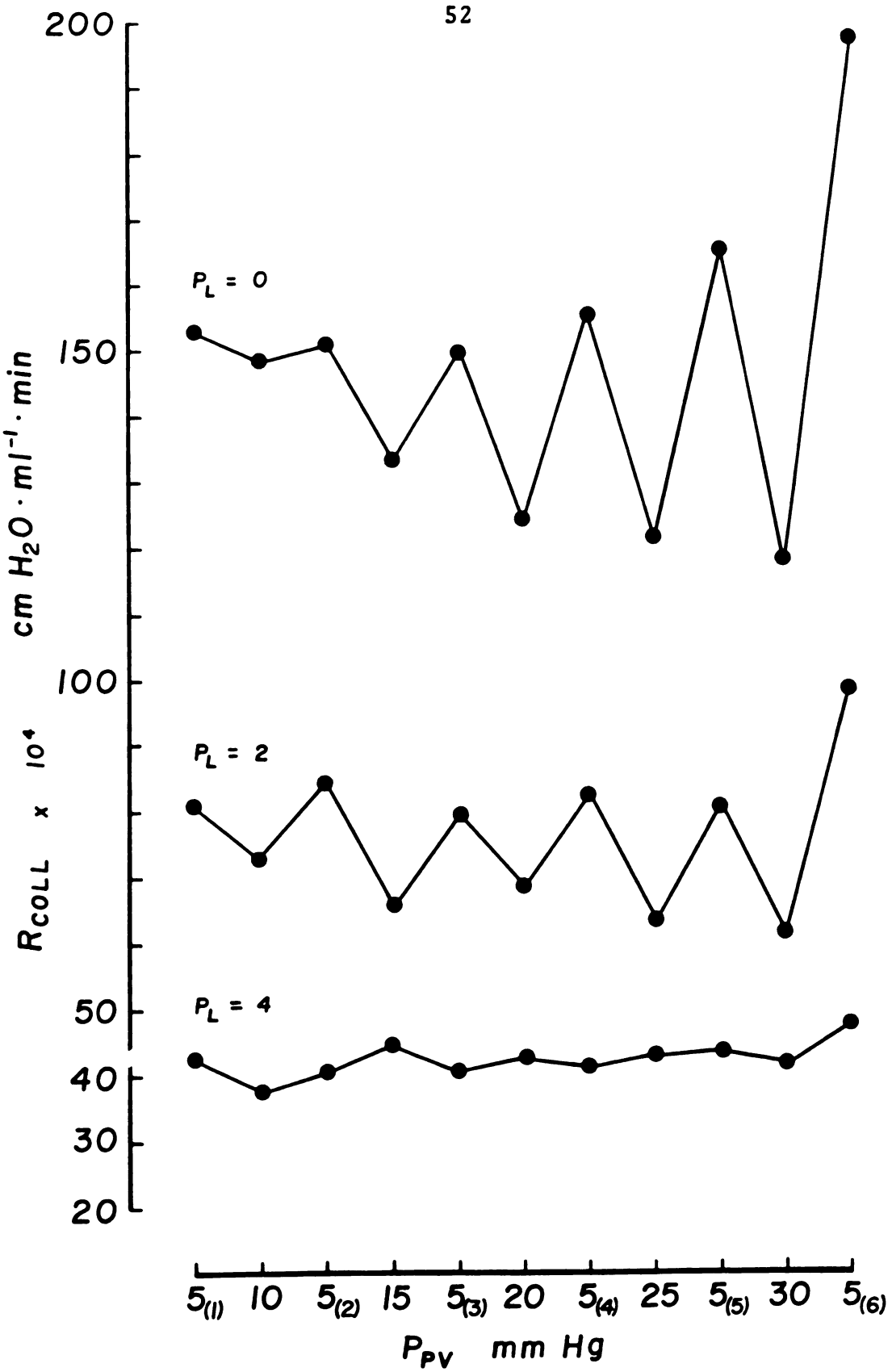

200
150
100
50
40
30
20
R_{COLL} x 10^4
cm $H_2O \cdot ml^{-1} \cdot min$
P_L = 0
P_L = 2
P_L = 4
$5_{(1)}$ 10 $5_{(2)}$ 15 $5_{(3)}$ 20 $5_{(4)}$ 25 $5_{(5)}$ 30 $5_{(6)}$
P_{PV} mm Hg

Figure 4A

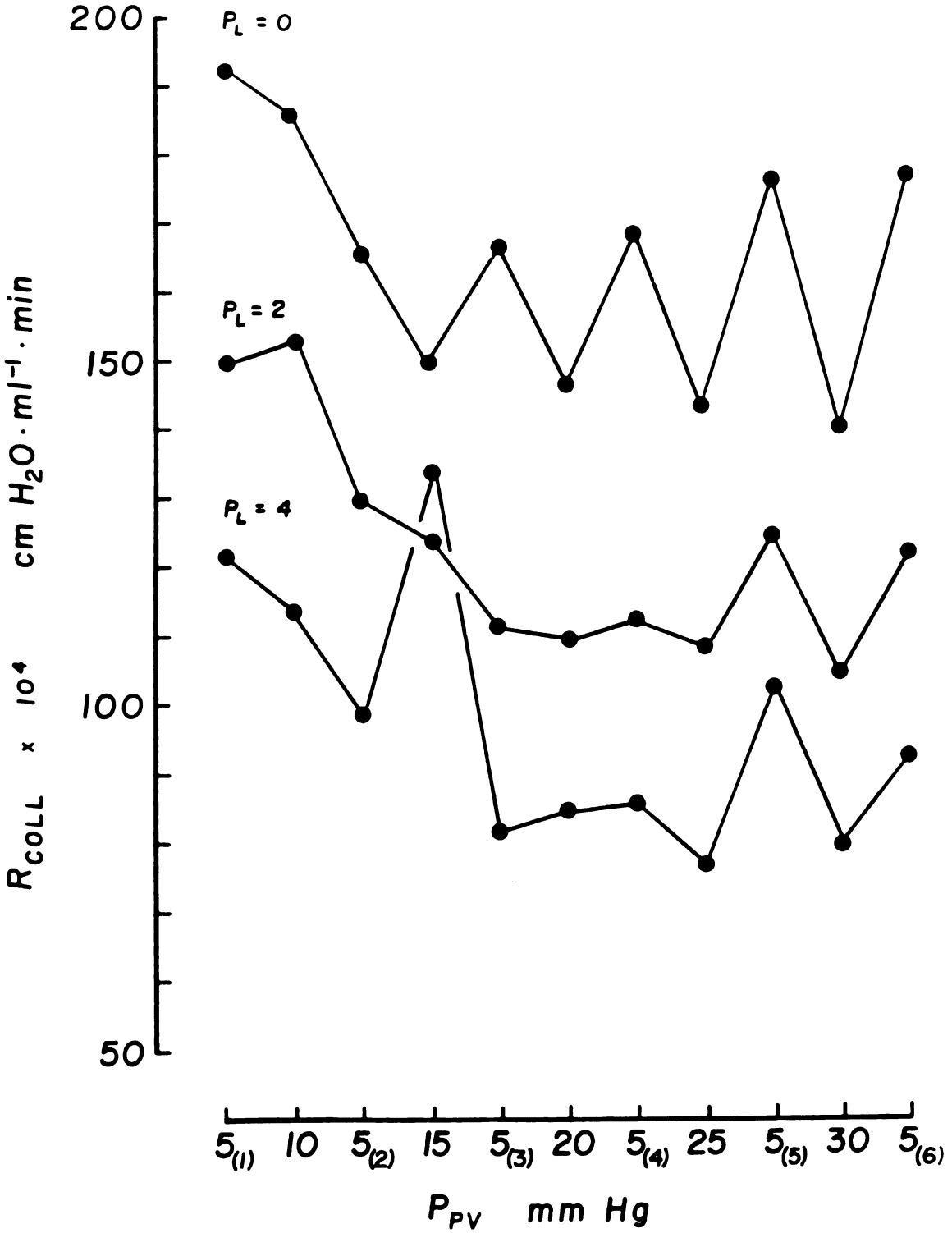

200
150
100
50
$P_L = 0$
$P_L = 2$
$P_L = 4$
$R_{COLL} \times 10^4$ cm $H_2O \cdot ml^{-1} \cdot min$
$5_{(1)}$ 10 $5_{(2)}$ 15 $5_{(3)}$ 20 $5_{(4)}$ 25 $5_{(5)}$ 30 $5_{(6)}$
P_{PV} mm Hg

Figure 4B

Ppv = 25 and $5_{(5)}$ mm Hg and Ppv = 30 and $5_{(6)}$ mm Hg using a paired t-test (Table 3). This is indicated in Figure 5 where Rcoll at elevated Ppv's is plotted against Rcoll at control Ppv's (Ppv = 5 mm Hg). A line of identity is drawn so that points falling on the line indicate that changes in Ppv have no effect on Rcoll while points falling below the line indicate that elevated Ppv's decrease Rcoll. It can be seen from Figure 5 that as Ppv increases to 15 mm Hg or above, most points fall below the line of identity.

Table 3. Results of a paired t test showing the average difference ($\bar{D}$) in Rcoll (mm Hg·ml^{-1}·min x 10^4) at adjacent Ppv's (mm Hg), the standard deviation of the difference (S_D), the calculated t value ($P < .05$, * indicate significant differences) and the degrees of freedom (df) for the grouped P_L's.

	Adjacent Ppv's				
	10 and $5_{(1)}$	15 and $5_{(2)}$	20 and $5_{(3)}$	25 and $5_{(5)}$	30 and $5_{(6)}$
$\bar{D}$	7.68	6.96	13.75	24.38	35.67
S_D	44.78	19.84	35.36	42.78	51.85
t	0.91	1.86*	2.06*	2.79*	3.37*
df	27	27	27	23	23

There was no significant difference between Rcoll's at Ppv = $5_{(1)}$, $5_{(2)}$ and $5_{(3)}$ mm Hg nor between Ppv = $5_{(4)}$, $5_{(5)}$ and $5_{(6)}$ mm Hg, indicating that Rcoll returns to control levels following each elevation of Ppv (see ANOVA table, Appendix B).

Figure 5

Steady state collateral resistance (Rcoll) at elevated pulmonary venous pressures (Ppv) is plotted against Rcoll at control Ppv's (Ppv = 5 mm Hg). A line of identity is drawn so that points falling below the line indicate that Rcoll at control Ppv's is greater than Rcoll at elevated Ppv's. Points falling on the line indicate that elevating Ppv has no effect on Rcoll.

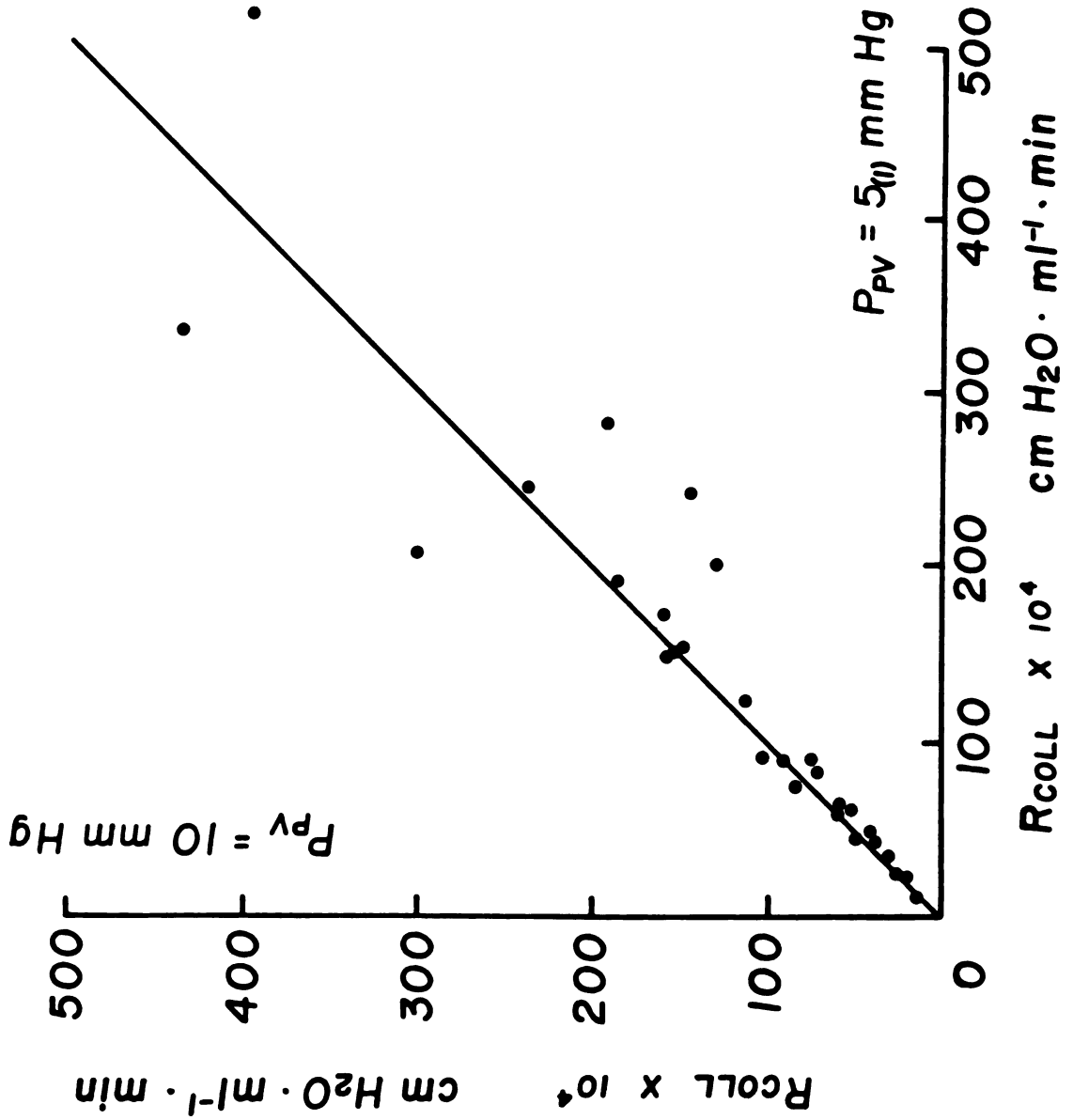

$P_{PV} = 5_{(11)}$ mm Hg
R_{COLL} x 10^4 cm $H_2O \cdot ml^{-1} \cdot min$
0
100
200
300
400
500
P_{PV} = 10 mm Hg
Rcoll x 10^4 cm $H_2O \cdot ml^{-1} \cdot min$

Figure 5A

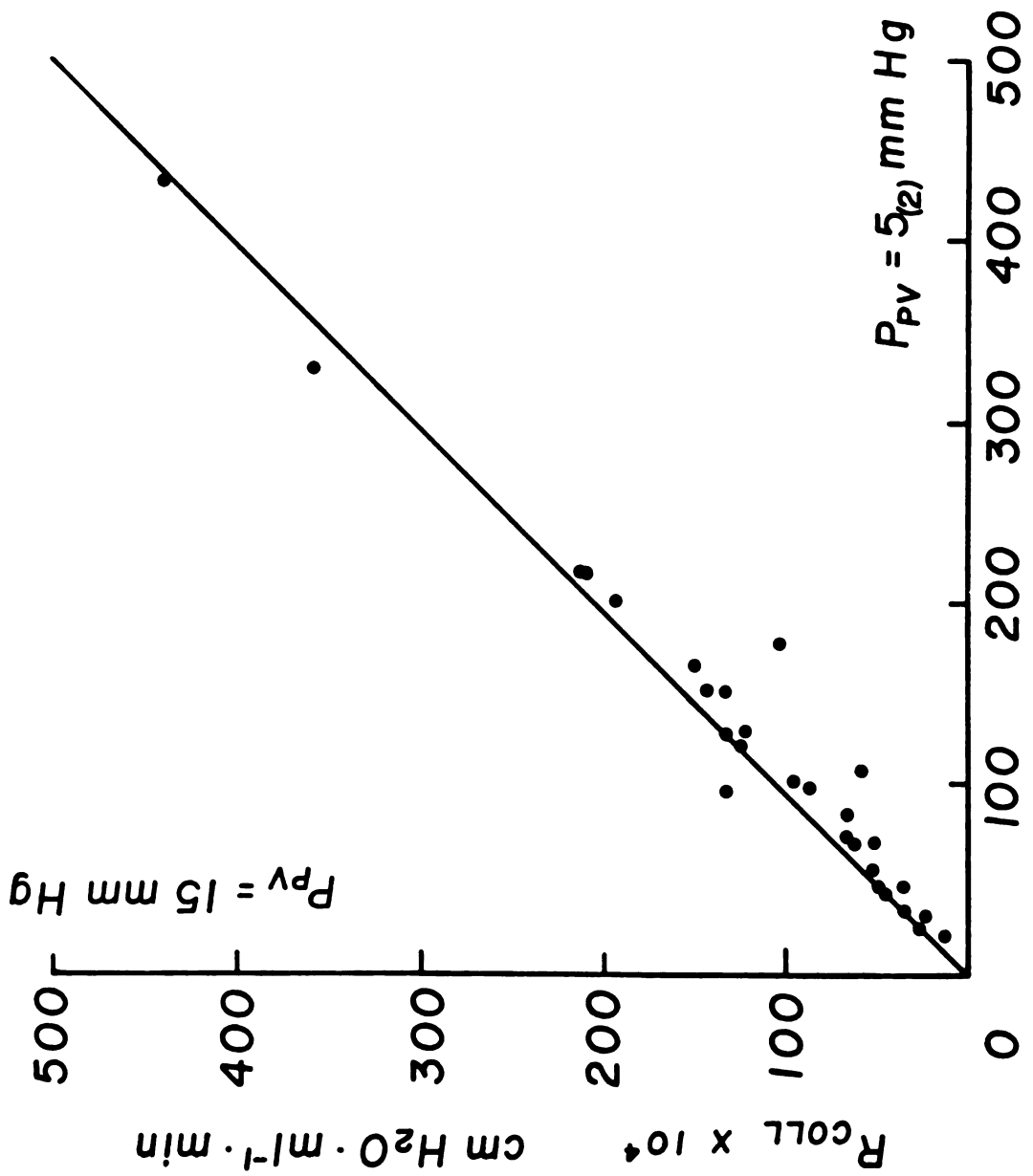

$P_{PV} = 5_{(2)}$ mm Hg
R_{COLL} x 10^4 cm $H_2O \cdot ml^{-1} \cdot min$
0
100
200
300
400
500
P_{PV} = 15 mm Hg
R_{COLL} x 10^4 cm $H_2O \cdot ml^{-1} \cdot min$

Figure 5B

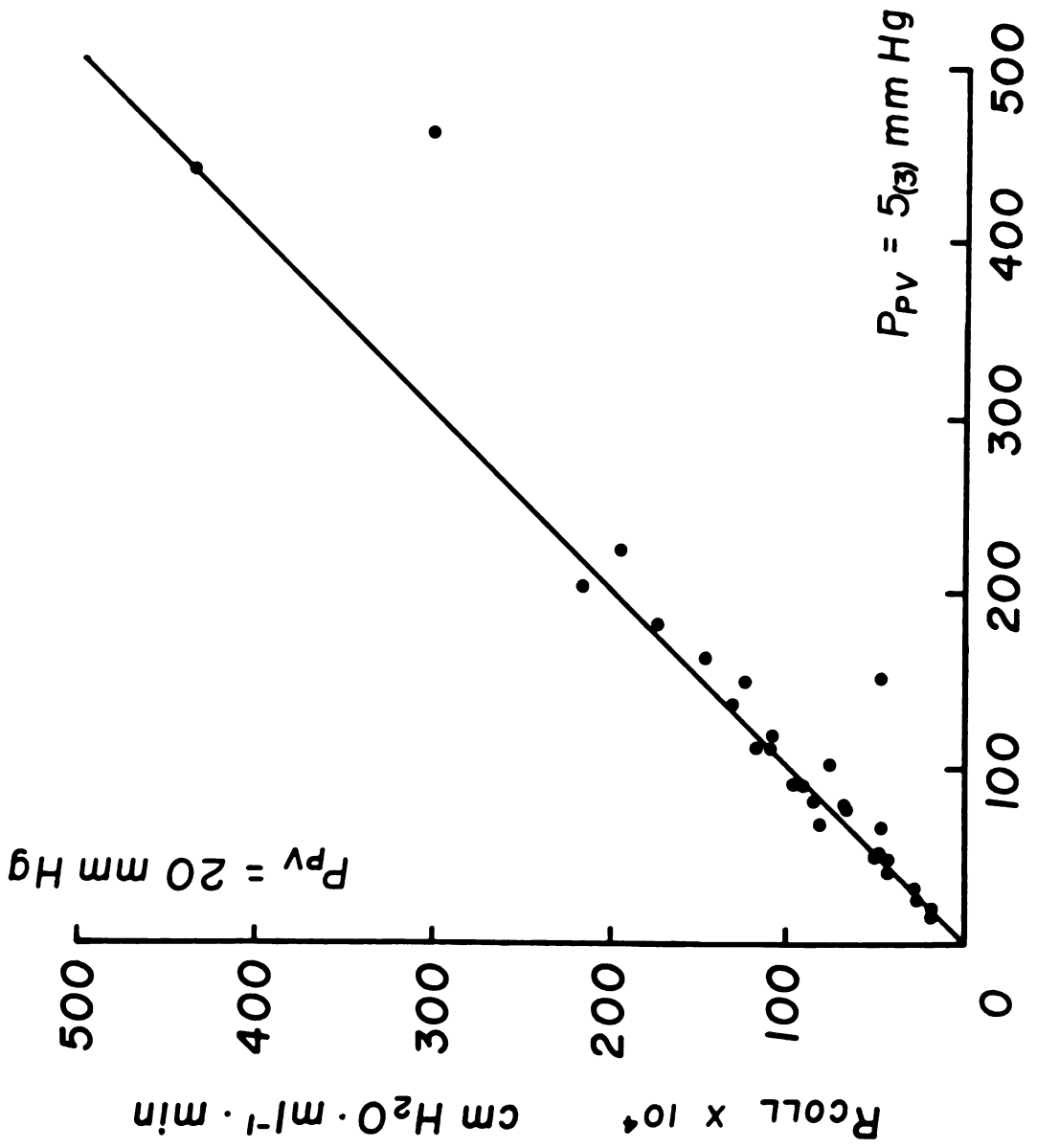

$R_{COLL} \times 10^4$ cm $H_2O \cdot ml^{-1} \cdot min$
0
100
200
300
400
500
$P_{PV} = 5_{(3)}$ mm Hg
$R_{COLL} \times 10^4$ cm $H_2O \cdot ml^{-1} \cdot min$
$P_{PV} = 20$ mm Hg

Figure 5C

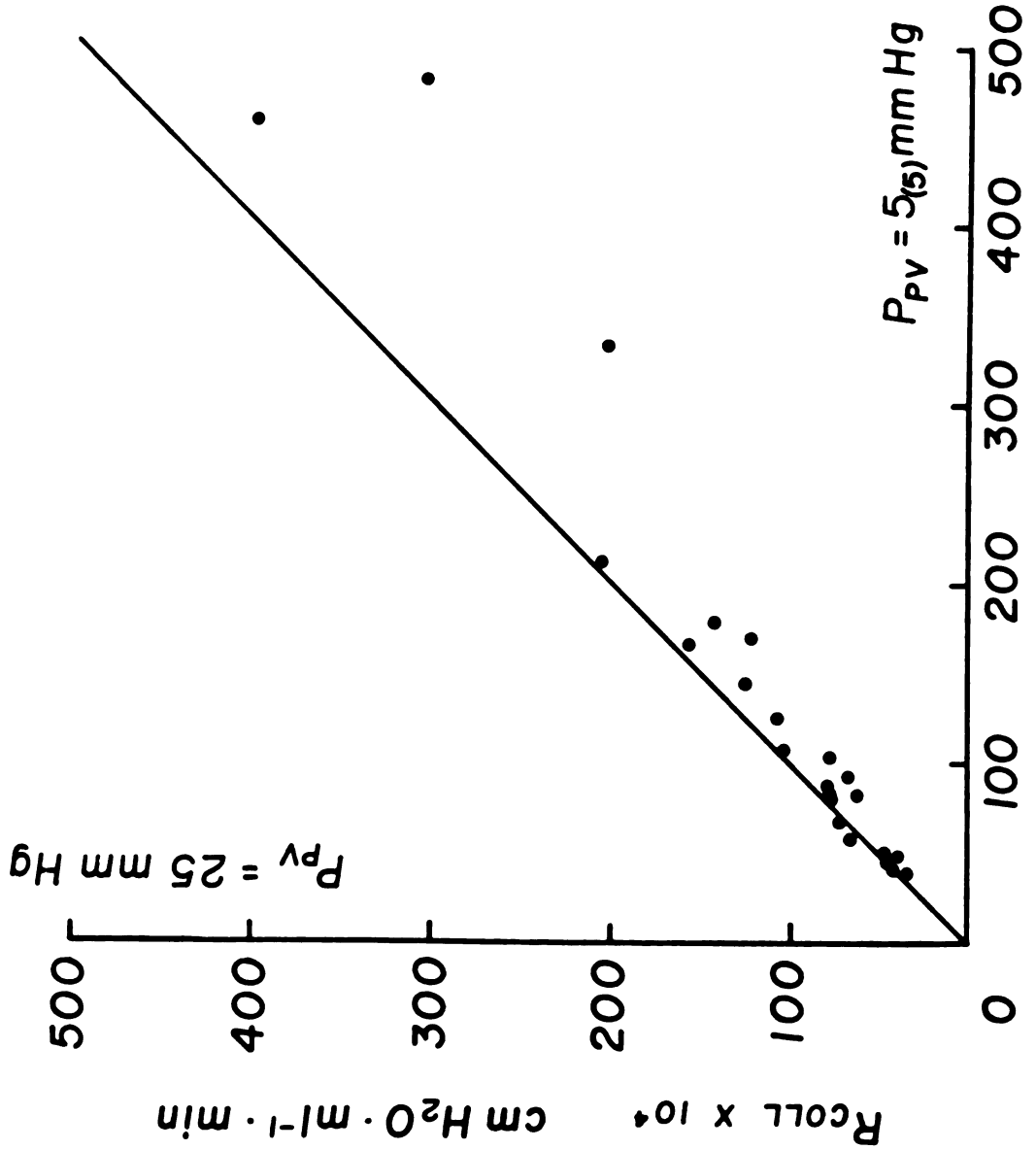

$R_{COLL} \times 10^4$ cm $H_2O \cdot ml^{-1} \cdot min$
0
100
200
300
400
500
$P_{PV} = 5_{(5)}$ mm Hg
$R_{COLL} \times 10^4$ cm $H_2O \cdot ml^{-1} \cdot min$
0
100
200
300
400
500
P_{PV} = 25 mm Hg

Figure 5D

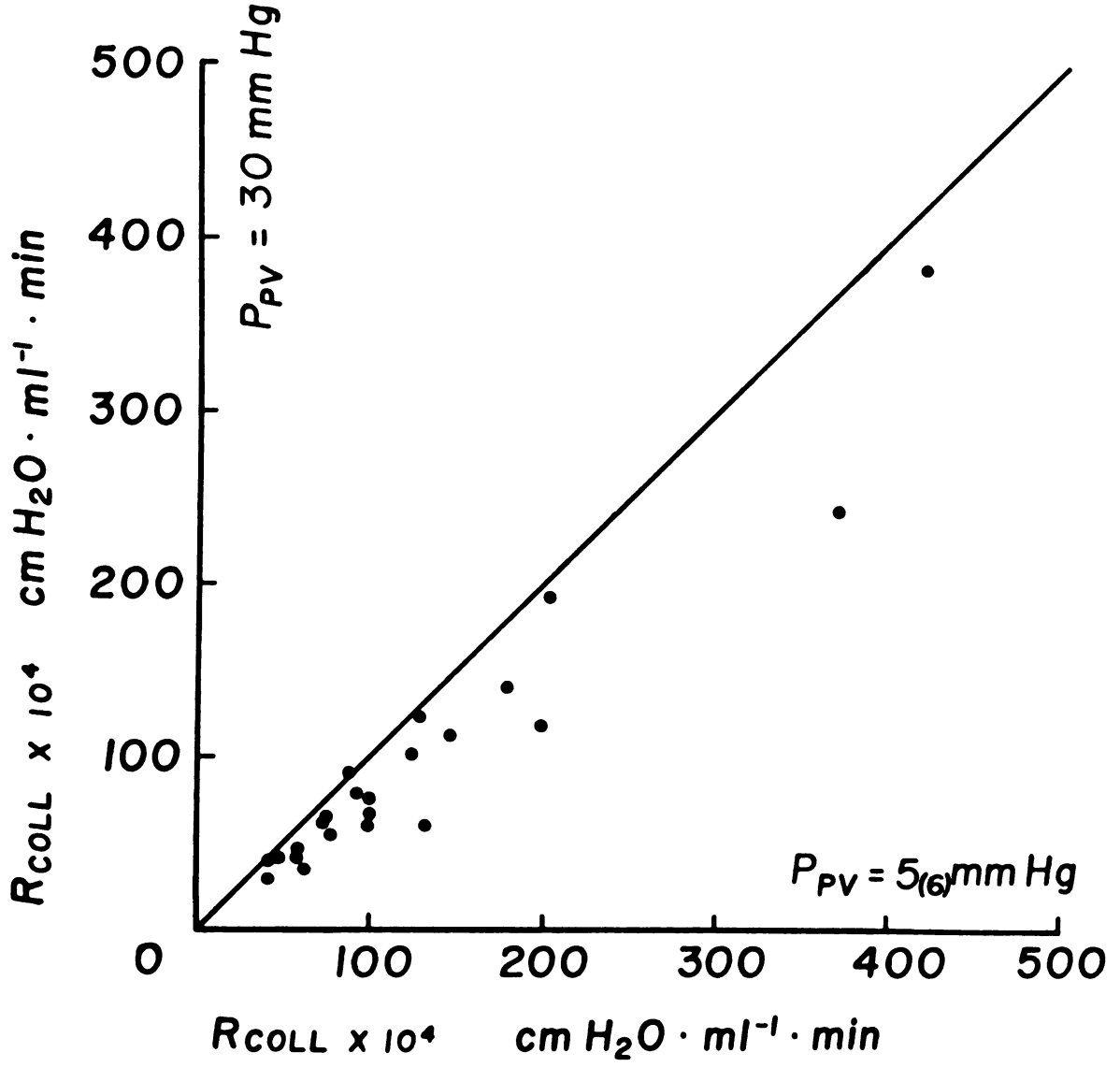

500
400
300
200
100
0
100
200
300
400
500
P_{PV} = 30 mm Hg
P_{PV} = 5(6) mm Hg
R_{COLL} x 10^4 cm $H_2O \cdot ml^{-1} \cdot min$
R_{COLL} x 10^4 cm $H_2O \cdot ml^{-1} \cdot min$

Figure 5E

C. The Effect of Pulmonary Venous Pressure on Residual Volume

Figure 6 shows the effect of Ppv on RV. Elevated Ppv's were generally associated with larger RV's while lower Ppv's resulted in smaller RV's. Statistically significant changes begin between Ppv = 10 and $5_{(2)}$ mm Hg.

D. The Effect of Pulmonary Venous Pressure on Lung Compliance

Pressure-volume curves were plotted in ten experiments. Figure 7 shows the effect of Ppv on the average compliance of the lung at the low and high portion of the pressure-volume curve (C_L and C_H, respectively). The only significant effect of Ppv on C_L exists between Ppv = 30 and $5_{(5)}$ mm Hg, while elevating Ppv is associated with decreasing C_H (and *vice versa*) beginning between Ppv = $5_{(2)}$ and 15 mm Hg and continuing throughout the protocol (see ANOVA table in Appendix B).

E. The Effect of Pulmonary Venous Pressure on Pulmonary Vascular Resistance

Table 4 indicates differences in Rvas between control Ppv's (Ppv = 5 mm Hg) and elevated Ppv's. In each case Rvas decreases at the higher Ppv. There is little or no further decrease once Ppv has reached 15 mm Hg (see ANOVA table and SNK test in Appendix B).

Figure 6

The effect of pulmonary venous pressure (Ppv) on residual volume (RV) in the isolated perfused lung (IPL). Elevating Ppv increases RV and lowering Ppv decreases RV. Stars indicate significant changes ($P < .05$). $n = 9$

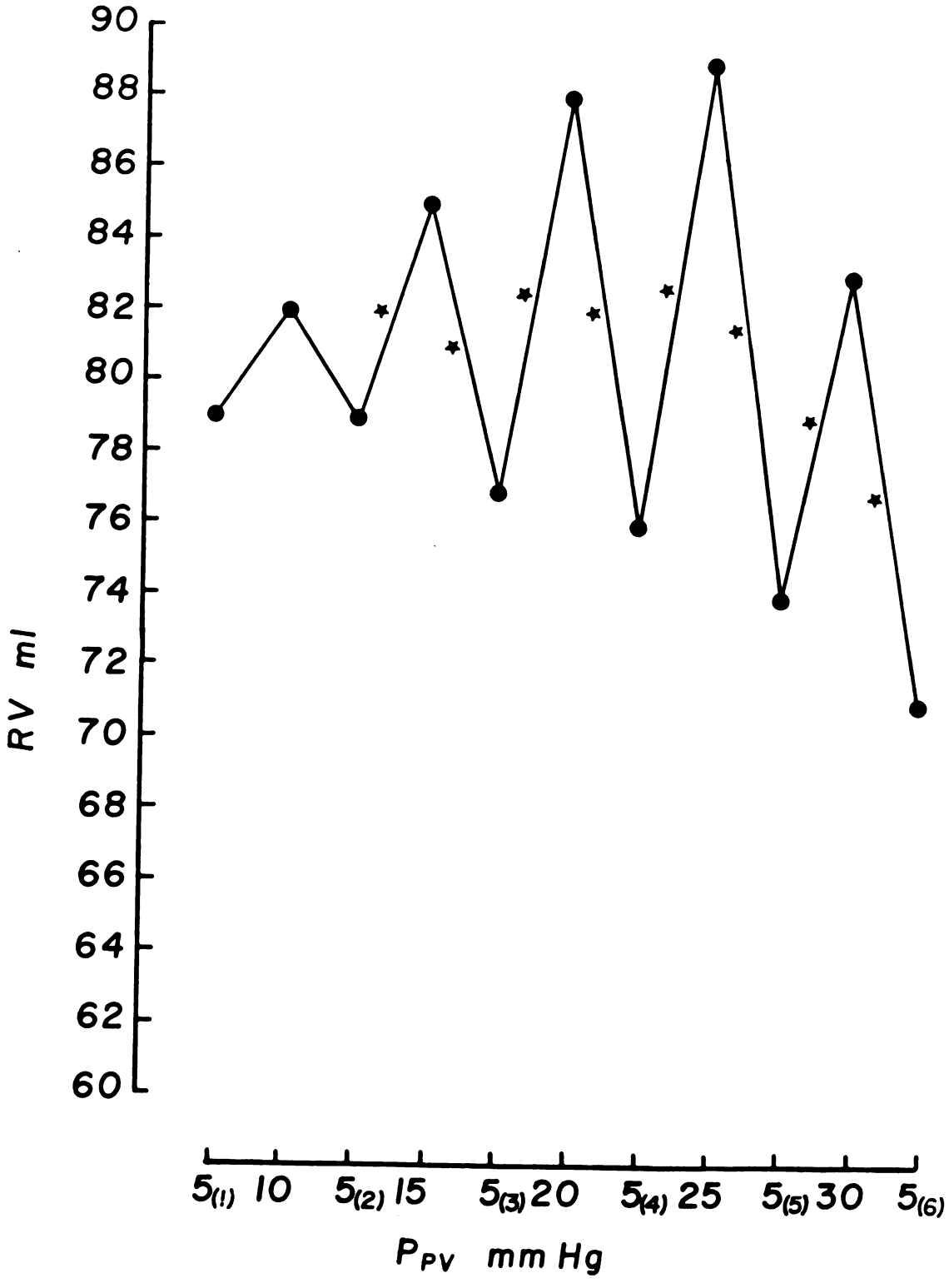

90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
RV ml
5(1) 10 5(2) 15 5(3) 20 5(4) 25 5(5) 30 5(6)
PPV mm Hg

Figure 6

Figure 7

The effect of pulmonary venous pressure (Ppv) on the compliance of the isolated perfused lung (IPL) at two different lung volumes. C_L = compliance between 40 and 50% TLC, C_H = compliance between 90 and 100% TLC. Stars indicate significant changes ($P < .05$). n = 10.

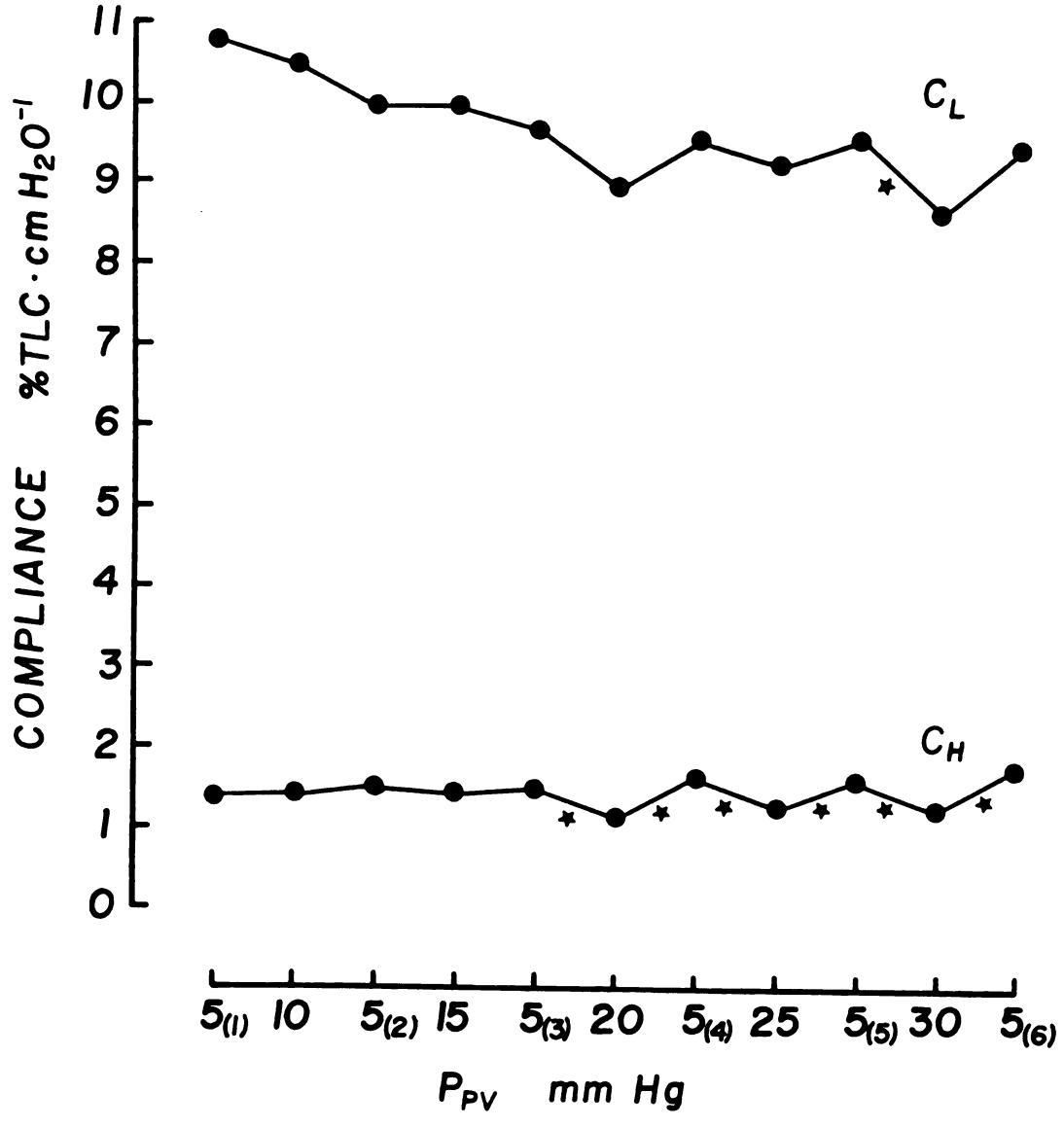

COMPLIANCE %TLC·cm H2O-1
11
10
9
8
7
6
5
4
3
2
1
0
CL
CH
5(1) 10 5(2) 15 5(3) 20 5(4) 25 5(5) 30 5(6)
PPV mm Hg

Figure 7

Table 4. The change in Rvas (mm Hg·ml^{-1}·min) between control Ppv's (Ppv = 5 mm Hg) and elevated Ppv's at P_L = 0, 2 and 4 cm H_2O.

P_L (cm H_2O)	Ppv (mm Hg)				
	$5_{(1)}$ - 10	$5_{(2)}$ - 15	$5_{(3)}$ - 20	$5_{(4)}$ - 25	$5_{(5)}$ - 30
P_L = 4	-0.017	-0.031	-0.035	-0.037	-0.038
± SE	0.002	0.004	0.006	0.006	0.007
P_L = 2	-0.016	-0.026	-0.031	-0.032	-0.037
± SE	0.002	0.005	0.005	0.005	0.006
P_L = 0	-0.016	-0.032	-0.039	-0.040	-0.039
± SE	0.006	0.007	0.007	0.008	0.009
n	11	11	11	10	10

IV. DISCUSSION

The results of the present study indicate that hypocapnia increases Rcoll in an IPL while the effects of 100% O_2 are not consistently different from 21% O_2 (21/0). Since the preparation lacks extrinsic neural supply, it is probable that CO_2 acts directly on airway smooth muscle so that hypocapnia causes constriction of airways and smooth muscle-containing collateral channels. The similar effects of 100% O_2 and 21/0 suggest the following possibilities: 1) hyperoxia has no effect on the airways, and the IPL responds only to the resultant hypocapnea. 2) Hyperoxia constricts airways in the IPL, but the effect is not seen because the airways may be maximally constricted by the hypocapnia. With the present methods, it is not possible to discern which mechanism occurs.

In most studies in which various gas mixtures were administered to either an isolated or intact lung, the gases were given only once. However, there is evidence that the quantitative response of the lung differs if the same gas is given more than once. Chen et al. (8) ventilated anesthetized dogs with several different mixtures of O_2 and CO_2 and found that if any one gas mixture was given a second time,

the amount of exhaled segmental gas volume (ESGV) was much greater than when the gas was first given. In the present studies, therefore, the three gas mixtures were each randomly given three times. As shown in Figure 3, Rcoll generally did not change with repeated exposures of the IPL to either 21/0 or 100/0. Rcoll progressively decreased, however, when measured during the second and third exposures of the IPL to 95/5. Chen et al. (8) suggest that once the lung is exposed to CO_2, the collateral channels either become larger or new channels open. This is not supported in the present study since Rcoll with either 21/0 or 100/0 changes little or not at all even after exposure to CO_2 (Figure 2).

The cause of the progressive decrease in Rcoll with repeated exposures to 95/5 remains unsolved. Sealy and Seaber (50) measured Rcoll in unperfused excised dog lungs ventilated with room air. ESGV increased only slightly during the initial 40 minutes after excision but then increased by 300% of its initial value after 4 hours. In this case, the lung may have been dying due to lack of nutrient delivery, but this is unlikely in the present studies since the lung is perfused with blood from a living animal. In speculation, it may be that CO_2 causes the release of a bronchoactive substance from the lung which produces bronchodilation. Upon repeated exposure to CO_2, airway smooth muscle may become hypersensitized to the substance and respond by

dilating in greater magnitude. Further studies are needed to clarify the mechanism.

Because the increased Rcoll in response to hypocapnea in the IPL is in agreement with the findings of other investigators (19, 21, 43, 47, 50, 51, 57) who demonstated that hypocapnea causes constriction of small airways and collateral channels, it is concluded that the IPL remains viable during the experiments and provides a suitable model for studying Rcoll. A major advantage of this preparation is lung denervation and absence of reflex changes in bronchiolar tone. In the intact preparation, lung inflation decreases vagal output and lung deflation increases vagal output to the airways, resulting in airway dilation on inflation and airway constriction on deflation (10). Measurements for Rcoll are thus affected not only by the volume history preceding the measurement but also by the lung volume at which the measurement is made.

Similarly, there is no reflex effect from changes in lung vascular volume. Increased left atrial or pulmonary venous pressure in the intact preparation activates low pressure receptors in this area and may alter the reflex vagal and/or sympathetic output to the lung (6, 7), resulting in changes in airway caliber. Also, any procedure having a chronotropic or inotropic effect on the heart influences the behavior of these receptors and reflexes by modifying atrial filling pressure.

Other advantages of the IPL preparation lie in the ability to precisely control alveolar gas composition by controlling the gas tensions in the inspired gas and perfusate, and in the ability to alter any of the pulmonary vascular parameters (Ppa, Ppv, $\dot{Q}$) without concern for maintaining a normal cardiac output as in the intact preparation.

A major difference when comparing an excised lung to an intact preparation is that in the former, Rcoll values are generally lower. In the IPL, control Rcoll at FRC ranges from 75 x 10^{-4} to 200 x 10^{-4} cm $H_2O \cdot ml^{-1} \cdot min.$, whereas in intact dog lungs at FRC Rcoll ranges from 150 x 10^{-4} to 2500 x 10^{-4} cm $H_2O \cdot ml^{-1} \cdot min.$ (57). Woolcock and Macklem (67) report Rcoll in excised unperfused human lungs near FRC to be approximately 233 x 10^{-4} cm $H_2O \cdot ml^{-1} \cdot min.$, whereas Terry et al. (56) report an average Rcoll of 510 x 10^{-4} cm $H_2O \cdot ml^{-1} \cdot min.$ in human volunteers at FRC. There are four possible explanations for these findings: 1) in excised lungs, FRC is defined as the lung volume when transpulmonary pressure equals 5 cm H_2O, and this may exceed FRC in close-chested animals which is the lung volume at the end of expiration. Since Rcoll is inversely proportional to lung volume, this would cause excised lungs to have a lower Rcoll. 2) Disruption of the normal blood supply to the IPL may cause death of airway smooth muscle. This is not believed to be a major factor, however, since: a) there is no edema in the airways at the end of the experiment,

indicating the alveolar epithelial and capillary endothelial membranes are still intact; b) gas exchange in the IPL remains satisfactory, as shown in Table 1; c) the airways change their caliber in response to variations in inspired gas mixtures, and this reaction is consistent, predictable and correlates with data from in vivo preparations. 3) Since the IPL lacks neural connections, absence of vagal tone to airway smooth muscle may cause dilation and a decrease in Rcoll. Olson (45), however, was unable to demonstrate any change in Rcoll with vagotomy. 4) The IPL is suspended from the mainstem bronchus and surrounded by atmospheric pressure, whereas intact lungs are suspended from the hilum, rest on the diaphragm and are surrounded by a negative intrapleural pressure. It is possible that these gravitational effects in the IPL cause the small airways and collateral channels to be relatively dilated, resulting in a decreased Rcoll.

Another difference between the IPL and intact lungs is that the blood perfusion rate in the IPL averaged only 16% of the in vivo rate. This is not unusual, however, since it is not possible to achieve more than 20% of the physiological flow rate without inordinately high vascular pressures and resultant pulmonary edema (N. C. Staub, personal communication). In the present studies it is felt that since Ppv is controlled, this low perfusion rate will not

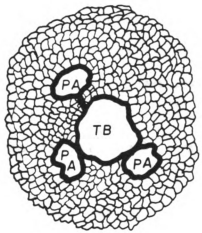
affect pulmonary vascular volume and is therefore of minor consequence.

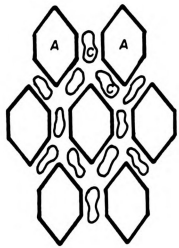
The result of the studies on the effect of Ppv on Rcoll indicate that pulmonary vascular pressures influence steady state collateral resistance when Ppv equals or exceeds 15 mm Hg, such that elevated Ppv's are associated with low Rcoll while low Ppv's are associated with high Rcoll. Residual volume is increased by high Ppv's, and lung compliance is not affected by these vascular pressures at the P_L's at which the measurements were made. The relationship between lung volume and pulmonary vascular pressure was first described by vonBasch (according to Gray et al. (18)) who suggested that pulmonary vascular engorgement produced an increase in resting lung volume or "Lungenschwellung." This observation is supported by data from excised cat and dog lungs (5, 15) where airway pressures were reported to decrease in response to elevated pulmonary vascular pressure, and also in the histological appearance of the human fetus and newborn lung (23, 24). The evidence suggests, therefore, that pulmonary vascular engorgement may exert an erectile force on the lung which increases lung volume and thereby decreases Rcoll. One possible mechanism in which this occurs is shown schematically in Figure 8. The airways are surrounded by, attached to and interdependent with alveoli, large blood vessels and their associated pulmonary capillary bed. Anything which tends to stiffen

Figure 8

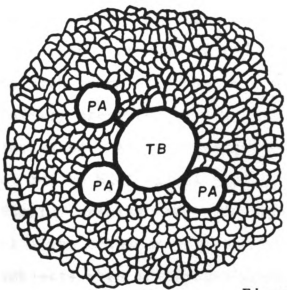
A schematic diagram showing a possible mechanism by which elevated pulmonary venous pressure (Ppv) decreases steady state collateral resistance (Rcoll). When Ppv is low, the alveolar capillaries (C) and pulmonary arterioles (PA) contain only a small blood volume, are very distensible and do not support the small airways (TB = terminal bronchiole) or the alveoli (A). When Ppv is high, the alveolar capillaries and pulmonary arterioles are engorged with blood and are expanded to their elastic limit. They are therefore more rigid and act to splint the small airways and alveoli and prevent them from collapsing.

LOW P_{PV}





HIGH P_{PV}



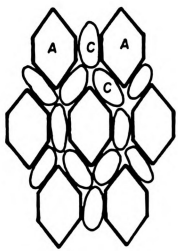


Figure 8

the parenchyma acts to support the compliant, noncartilaginous small airways and tends to prevent collapse. On the other hand, surface tension forces and creeping of smooth muscle tend to constrict small airways which do not have adequate support from the surrounding parenchyma. At low vascular pressures, the alveolar capillaries and larger vessels contain only a small volume of blood; they are therefore distensible and not supportive to the airways. At very high vascular pressures the vessels expand to their elastic limit, becoming much stiffer and tending to support and stabilize the airways. This stabilization then increases resting (residual) volume and decreases Rcoll.

The erectile effect exerted by the pulmonary vessels on the small airways may not occur at all lung volumes. Frank (15) measured airway pressure in excised cat lungs while simultaneously increasing left atrial pressure to 20-30 cm H_2O. At low lung volumes (airway pressures of less than 3 cm H_2O) airway pressure decreased in response to high vascular pressures, while at high lung volumes (airway pressures of 5 cm H_2O or more) airway pressure increased. At intermediate lung volumes (airway pressures of 3-5 cm H_2O) airway pressure did not change significantly. Similar results were also demonstrated by Goldberg et al. (17) who obtained pressure-volume curves from normal human subjects when mouthpiece pressure was at atmospheric pressure and also when mouthpiece pressure was 30 cm H_2O below

atmospheric pressure. They found in the latter case that lung compliance decreased above FRC and increased below FRC in comparison to the former and attributed its effect to the increased pulmonary vascular volume when mouthpiece pressure was -30 cm H_2O. This suggests that vascular engorgement tends to move the vessels and the airways they surround and the matrix of tissue in which they are embedded to a "resting volume" which is approximately FRC. The vasculature then resists changes in lung volume in either direction: that is, it tends to expand lungs held at lower volumes and compress lungs held at higher volumes. This may explain why in the present studies elevated Ppv's had the smallest effect at P_L = 4 cm H_2O and the greatest effect at P_L = 0 cm H_2O.

It may be argued that the increased RV at high vascular pressures is the cause of the decreased Rcoll since Rcoll is inversely proportional to lung volume (20, 22, 39, 49, 67). But there is some evidence which suggests this may not be true: 1) the changes in RV were small in comparison to the TLC of the left lung ($\Delta RV/TLC \times 100 \leq 5\%$). If this resulted in a subtle change in Rcoll, the change may be too small to be measured by the present methods. 2) In two experiments there was no change in RV throughout the entire protocol, and yet Rcoll still changed in response to changes in Ppv. 3) In portions of nearly all the experiments there were changes in RV without corresponding changes in Rcoll.

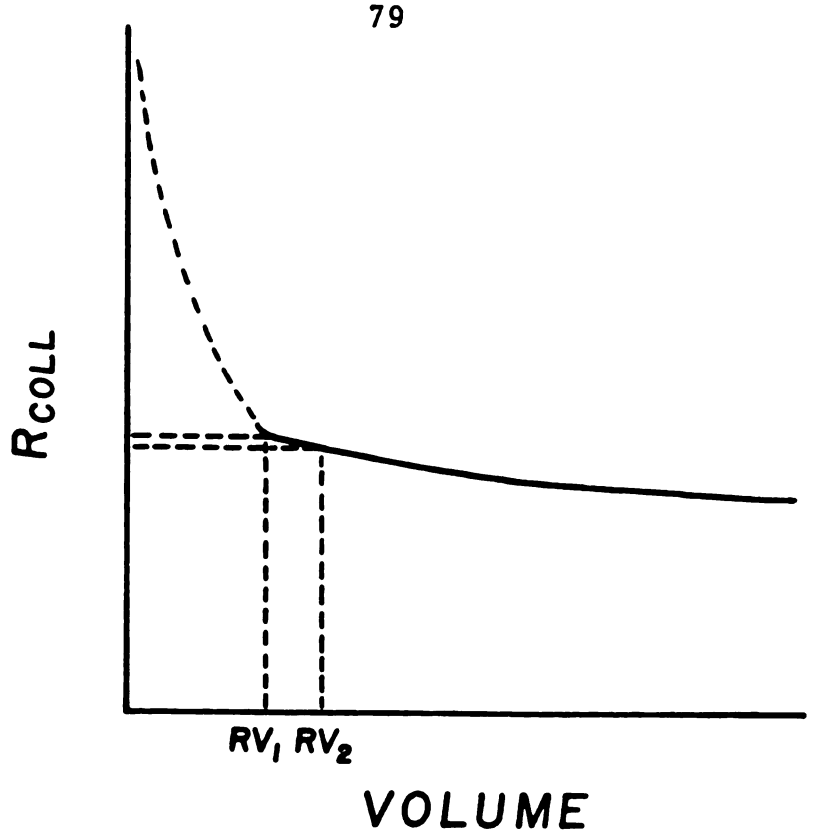
An hypothesis is that the increased RV caused by elevated Ppv's is confined mainly to the small airways (i.e., alveolar ducts) while the decreased Rcoll is due to a greater cross-sectional area of the collateral channels. If the longitudinal dimension of the channels decreased as the cross-sectional area increased, the increased RV would thus occupy only the small airways since the volume within the channels would be unchanged.

It is still possible, however, that changes in RV influence Rcoll in some dogs but not in others. The graphs in Figure 9 schematically show the relationship between Rcoll and lung volume taken from two different dogs (unpublished observations, Robinson and Sorenson, 1975). In Figure 9A a slight increase in RV (RV_1 to RV_2) has no effect on Rcoll, whereas in Figure 9B a slight increase in RV has a marked effect in Rcoll. These curves were not plotted in the present studies, so it is possible that this effect of residual volume on Rcoll was present in some of the experiments.

In consideration of the relationship between residual volume and Rcoll, the following question is raised: Where, within the isolated segment, does the change in Rcoll occur? If the increased residual volume at high Ppv's causes the decreased Rcoll, then perhaps the major site of Rcoll is in the small airways between the tip of the wedged catheter and the beginning of the collateral channels. These airways may

Figure 9

Schematic curves showing two different relationships between steady state collateral resistance (Rcoll) and lung volume. In 9A, a small change in residual volume (RV) has little effect on Rcoll. In 9B, a small change in RV has a marked effect on Rcoll.



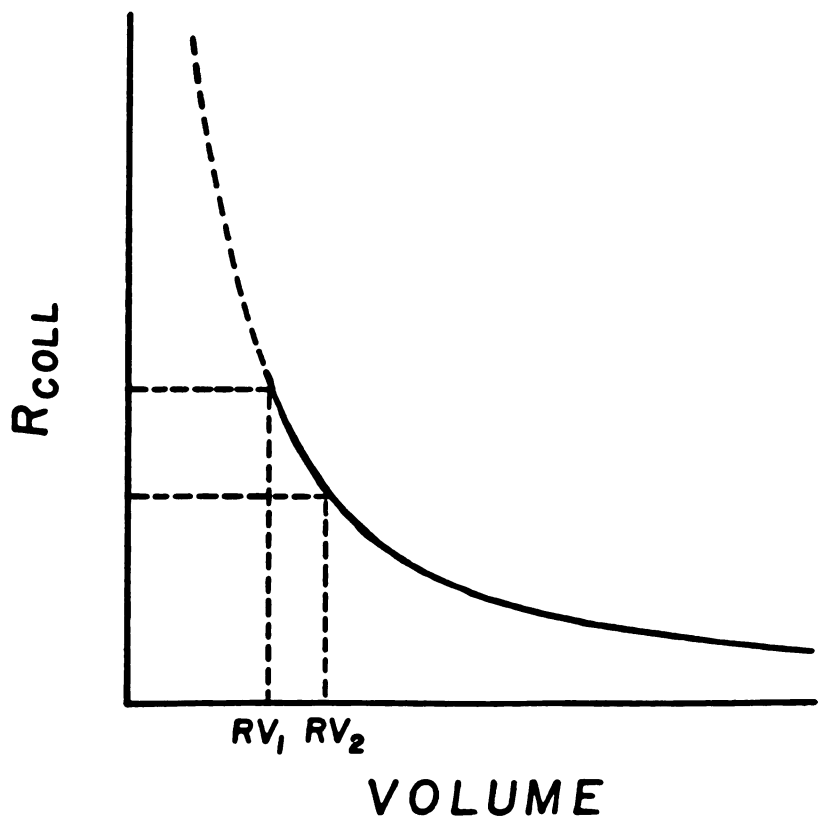


Figure 9

be dilated to contain the additional volume, and the resistance to gas flow may be decreased. Conversely, if there is no relationship between residual volume and Rcoll, then perhaps the major site of Rcoll is within the collateral channels, explained as follows: suppose the total resistance to gas flow through the isolated segment ($Rcoll^{(T)}$) is composed of two resistances in series, resistance through small airways ($Rcoll^{(1)}$) and resistance through collateral channels ($Rcoll^{(2)}$), and suppose further that $Rcoll^{(2)} >> Rcoll^{(1)}$. A small change in $Rcoll^{(1)}$ due to a change in residual volume would not effect $Rcoll^{(T)}$ since $Rcoll^{(2)}$ is the rate-limiting factor. $Rcoll^{(2)}$ would thus be the major site of resistance. It is not yet possible with the present methods to determine which mechanism occurs.

An additional consideration is the question of why significant decreases in Rcoll did not occur until Ppv had reached 15 mm Hg. A possibility is that the compliance of the pulmonary vessels remains unchanged until Ppv nears 15 mm Hg. At this point, the increased blood volume has expanded the vessels to their elastic limit, and they become stiffer and supportive to the airways. This is suggested by the data in Table 4 which shows that there are no further changes in Rvas when Ppv is raised above 15 mm Hg. The effect of Ppv on Rcoll becomes obvious only when Ppv equals or exceeds 15 mm Hg. Perhaps recruitment of pulmonary vessels occurs <u>pari passu</u> as Ppv is raised.

At Ppv = 15 mm Hg, the critical opening pressure of all the vessels may have been exceeded so that the entire population of vessels participate in supporting the airways. It is possible that both recruitment and distension of vessels occurs simultaneously and that vascular support of the airways depends on vessel compliance as well as the total number of open vessels surrounding the airways.

V. SUMMARY AND CONCLUSIONS

1) Elevated Ppv's decrease Rcoll and low Ppv's increase Rcoll.

2) Elevated Ppv has no effect on lung compliance at 50 percent TLC.

3) Elevated Ppv decreases lung compliance at 90-100 percent TLC.

4) Elevated Ppv increases RV.

5) The increased RV with elevated Ppv's may be associated with the decreased Rcoll.

6) Inspired hypocapnea increases Rcoll, probably by a direct effect on airway smooth muscle.

7) The effect of inspired hyperoxia on Rcoll is not consistently different than that of inspired normoxia.

8) The IPL remains responsive to changes in inspired gas composition during the course of the experiments.

9) The IPL provides a suitable model for studying Rcoll.

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APPENDICES

APPENDIX A

TYPICAL DATA SHEETS

APPENDIX A

TYPICAL DATA SHEET FOR ONE DOG

RESPONSE OF THE IPL TO HYPOCAPNEA AND HYPEROXIA

R_{coll} ($mm\ Hg \cdot ml^{-1} \cdot min$)	Gas								
	Group I			Group II			Group III		
	95/5	21/0	100/0	21/0	100/0	95/5	100/0	95/5	21/0
P_L = 4 ($cm\ H_2O$)	.0198	.0236	.0221	.0238	.0239	.0200	.0238	.0164	.0241
	.0186	.0241	.0224	.0213	.0240	.0173	.0233	.0168	.0234
	.0185	.0233	.0226	.0242	.0238	.0169	.0238	.0159	.0231
$\bar{x}$	.0187	.0237	.0224	.0231	.0239	.0181	.0237	.0164	.0235
± SE	.0001	.0002	.0001	.0009	.0001	.0010	.0002	.0003	.0003
P_L = 2 ($cm\ H_2O$)	.0244	.0257	.0254	.0264	.0246	.0223	.0270	.0213	.0265
	.0242	.0276	.0260	.0272	.0251	.0226	.0284	.0218	.0265
	.0242	.0260	.0261	.0257	.0268	.0224	.0281	.0205	.0264
$\bar{x}$	.0243	.0264	.0258	.0264	.0255	.0224	.0284	.0212	.0271
± SE	.0001	.0006	.0002	.0004	.0007	.0001	.0006	.0004	.0006

APPENDIX A

TYPICAL DATA SHEET FOR ONE DOG

THE EFFECT OF Ppv ON Rcoll

Rcoll ($mm\ Hg \cdot ml^{-1} \cdot min$)	Ppv (mm Hg)											
	$5_{(1)}$	10	$5_{(2)}$	15	$5_{(3)}$	20	$5_{(4)}$	25	$5_{(5)}$	30	$5_{(6)}$	
$P_L = 4$ ($cm\ H_2O$)	.0042	.0036	.0036	.0040	.0042	.0051	.0043	.0042	.0039	.0038	.0043	
	.0040	.0038	.0043	.0050	.0040	.0039	.0041	.0042	.0048	.0042	.0048	
	.0046	.0041	.0043	.0046	.0042	.0040	.0041	.0044	.0045	.0047	.0052	
$\bar{x}$	.0043	.0038	.0041	.0045	.0041	.0043	.0042	.0043	.0044	.0042	.0048	
$\pm$ SE	.0002	.0001	.0002	.0003	.0001	.0004	.0001	.0001	.0003	.0003	.0003	
$P_L = 2$ ($cm\ H_2O$)	.0077	.0075	.0086	.0063	.0077	.0068	.0085	.0064	.0079	.0061	.0093	
	.0083	.0070	.0085	.0069	.0076	.0070	.0082	.0062	.0082	.0062	.0095	
	.0083	.0075	.0085	.0073	.0087	.0068	.0081	.0065	.0082	.0063	.0109	
$\bar{x}$	.0081	.0073	.0085	.0066	.0080	.0069	.0083	.0064	.0081	.0062	.0099	
$\pm$ SE	.0002	.0002	.0000	.0003	.0004	.0001	.0001	.0001	.0001	.0001	.0005	
$P_L = 0$ ($cm\ H_2O$)	.0147	.0152	.0157	.0133	.0152	.0125	.0157	.0121	.0153	.0117	.0195	
	.0155	.0150	.0147	.0136	.0147	.0127	.0155	.0121	.0173	.0118	.0199	
	.0158	.0144	.0149	.0132	.0152	.0124	.0157	.0123	.0173	.0121	.0201	
$\bar{x}$	.0153	.0149	.0151	.0134	.0150	.0125	.0156	.0122	.0166	.0119	.0198	
$\pm$ SE	.0003	.0002	.0003	.0001	.0002	.0001	.0001	.0001	.0007	.0001	.0002	

APPENDIX B

ANOVA TABLES AND RESULTS OF COMPARISON OF MEANS OF ALL DATA

APPENDIX B

ANOVA

COMPARISON OF THE EFFECTS OF DIFFERENT GAS MIXTURES ON Rcoll

P_L = 4 cm H_2O

Source of Variation	df	SS	MS	F
Group I				
Dogs	3	.00145	.00048	1542.9*
Treatment	2	.00003	.000017	53.7*
Interaction	6	.00008	.000013	40.7*
Error	24	.000008	.0000003	
Total	35	.00157		
w = .0012	There is a significant difference between 21/0 and 95/5, and 21/0 and 100/0.			
Group II				
Dogs	3	.0013	.000448	408.3*
Treatment	2	.000049	.000024	22.3*
Interaction	6	.000029	.000005	4.4*
Error	24	.000026	.000001	
Total	35	.0014		
w = .0023	There is a significant difference between 21/0 and 95/5, and 95/5 and 100/0.			
Group III				
Dogs	3	.001216	.000405	1206.9*
Treatment	2	.000098	.000049	145.8*
Interaction	6	.000044	.000007	22.1*
Error	24	.000008	.00000034	
Total	35	.001366		
w = .0003	There is a significant difference between 21/0 and 95/5, and 95/5 and 100/0.			

ANOVA

COMPARISON OF THE EFFECTS OF DIFFERENT GAS MIXTURES ON Rcoll

P_L = 2 cm H_2O

Source of Variation	df	SS	MS	F
Group I				
Dogs	3	.001502	.000501	934.7*
Treatment	2	.000023	.000012	21.9*
Interaction	6	.000093	.000015	28.8*
Error	24	.000013	.000001	
Total	35	.001632		
w = .0018	There are no significant treatment differences			
lsd(.05)= .0012	There is a significant difference between 21/0 and 95/5, and 21/0 and 100/0.			
Group II				
Dogs	3	.001502	.000501	331.3*
Treatment	2	.000073	.000036	24.0*
Interaction	6	.000037	.000006	4.1*
Error	24	.000036	.000002	
Total	35	.001648		
w = .0025	There is a significant difference between 21/0 and 95/5, and 95/5 and 100/0.			
Group III				
Dogs	3	.001370	.000457	493.5*
Treatment	2	.000126	.000063	68.0*
Interaction	6	.000038	.000006	6.9*
Error	24	.000022	.000001	
Total	35	.001556		
w = .0018	There is a significant difference between 21/0 and 95/5, and 95/5 and 100/0.			

ANOVA

COMPARISON OF THE EFFECTS OF LIKE GAS MIXTURES ON Rcoll

P_L = 4 cm H_2O

Source of Variation	df	SS	MS	F
Group A				
Dogs	3	.00157	.00052	868.3*
Treatment	2	.00002	.00001	16.5*
Interaction	6	.00008	.00001	23.2*
Error	24	.00001	.000001	
Total	35	.00169		
w = .0018	There are no significant treatment differences.			
lsd(.05) = .0012	There is a significant difference between $21/0_{(1)}$ and $21/0_{(2)}$, and $21/0_{(1)}$ and $21/0_{(3)}$.			
Group B				
Dogs	3	.00093	.00031	404.9*
Treatment	2	.00005	.00003	34.2*
Interaction	6	.00006	.00001	12.3*
Error	24	.00002	.000001	
Total	35	.00105		
w = .0018	There is a significant difference between $95/5_{(1)}$ and $95/5_{(3)}$.			
Group C				
Dogs	3	.00152	.00051	1321.2*
Treatment	2	.000001	.0000005	1.5
Interaction	6	.000011	.000002	4.8*
Error	24	.000009	.0000004	
Total	35	.00154		

ANOVA

COMPARISON OF THE EFFECTS OF LIKE GAS MIXTURES ON Rcoll

P_L = 2 cm H_2O

Source of Variation	df	SS	MS	F
Group A				
Dogs	3	.00164	.00055	274.7*
Treatment	2	.00001	.000003	1.7
Interaction	6	.00004	.000007	3.6*
Error	24	.00005	.000002	
Total	35	.00174		
Group B				
Dogs	3	.00118	.00039	1421.2*
Treatment	2	.00008	.00004	152.3*
Interaction	6	.00007	.00001	41.2*
Error	24	.00001	.0000003	
Total	35	.00133		
w = .0010	There is a significant difference between $95/5_{(1)}$ and $95/5_{(2)}$, $95/5_{(1)}$ and $95/5_{(3)}$, and $95/5_{(2)}$ and $95/5_{(3)}$.			
Group C				
Dogs	3	.00152	.00051	723.5*
Treatment	2	.00001	.000005	7.8*
Interaction	6	.00009	.00001	21.0*
Error	24	.00002	.000001	
Total	35	.00164		
w = .0018	There are no significant treatment differences.			
lsd(.05) = .0012	There is a significant difference between $100/0_{(2)}$ and $100/0_{(3)}$.			

ANOVA

THE EFFECT OF Ppv ON Rcol1

P_L = 4 cm H_2O

Source of Variation	df	SS	MS	F
Ppv = $5_{(1)}$ through Ppv = 20 mm Hg				
Dogs	10	.00227	.00023	71.5*
Treatment	5	.00003	.00001	2.12
Error	50	.00016	.000003	
Total	65	.00246		
Ppv = $5_{(4)}$ through Ppv = $5_{(6)}$ mm Hg				
Dogs	9	.00242	.00027	52.6*
Treatment	4	.00004	.00001	2.19
Error	36	.00018	.00001	
Total	49	.00265		

ANOVA

THE EFFECT OF Ppv ON Rcoll

P_L = 2 cm H_2O

Source of Variation	df	SS	MS	F
Ppv = $5_{(1)}$ through Ppv = 20 mm Hg				
Dogs	10	.00570	.00057	68.0*
Treatment	5	.00007	.00001	1.7
Error	50	.00042	.00001	
Total	65	.00619		
Ppv = $5_{(4)}$ through Ppv = $5_{(6)}$ mm Hg				
Dogs	9	.00622	.00069	41.6*
Treatment	4	.00016	.00004	2.44
Error	36	.00060	.00002	
Total	49	.00698		

ANOVA

THE EFFECT OF Ppv ON Rcoll

P_L = 0 cm H_2O

Source of Variation	df	SS	MS	F
Ppv = $5_{(1)}$ through Ppv = 20 mm Hg				
Dogs	5	.00606	.00121	178.9*
Treatment	5	.00006	.00001	1.7
Error	25	.00017	.00001	
Total	35	.00628		
Ppv = $5_{(4)}$ through Ppv = $5_{(6)}$ mm Hg				
Dogs	3	.00251	.00084	312.9*
Treatment	4	.00007	.00002	6.5*
Error	12	.00003	.000003	
Total	19	.00262		

lsd(.05) = .0023 There is a significant difference between $5_{(5)}$ and 25 mm Hg, Ppv = $5_{(5)}$ and 30 mm Hg and Ppv = $5_{(6)}$ and 30 mm Hg.

ANOVA

THE EFFECT OF TIME ON THE IPL

ALL Ppv's = 5 mm Hg

Source of Variation	df	SS	MS	F
Ppv = $5_{(1)}$, $5_{(2)}$, $5_{(3)}$ mm Hg				
Dogs	27	870426.0	32238.0	43.0*
Treatment	2	3496.1	1748.1	2.3
Error	54	40517.2	750.3	
Total	83	914438.7		
Ppv = $5_{(4)}$, $5_{(5)}$, $5_{(6)}$ mm Hg				
Dogs	23	997252.0	43358.8	41.6*
Treatment	2	4637.5	2318.8	2.22
Error	46	47947.8	1042.34	
Total	71	1049837.3		

ANOVA

THE EFFECT OF Ppv ON RV

Source of Variation	df	SS	MS	F
Group I				
Dogs	8	22456.6	2807.1	69.6*
Treatment	5	865.9	173.2	4.3*
Error	40	1612.4	40.3	
Total	53	24934.9		
lsd(.05) = 5.0				
Group II				
Dogs	7	9899.9	1414.3	11.8*
Treatment	4	1738.1	434.5	3.6
Error	28	3362.3	120.1	
Total	39	15000.3		
lsd(.05) = 9.4				

ANOVA

THE EFFECT OF Ppv ON C_L

Source of Variation	df	SS	MS	F
Group I				
Dogs	9	36.3	4.0	2.8*
Treatment	5	19.7	3.9	2.7*
Error	45	65.0	1.4	
Total	59	121.0		
w = 1.6				
Group II				
Dogs	7	55.8	8.0	26.6*
Treatment	4	4.7	1.2	3.9*
Error	28	8.4	0.3	
Total	39	68.9		
w = 0.8				

Note: In both ANOVA's, the significant treatment F indicates there is a significant difference between means within the Groups. However, in Group I there are no significant differences between adjacent Ppv's, and in Group II the only significant difference between adjacent Ppv's is between Ppv = $5_{(5)}$ and 30 mm Hg.

ANOVA

THE EFFECT OF Ppv on C_H

Source of Variation	df	SS	MS	F
Group I				
Dogs	9	4.5	0.5	16.7*
Treatment	5	0.5	0.1	3.3*
Error	45	1.4	0.03	
Total	59	6.5		
w = 0.23	There is a significant difference between Ppv = $5_{(3)}$ and 20 mm Hg.			
Group II				
Dogs	7	1.9	0.3	19.3*
Treatment	4	1.4	0.4	25.0*
Error	28	0.4	-.014	
Total	39	3.7		
w = 0.16	There is a significant difference between the means of all adjacent Ppv's.			

ANOVA

THE EFFECT OF Ppv ON Rvas

Source of Variation	df	SS	MS	F
P_L = 4 cm H_2O				
Dogs	9	.009	.00100	12.5*
Treatment	4	.003	.00075	9.5*
Error	36	.003	.00008	
Total	49	.015		
P_L = 2 cm H_2O				
Dogs	9	.008	.00089	16.8*
Treatment	4	.003	.00075	12.0*
Error	36	.002	.00006	
Total	49	.0013		
P_L = 0 cm H_2O				
Dogs	3	.003	.00100	20.2*
Treatment	4	.002	.00050	8.6*
Error	12	.001	.00008	
Total	19	.005		

Results of SNK Test Comparing Rvas Means ($P < .05$)

Ppv (mm Hg)	$5_{(1)}$-10	$5_{(2)}$-15	$5_{(3)}$-20	$5_{(4)}$-25	$5_{(5)}$-30
$\bar{x}$ (P_L = 4)	-0.017	-0.031	-0.035	-0.037	-0.038
$\bar{x}$ (P_L = 2)	-0.016	-0.026	-0.031	-0.032	-0.037
$\bar{x}$ (P_L = 0)	-0.016	-0.032	-0.039	-0.040	-0.039