Korean J. Vet. Res., Vol. 12, No. 1 (1972) 37—50

Studies of Alveolar-Mixed Venous CO_2 and O_2 Gradients in the Rebreathing Dog Lung

Chang Jun Yu, D.V.M.

College of Agriculture, Kyungpook University

Introduction

In the first paper of this series gas composition in the continuously rebreathing dog lung was compared with the gas tesions in blood entering and leaving the lung. However, because of some uncertainty with the pulmonary vein sampling technique these measurements have been omitted in the present study and only compared alveolar gas with mixed venous blood, while altering the conditions more extensively than before. Five factors have been examined which could alter CO_2 and O_2 differences between blood and gas (a) time, the possible deterioration of the preparation over the working period, (b) plasma pH changes, (c) alteration in blood flow and distribution, (d) failure of gas compositions in bag to reach steady state, and (e) failure of CO_2, bicarbonate reactions in blood to reach equilibrium.

Materials and Methods

The author used the same basic dog preparation discussed in the first paper and the same sampling and analytical techniques, but did not cannulate any pulmonary vein, and permitted the whole left lung to rebreath.

(a) In the time studies the author used 4 dogs. After setting up the preparation and obtaining 6 pairs of gas, blood readings, the rebreathing bag was removed and allowed the animal to rest for 2 to 3 hours. The bag was next connected to the right lung, in order to examine any possible differences between the lungs that might have been caused, for example, by damage to the left lung during surgery, and obtained 6 more gas and blood samples. Finally, the bag was reconnected to the left lung and took a last set of 6 gas, blood samples. In all cases, the author waited 15 minutes after connecting the bag before started sampling.

(b) The author altered plasma pH either by inducing a respiratory acidosis or metabolic acidosis or alkalosis. In the former cases the author varied $P\bar{v}\ co_2$ by allowing the dog to breath air or a CO_2 air mixture with his normal right lung from a closed circuit (Fig. 1). The main volume of this circuit was provided by a spirometer, and gas was continuously circulated with a rotary pump. P_{CO_2} in the circuit was monitored with a rapid infra red analyser (Beckman LBI) and was a balance between the rate of production by the dog,and the rate of absorption by a soda lime column fitted with an adjustable bypass in parallel, to vary gas flow through it. O_2 was continuously added, and its level monitored with a paramagnetic analyser (Beckman C).

In 4 dogs, groups of 6 readings were made breathing air, and the air CO_2 mixture, the order in which the two mixtures were used was alternated between dogs. Metabolic acidosis and alkalosis were induced in 6 dogs by infusing HCl or $NaHCO_3$ solutions through the femoral vein. After a control set of 6 readings, an infusion was made either of 20ccs/Kg body weight of 0.5N $NaHCO_3$ solution (3 dogs) or 50ccs/Kg of 0.1N HCl in saline(3 dogs) at a rate of 1 to 3 drops a second. Six more sets of readings were made following a 50 minute recovery period at the end of infusion. In 2 dogs rendered acidotic, 40 ccs/Kg of $NaHCO_3$ were then administered, while in one alkalotic

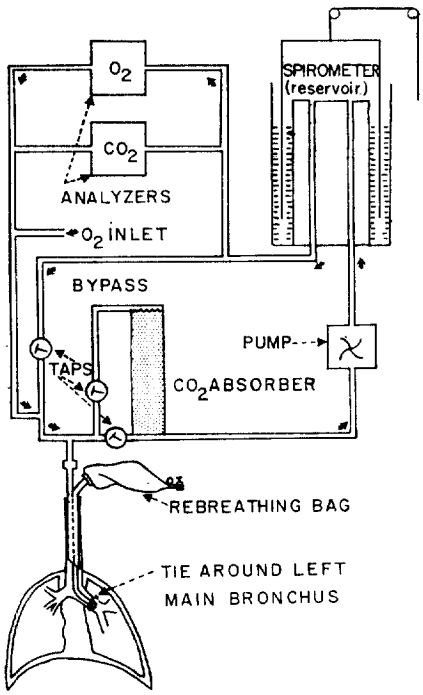

Fig. 1. Circuit used to produce elevated P_{CO_2} levels in the preparation.

100ccs/Kg of HCl solution were given, and further sets of 6 readings were made after another recovery period. One dog, treated initially with acid, received only 40ccs/Kg, as this was sufficient to produce a very large fall in plasma pH.

(c) Blood flow to the left lung was varied in 4 dogs by restricting the left pulmonary arterial blood flow. The artery was isolated and divided, and "L" shaped cannulae were inserted into the cut ends of the artery. The long limbs of the cannulae served to convey the blood outside the chest, where it flowed through a short interconnecting Tygon tube. Flow was measured with an electromagnetic flow meter (Medicon Microflow, model K 2000 with 4mm flow through probe) and was restricted by applying a screw clamp to the tube. It proved impractical to restore the flow rate to control levels following restriction, so that 6 control readings were done first (in one dog only 3) followed by 6 readings at reduced flow.

A logical extension of these flow studies is to examine the effects of total interruption of pulmonary flow. The author was particularly interested to see what effects lung tissue metabolism and the bronchial circulation would have on gas composition in the bag during the maneuver. Interruption was achieved in 4 dogs, by placing around the left pulmonary artery a plastic loop, the free end of which ran through a plastic tube to the outside. The loop could be tightened or released at will without necessitating the reopening of the chest. A set of 6 readings was made with the artery patent, then 6 following occlusion, and finally 6 more with the artery patent again.

The distribution of blood in the lungs was varied in 4 dogs by changing the posture of the body. Two animals were laid left side down (rebreathing lung well perfused, other lung poorly perfused), 6 sets of readings were made, then the animal was turned over (rebreathing lung poorly perfused) and the process was repeated. In the other dogs the tests were done in the reverse order.

(d) The author considered the rate of O_2 equilibration in the lung. A steady CO_2 level in the rebreathing bag is achieved very rapidly after connecting it to the left lung. Preliminary studies made with the rapid infra red analyser, continuously monitoring the bag concentration, showed that a steady state was reached within 5 minutes, as indicated by a lack of perceptible fluctuation in P_{CO_2} throughout the breathing cycle. The time needed to achieve a steady O_2 level in the lung is likely to be greater than for CO_2 because of the lower O_2 diffusing capacity. The author was anxious to meassure this O_2 equilibration time both to assure that sufficient time was allowed at the beginning to reach steady conditions (some of the measurements of P_{AO_2} in the first study appeared to have been made prematurely) and also because this would give an estimate of the rate of gas exchange in the rebreathing lung, both with the pulmonary flow intact and occluded.

Four dogs were used, prepared in the usual way, with the addition of the pulmonary artery occluder and femoral arterial cannulation. After achieving a steady state of rebreathing, 2 sets of gas, mixed venous and femoral arterial blood samples were taken and analysed, then the dog was switched to a bag containing 750ccs of an air, CO_2 mixture (the concentration was matched to the previously measured P_{ACO_2} to avoid any possible interreaction between the

process of equilibration of the gases). Samples of gas were taken at one minute after connection to the new bag, and at 1.5 minute intervals thereafter, until 13 minutes after commencement, while mixed venous and femoral blood samples were taken both at 3 and 8 minutes. Gas samples were analysed immediately, and the blood samples after the last gas analysis; only P_{O_2} was measured in the interests of saving time on the gas and blood samples collected during the 13 minutes period. Finally, two more sets of gas and blood from the two sites were taken, and a full analysis was done on them.

The whole procedure was repeated after occluding the pulmonary artery, except that no mixed venous blood samples were taken, as these were deemed irrelevant here. In the first dog studied, no control samples were taken after the 13 minute period. Two dogs were given a N_2, CO_2 mixture to rebreath in the occlusion experiments rather than air, CO_2 mixtures used in the other tests. In two dogs, the experiment with the patent artery was performed first, in the others the occlusion experiment preceded it.

(e) The author examined the possible role of delayed CO_2, bicarbonate equilibrium in the blood, both by attempting to exaggerate it, by inhibiting carbonic anyhydrase, and by trying to reduce it by increasing the time available for the process to come to completion. Blood drains from tissues with widely different metabolic rates, so that some redistribution of CO_2 and HCO_3 must occur when the blood is mixed in the right heart. It is possible that this process has not been completed during the usual transit time through the pulmonary bed.

In 4 dogs the author obtained a set of 6 control readings, then administered a dose of 50mg/kg of acetazolamide to inhibit carbonic anhydrase (as also used by Cain and Otis, 1960)[3]. The author then waited an hour and made 6 more sets of readings. Since $P\bar{v}co_2$ rises considerably after carbonic anhydrase inhibition, the control readings were made at an elevated P_{CO_2}, using the circuit shown in Fig. 1, to minimize any effects a simple change in CO_2 level would produce by itself.

The author varied the right heart-left lung circulation time in 4 dogs using the preparation with the "L"

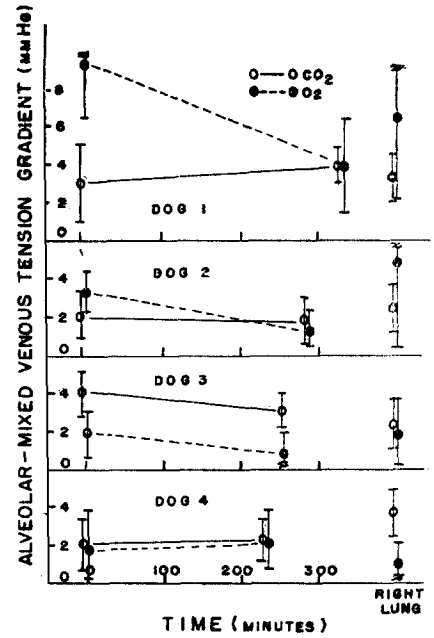

Fig. 2. Control experiment. Effects of time, and alternating the lung used to rebreathe, on CO_2 and O_2 gradients. Time measured between mid points of each group of readings. Test on right lung done respectively 265, 210, 185 and 160 minutes after first set of readings (points represent mean of six readings, bars represents standard deviations).

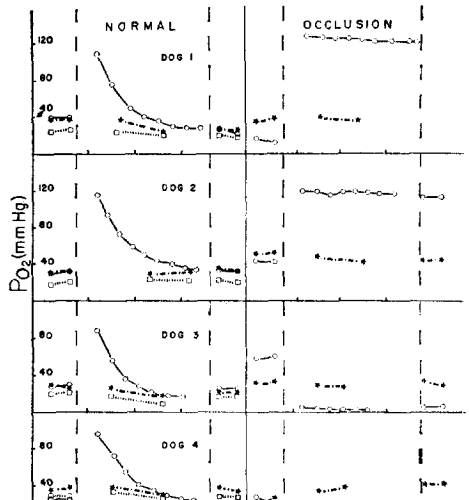

Fig. 3. Control experiment. Changes in blood gases, bicarbonate and rectal temperature with time in experiment shown in Fig. 2 (each point represents mean of 6 readings).

shaped cannulae described above, again measuring blood flow with the electromagnetic flow meter, and varying the circulation time by connecting the cannulae with short or long Tygon tubes. The long tube had a capacity of 100ccs more than the short one and $\frac{1}{2}$ inch bore tubing was used to add as little extra resistance as possible to the system. In 2 dogs, three sets of readings were made with the short tube, 6 wit the long and 3 more with short tube again. In the other dogs the same plan was used starting with the long tube.

Results

For most experiments, the author presents the alveolar-mixed venous gradients for each gas (ΔP_{CO_2} and ΔP_{O_2}) but only give other measurements, such as $P\bar{v}_{CO_2}$, $P\bar{v}_{O_2}$, pH and HCO^-_3 when they are relevant to the discussion.

(a) Data from the control study are presented in Figs. 2 and 3. ΔP_{CO_2} and ΔP_{O_2} values, (means of 6 readings with S.Ds shown by bars), are plotted against time in Fig. 2. This time represents the intervla between the first and second sets of measurements (being estimated from the mid point in time of each set of readings), it varied between 235 and 330 minutes. Values obtained with the right lung re-breathing are shown at the extreme right of this figure (the time at which these tests were measured is given in the footnote to the Figure).

Mean values of the gradients were always positive (P_{ACO_2} and P_{AO_2} were higher than the corresponding mixed venous blood values), the range being 2-4 mm Hg for ΔP_{CO_2} and 1-9mm Hg for ΔP_{O_2}. It is immediately obvious from these ranges and from the S. Ds derived from individual sets of readings that ΔP_{O_2} is much more variable (as shown also in the first paper). In neither case, however, were these any systematic trends with time, nor was there a consistent difference between data obtained using the left or right lung.

The author has also related the mean values of $P\bar{v}_{CO_2}$, $P\bar{v}_{O_2}$, HCO^-_3 and rectal temperature obtained from this experiment, to time (Fig.3.). The first three parameters declined with time, while the last one increased, but the changes were all small except for the fall in $P\bar{v}_{CO_2}$ observed in dog 1.

(b) The author expressed the data on the effects of respiratory acidosis in two ways. The author first compared indivual $P\bar{v}_{CO_2}$ and $P\bar{v}_{CO_2}$ values for the 4 dogs (Fig.4). If ΔP_{CO_2} was zero, that is if both readings were the same, the point would lie on the dotted line of identity, but almost all the values lay above this line, indicating a positive ΔP_{CO_2}. The author fitted regression lines to this data (solid lines) and found in each case that ΔP_{CO_2} increased as $P\bar{v}_{CO_2}$ rose, with calculated values of 3.00 and 6.78 at blood CO_2 levels of 30 and 60 mm Hg. The author wished to see if this effect was significant, so compared the mean value for the four regression slopes with the slope of the line of identity (that is 1.0) and found a significant difference at the 0.025 level.

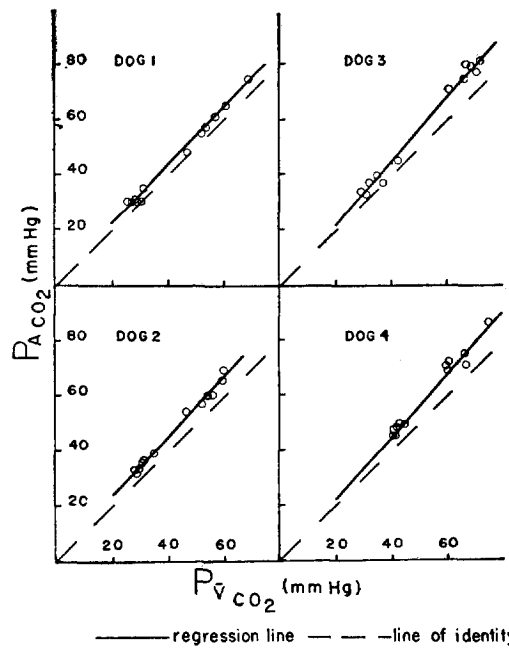

Fig. 4. Effects of varying CO_2 level. Comparison of alveolar and mixed venous CO_2 pressures(Points represent individual readings).

The author also compared the ΔP_{CO_2} and ΔP_{O_2} values from these experiments with plasma pH (Fig. 5). ΔP_{CO_2} (top Figure) varies inversely with pH, and the author has fitted a linear y on x regression line to the pooled data. This yields predicted values of ΔP_{CO_2} of 9.55 and 0.92mm Hg at pH levels of 7.00 and 7.60 respectively (coefficient of variation 0.57, slope

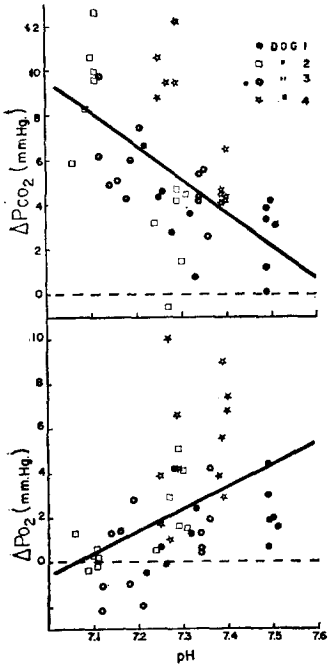

Fig. 5. Effects of varying CO_2 level. Relationship of ΔP_{CO_2}(top)and ΔP_{O_2}(bottom) and plasma pH. Same experiments as in Fig. 6(points represent individual readings).

significantly different from zero at 0.001% level). There was some tendency for dogs with lower plasma HCO_3^- values to yield data lying to the left of the regression line; the mean HCO_3^- values for the 4 animals were 24.9, 17.1, 18.8 and 27.5 mEq/L respectively.

ΔP_{O_2} decreased as pH fell with hypercapnia (Fig. 5, bottom). A linear y on x regression line on the pooled data yielded predicted mean values of −0.51 and +5.36 mm Hg at pH levels of 7.00 and 7.60 respectively (coefficient of variation 0.44, slope significantly different from zero at the 0.005% level).

The relationship between ΔP_{CO_2} and non-respiratory changes in plasma pH is shown in Fig. 6 (left). Each point represents the mean of the 6 readings in one set, while the lines and their arrows indicate the direction in which plasma pH was changed. There are no consistent changes with alteration in pH; this work was done without attempting to keep the P_{CO_2} level constant, so the author estimated what effect this P_{CO_2} variation would have by taking the mean ΔP_{CO_2} and $P\bar{v}_{CO_2}$ values for each animal and adjusting

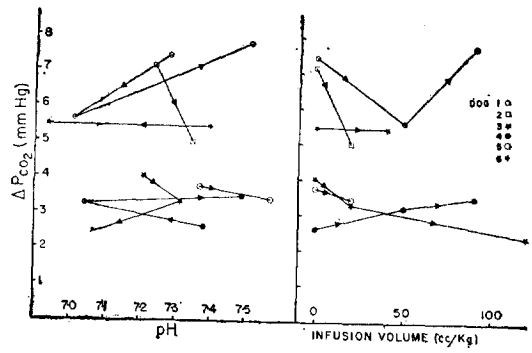

Fig. 6. Effects of acid and bicarbonate infusion. Relationship of P_{CO_2} and plasma pH(left) and infused liquid volume(right) (points represent mean of 6 readings).

the ΔP_{CO_2} values to correspond to a constant $P\bar{v}_{CO_2}$ value, using the relationship between the indices (Fig. 4), but this did not alter the overall picture, so that the author has presented the original unadjusted data. It is possible that the large volumes of liquid that were infused to produce these pH changes, would themselves affect ΔP_{CO_2}, so the author has also compared the gradient with the infused liquid volume (Fig. 6, right), but has been unable to show any consistent trends here either.

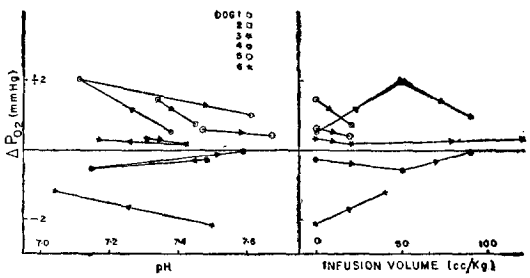

Fig. 7. Effects of acid and bicarbonate infusion. ΔP_{O_2} data from experiment shown in Fig. 6, presented in the same way.

A similar presentation for the ΔP_{O_2} data (Fig. 7) also failed to reveal a consistent relationship with either plasma pH or infused liquid volume under these conditions. It should be noted in these particular

experiments that the mean O_2 gradient exceeded 2mm Hg only in one set of readings, and that for 2 dogs the mean value was always negative.

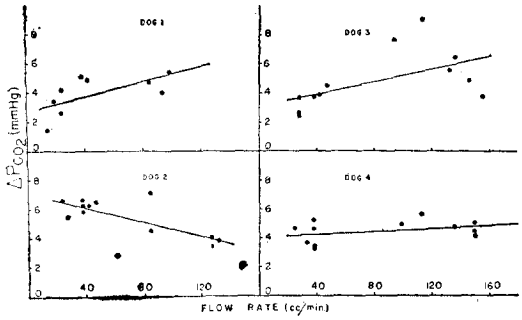

Fig. 8. Effects of varying blood flow. Relationship of ΔP_{CO_2} and blood flow through rebreathing lung (points represent individual readings).

(c) In 3 out of 4 dog ΔP_{CO_2} fell as pulmonary blood fow decreased (Fig. 8), but these effects were not significant at the 5% level ($p<0.1$, 0.1 and 0.3 respectively). Dog 2 showed a rise in ΔP_{CO_2} as flow rate fell, an effect which was significant at the 2% level. In no case did the estimated value of P_{CO_2} at zero flow fall below 2 mm Hg. Close inspection of the data in dogs 1 and 3, however, suggests there is an inflection in the data at a flow rate of about 40 ccs/minute, and it is possible that in these two animals ΔP_{CO_2} would really be zero if the blood flow were interrupted. $P\bar{v}CO_2$ remained fairly constant throughout these experiments except in dog 1, where it rose when the blood flow was reduced (this was probably coincidental). ΔP_{O_2} tended to become less positive as blood flow decreased in 3 out of 4 animals (Fig. 9), but the effect was only significant in dog 2 ($p<0.001$, for the other dogs $p<0.6$, 0.2 and 0.7 respectively). There was again a wide difference between the mean levels of ΔP_{O_2}, while most of the readings in dogs 1 and 2 were negative.

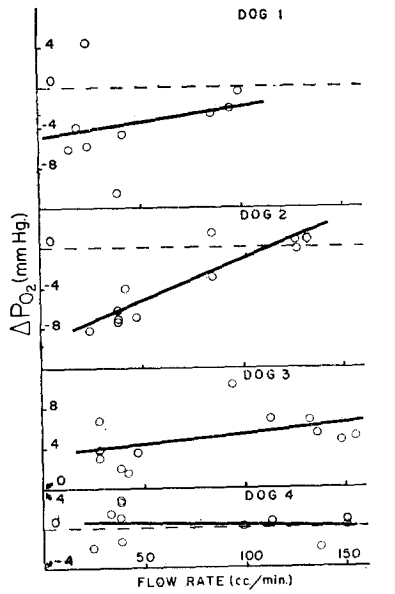

Fig. 9. Effects of varying blood flow. ΔP_{O_2} data from experiment shown in Fig. 8, presented the same way.

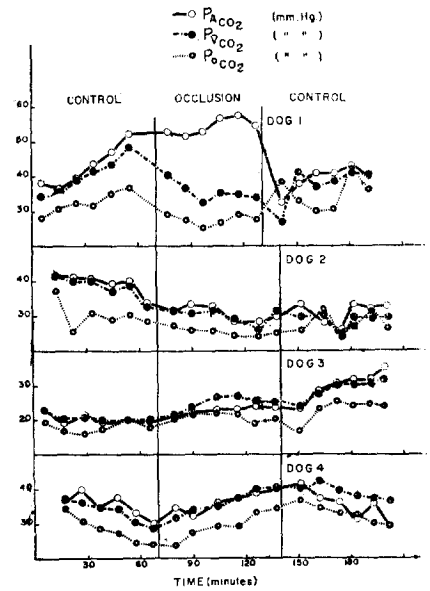

Fig. 10. Effects of pulmonary arterial occlusion on alveolar and blood gas pressures. Data plotted against time before, during and after occlusion (points represent individual readings).

The author has presented the data from the occlusion experiments by plotting individual readings of gas tension in alveolar, femoral arterial, and mixed venous samples, against the time of sampling, for CO_2 (Fig. 10) and for O_2 (Fig. 11). The $P\bar{v}$-Pa CO_2 gradient remained fairly constant throughout each experiment apart from an occasional aberrant reading, but its magnitude varied from dog to dog (P_{aco_2} was naturally the lower reading because of the ventilation

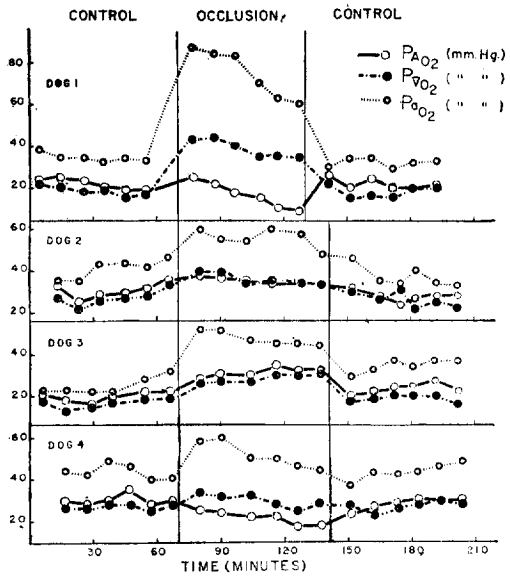

Fig. 11. Effect of pulmonary arterial occlusion. O_2 data from experiment shown in Fig. 10, presented the same way.

occurring in the right lung: the constant gradient suggests a steady state was achieved in each animal). There were no consistent trends in either these, or the P_{ACO_2} readings, upon occlusion or release of the left pulmonary artery.

Close inspection of Fig. 10 (dogs 3 and 4) reveals that P_{ACO_2} was frequently less than $P\bar{v}_{CO_2}$. This finding was so unusual in the study (apart from an occasional individual reading) that the author has tabulated these data separately (Table 1) giving mean values of ΔP_{CO_2}, ΔP_{O_2} and $P\bar{v}_{CO_2}$, $P\bar{v}_{O_2}$ for the control periods before and after occlusion (the gradients became meaningless if the mixed venous blood can no longer enter the lung, and the author has shown $P\bar{v}_{CO_2}$ and $P\bar{v}_{O_2}$ values during occlusion in Figs. 10 and 11, simply as parameters to indicate the condition of the animal). In dog 3, first control set, $P\bar{v}_{CO_2}$ was exceptionally low, and the author should expect ΔP_{CO_2} to be minimal, although not actually negative as found here. The author explain the more negative mean value observed in dog 4 during the second control set either, except possibly as being the result

Table 1. Control Data, Before and After Occlusion of Pulmonary Artery

	ΔP_{CO_2}		$P\bar{v}_{CO_2}$		ΔP_{O_2}		$P\bar{v}_{O_2}$	
	Before	After	Before	After	Before	After	Before	After
Dog 1	2.4	1.5	40.5	37.7	3.1	3.6	18.4	18.0
S. D.	1.7	3.2	5.2	5.5	2.1	3.2	2.0	3.1
Dog 2	1.1	2.2	38.2	28.6	2.9	1.7	27.4	25.8
S. D.	0.6	2.4	3.1	2.2	1.1	5.3	4.3	4.7
Dog 3	−0.5	1.3	21.0	28.9	3.8	4.9	16.1	18.4
S. D.	1.0	1.4	1.0	2.7	1.5	1.3	2.3	2.0
Dog 4	1.7	−3.7	33.7	38.8	3.3	1.8	26.4	25.9
S. D.	2.0	3.5	3.5	2.2	2.5	3.2	1.2	2.3
Mean	1.2	0.3	33.3(5)	33.5	3.3	3.0	22.1	22.0

Before: Usual control readings.
After: Measurements made after releasing occlusion which had been maintained for an hour.
All measurements in mm Hg.

of an artefact following pulmonary arterial occlusion. However, this seems unlikely since other measurements were normal in this experiment, suggesting that the extreme conditions had not affected the readings.

P_{aO_2} (Fig. 11) always increased upon occlusion and fell on release; this is to be expected since occlusion prevents blood being shunted through the non-ventilated rebreathing left lung. These changes are strong evidence that tightening the loops around the artery causes drastic reduction or complete cessation of blood flow. Similar, though small changes, were observed with $P\bar{v}_{O_2}$. In 3 dogs P_{AO_2} fell during the occlusion period, and in two rose upon release, but in dog 3 the changes were in the reverse direction.

The author has been able to use this O_2 data to give an indication of possible changes in cardiac output, and provide an estimate of the relative blood flow through the two lungs, and the theoretical bronchial flow, if this system is assumed to be source of O_2 needed to maintain ΔP_{O_2} positive. The author calculated the blood O_2 saturation (Radiometer BGCI with extended cursor) corresponding to the mean values of $P\bar{v}_{O_2}$, P_{AO_2} and P_{aO_2} (the latter being assumed to be the same as the end pulmonary capillary tension $P\bar{c}_{O_2}$) in Table 2. If the O_2 consumption of the body remains constant any change in cardiac output will be reflected in alterations in the Sa-$S\bar{v}$ gradient. However, there were no systematic changes, the mean values for all 4 dogs were 31.75, 31.25 and 32.75 before, during and after occlusion respectively, so the author assumes cardiac output remains constant.

Table 2. Estimation of Arterial-Venous Oxygen Saturation Gradients, Relative Blood Flow Through the two Lungs and Relative Magnitude of Bronchial Circulation Assuming this is to be Responsible for the Oxygen Gradient

	$\bar{v}$	a	A	a-$\bar{v}$	Ratio 1	Ratio 2
Dog 1 c	20.0	58.5	27.0	38.5	0.88	0.22
o	60.0	92.5	—	32.5	—	—
c	18.5	51.5	26.0	33.0	1.24	0.29
Dog 2 c	41.5	70.0	48.0	28.5	0.60	0.30
o	62.5	87.0	—	24.5	—	—
c	43.0	68.0	47.0	25.0	0.76	0.19
Dog 3 c	22.5	49.5	33.0	27.0	1.52	0.64
o	46.5	80.5	—	34.0	—	—
c	25.0	65.0	38.0	40.0	0.39	0.48
Dog 4 c	40.5	73.5	48.5	33.0	0.21	0.32
o	46.5	80.5	—	34.0	—	—
c	33.0	66.0	37.0	33.0	0.44	0.14
				Mean	0.75	0.32

All estimates of O_2 saturation based on means of 6 readings of P_{O_2}.
c: control tests made before and after occlusion.
o: tests made during pulmonary arterial occlusion.
a-$\bar{v}$: arterial-venous O_2 saturation gradient.
Ratio 1=(Sao-Sac)/(Sac-$S\bar{v}c$) an estimate of the blood flow through the rebreathing lung (shunted blood) relative to that through the ventilated lung.
Ratio 2=(S_{Ac}-$S\bar{v}c$)/(Sac-S_{Ac}) an estimate of the bronchial systemic flow if this supplies all the O_2 needed to keep ΔP_{O_2} positive.

The arterial systemic O_2 saturation during occlusion, Sao represents blood which has been equilibrated in the ventilated lung alone. If the author assumes that blood leaving this lung always has the same value of Sao, then Sac, the systemic arterial saturation in normal control conditions, will be the result of mixing bloods with O_2 contents, corresponding to values of $S\bar{v}c$ from the rebreathing lung and Sao. The rate of blood flow through the rebreating lung to that through the ventilated lung is, therefore, given by the ratio (ratio 1 in Table 2) (Sao-Sac)/(Sac-$S\bar{v}c$).

The values ranged from 0.21 to 1.52, but there was little difference in the mean values from the two control periods, 0.80 and 0.71 respectively,and the overall mean of 0.75 corresponds to a flow of about 43% of the cardic output through the rebreathing lung.

If the O_2 needed to maintain a positive ΔP_{O_2} is supplied by the bronchial circulation, the author can see that the maximum change in O_2 tension in this bed is Pa-P_A, since blood P_{O_2} would not be expected to fall below alveolar levels. The O_2 absorbed by the pulmonary blood would cause a change of tension in this bed of P_A-$P\bar{v}$(at these low O_2 levels $P\bar{c}_{O_2}$ will be closely similar to P_{AO_2}). The blood flows in the

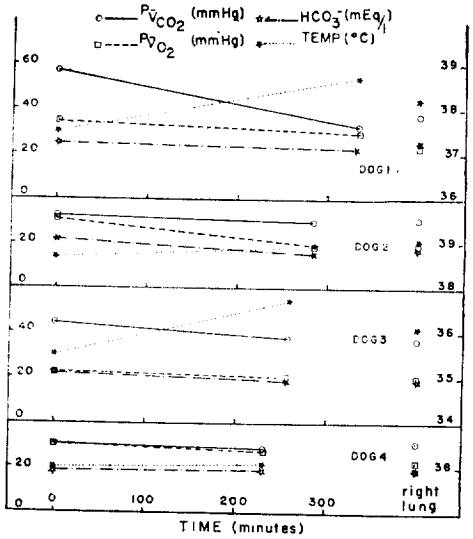

Fig. 12. Rate of O_2 equilibrium at start of rebreathing. Changes in P_{O_2} in 750cc bag, connected to dog previously rebreathing from another bag (control values) and changes in blood gas measurements. Tests done either in normal conditions (left) or after occlusion of pulmonary artery(right). Control values not plotted on the time scale(points represent individual readings).

bronchial and pulmonary circuits will, by this theory, be inversely proportional to the change in O_2 content, or saturation in the blood in each system (ratio 2, Table 2), i.e. bronchial flow/pulmonary flow= $(S_{AC}-S\bar{v}c)/(Sac-S_{AC})$. The ratio ranges from 0.14 to 0.64, mean 0.32, equivalent to a bronchial flow of 24% of the cardiac output (this argument ignores the O_2 requirements of the lung tissue which would increase the necessary bronchial flow still further).

(d) The data from the O_2 equilibrium experiments are presented in Fig. 12. Individual values of P_{AO_2}, Pao_2 and $P\bar{v}o_2$ were plotted aganist time, measured from the point when the bag was connected. This graph is flanked by data from the two control periods (this latter data is not plotted on the same time scale). With the pulmonary flow intact (left side of Figure) P_{AO_2} always returned to control values within 10 to 13 minutes in an exponential fashion; the author obtained half life values for this process using a log plot of 2.0, 4.5, 1.8 and 2.1 minutes respectively, a mean of 2.6 minutes for the 4 dogs studied. Pao_2 was normally elevated at the beginning of this rebreathing phase, probably because of the extra O_2 passing into the blood from the left lung. When the pulmonary artery was occluded, P_{AO_2} and Pao_2 hardly altered over the 13 minute period, while in the dogs where the N_2, CO_2 mixture was used, the alveolar O_2 level even tended to fall to zero (there was a residual amount of O_2 left in the lungs at the begin-

Table 3. Postural Changes

	ΔPco_2		$P\bar{v}co_2$		ΔPo_2		$P\bar{v}o_2$	
	Up	Down	Up	Down	Up	Down	Up	Down
Dog 1	2.00	4.15	36.2	48.2	3.32	3.22	23.5	30.4
S. D.	2.54	1.73	1.5	1.5	1.22	2.08	4.8	4.0
Dog 2	3.08	3.27	50.6	68.0	0.70*	3.37	23.6	21.0
S. D.	3.00	1.86	3.2	4.7	1.46*	2.91	2.9	5.2
Dog 3	2.60	4.32	36.5	50.0	3.73	1.52	26.5	28.1
S. D.	1.93	1.62	1.6	4.7	2.06	2.50	2.4	3.0
Dog 4	1.65	2.55	32.6	28.6	3.43	3.18	20.5	23.3
S. D.	0.97	2.32	1.6	0.9	1.45	1.40	3.3	0.7
Mean	2.33	3.57	39.0	48.7	2.80	2.82	23.5	25.7

Up=Rebreathing lung uppermost,poorly perfused.
Down=Rebreathing lung downwards, well perfused.
* one missing reading.
All readings in mm Hg.

ning of rebreathing which mixed with the N_2 in the bag).

The posture experiments are summarized in Table 3. In each dog ΔP_{CO_2} was greater when the rebreathing lung was well perfused (down), the mean difference in reading between the postures being 1.24mm. However, $P\bar{v}_{CO_2}$ also rose in these conditions in 3 out of 4 animals, by a mean of 9.7mm, due presumably to a reduction of perfusion in the ventilated lung. The author cann ot therefore distinguish any specific effects of posture from those occurring through changes in P_{CO_2} level (as shown in Fig.4). Neither ΔP_{O_2} or $P\bar{v}_{O_2}$ altered consistently with posture change.

(e) The acetazolamide experiments are tabulated in Table 4. ΔP_{CO_2} increased by an average of 3.03mm in the 4 dogs after carbonic anhydrase anhydrase inhibition, while $P\bar{v}_{CO_2}$ remained almost constant. Individual changes in ΔP_{CO_2} on inhibition were quite variable, however, ranging from 0.17 to 7.49 in dogs 2 and 3 respectively. There were no consistent changes in ΔP_{O_2}

The experiments where the right heart-left lung circulation time was varied, are summarized in Table 5. The long tube itself imposed an extra delay of 45 seconds, and since at the same time, the mean flow rate fell from 152 to 131ccs/min, the actual delay

Table 4. Carbonic Anhydrase Inhibition

	ΔP_{CO_2}		$P\bar{v}_{CO_2}$		ΔP_{O_2}	
	Control	Diamox	Control	Diamox	Control	Diamox
Dog 1	5.22	7.47	58.7	70.3	0.42	0.78
S. D.	1.91	2.11	2.1	5.3	3.89	2.51
Dog 2	8.52	8.69	75.9	71.5	1.75	1.03
S. D.	1.58	1.43	5.8	5.3	2.40	1.09
Dog 3	6.35	13.84	67.9	69.4	3.60	0.60
S. D.	1.81	1.49	3.5	5.9	1.89	1.31
Dog 4	8.27	10.49	69.9	60.1	0.07	0.22
S. D.	1.88	1.37	3.0	2.3	0.80	0.65
Mean	7.09	10.12	68.1	67.8	1.46	0.66

Control readings before inhibition, dog ventilated with CO_2, air mixture.
Diamox reading after inhibition, dog ventilated with air.
All reading in mm Hg.

Table 5. Alteration of Right Heart-Left Lung Circulation Time

	ΔP_{CO_2} (mm Hg)		ΔP_{O_2} (mm Hg)		Flow Rate (ccs/min)		Extra delay in long tube (seconds)
	Short	Long	Short	Long	Short	Long	
Dog 1	5.25	4.67	0.12	0.23	158	133	44
S. D.	0.69	1.67	1.07	1.33	14	9	
Dog 2	3.88	2.80	0.15	−0.48	163	135	44
S. D.	0.58	1.55	0.47	1.33	14	13	
Dog 3	3.83	3.30	0.58	−0.27	132	121	48
S. D.	0.86	1.69	1.20	1.80	32	16	
Dog 4	3.27	2.22	−1.33	−1.92	155	136	43
S. D.	0.83	1.44	1.21	1.94	18	50	
Mean	4.06	3.25	−0.12	−0.61	152	131	45

Short: shortest connection between cannulae.
Long: tube of 100cc capacity added between cannulae.

imposed by this tube was greater still. ΔP_{CO_2} decreased with the long tube in all dogs, the mean fall being 0.76mm, and ΔP_{O_2} decreased in 3 out of 4 animals, the mean fall being 0.40mm.

In one experiment using the long tube, pairs of blood samples were taken simultaneously from both ends of the tube. The mean values of P_{CO_2} on a set of 6 pairs of samples differed only by 0.1mm Hg, so it seems unlikely that any CO_2 was lost by diffusion through the walls of the tube. Temperature measurements made with a thermistor probe in two experiments however, showed that blood temperature fell from between 0.5 to 1.0°C during its passage through the long tube, despite the fact that the tube was insulated to reduce heat loss. This effect would reduce gas tensions in the blood perfusing the lungs, and it is of the right magnitude to account for the observed fall in ΔP_{CO_2} and ΔP_{O_2}.

Discussion

The scope of this present discussion is limited to evaluating these experimental results and comparing them with those other workers, the theoretical implications are explored of in the last paper of this series.

The main characteristics of the CO_2 gradient are its persistence and its consistency. In a allowing the lung 15 minutes to rebreath before sampling, the author has enabled the gas composition in the bag to approach that of the mixed venous blood so which should has been reached a steady state. However, the CO_2 gradient persists, and can be demonstrated for as long as the author cares to make measurements. There is the one unlikely possibility that the preparation has deteriorated, so that its capacity for gas exchange is grossly impaired, and in this case the gradient would merely reflect excess CO_2 held passively by the lung-bag system. This idea can be speedily discounted both by the rapid gas exchange demonstrated in the equilibrium experiments above, and by the fact that changes in the gas composition in the bag faithfully mirror random changes in mixed venous blood gas tensions. The gradient exists therefore, despite considerable gas exchange potential.

The consistency with which the author found a positive CO_2 gradient is striking. The author only observed negative mean values of ΔP_{CO_2} gradient is striking. The author observed negative mean values of ΔP_{CO_2} on three occasions, two recorded in Table 1, and one on a dog with frank pulmonary edema. This is out of a total of 48 dogs used in studies presented in this and in the preceding paper, and a similar number used in preliminary studies, or in experiments terminated prematurely for technical reasons.

Another feature of these studies was the paucity of factors which affect ΔP_{CO_2}; the author was only able to find three, change in P_{CO_2} level, carbonic anhydrase inhibition, and with much less certainty, reduction in pulmonary blood flow. The author can now review the experimental results in light of this summary.

The control experiments served not only as a check on the consistency of the results, but as an indication of the stability of the preparation which, in view of the extensive surgery, might have been expected to deteriorate rapidly. The changes observed in Fig. 3 in $P\bar{v}_{CO_2}$, $P\bar{v}_{O_2}$, HCO_3^- and rectal temperature, suggest that while with time, the depth of anesthesia decreased, the status of gas exchange deteriorated, some metabolic acids accumulated, and the animal recovered from the heat loss incurred during the opening of the chest, that all these effects were very small, while in any case the design of most of the experiments would have minimized the influence of these effects. This stability of the preparation is also borne out by the slight changes in the Sa_{O_2}-$S\bar{v}_{O_2}$ gradient, (as shown in Table 2) which suggests cardiac output, remained constant over a period of at least three hours.

The plasma pH studies suggest that while ΔP_{CO_2} appears to be proportional to $P\bar{v}_{CO_2}$ it is unaffected by pH changes of nonrespiratory origin. These results are consistent with those of Gurtner et al (1969)[5]. However, the measurements of ΔP_{CO_2} give values which are only about half of those found by these other workers.

The author also wished to study the effect of varying P_{O_2} on ΔP_{CO_2}, but this was not practical with the preparations, since gas composition in the bag is closely related to that in mixed venous blood, and

the author found that it was impossible to vary $P\bar{v}o_2$ very much even when the animal was given pure O_2 or a low O_2 mixture to breath.

The author has difficulty in reconciling the observations on the interrelationship of ΔPco_2 and blood flow to those of Gurtner et al[5]. They found that if cardiac output was reduced below about one half of normal by hemorrhage, that ΔPco_2 decreased, and that it disappeared at flows of about fifth of control values. Their technique did not give the direct blood flow to the rebreathing lung, but only the total flow, and the flow to the rebreathing lung might fluctuate considerably at the lowest cardiac outputs when the circulatory system would be near collapse. In these conditions too, many of the body tissues would be experiencig ischemia and this might introduce effects which could influence the measurements to an unknown degree. The author varied blood flow to the rebreathing lung independently of cardiac out put and measured it directly, but as can be seen from Figs. 8 and 9 these flow rates were low. If the author assumes a cardiac output in the anesthetized dog of about 120ccs/minute/kg body weight (based on data collated by Altman, 1959)[1] the author can estimate a total pulmonary blood flow of about 1450ccs/minute for a 12kg animal. The rebreathing lung is relatively hypoxic and this may reduce its share of the total flow (Arborelius et al. 1967)[2]. The experiments based on the occlusion experiments suggest it is about 43% of the total (Table 2) or about 500~700ccs/minute, 3 or 4 times of the maximum values. This reduction in the flow studies was probably due to the kind of cannulae the author used, but despite this limitation these experiments have allowed to study the most interesting part of the ΔPco_2, blood flow relationship. The similarity of ΔPco_2 values in this experiment to those found in the other studies, suggest moreover that the gradient would be little changed if the blood flow was varied between normal values and the highest values obtained here. The results do not finally exclude the possibility that ΔPco_2 may sometimes become zero at low flow rates, but they do show that this does not occur in all animals. These results differ quantitatively and qualitatively from those of Gurtner et al[5].

There still remains the possibility that the abnormally low flow rates used in this experiment have caused deterioration of the lung by causing the accumulation of CO_2 from lung tissue metabolism, and excessive removal of O_2. The occlusion experiments seem to exclude this possibility, since even with cessation of pulmonary flow there was no consistent rise in CO_2 or fall in O_2 in the rebreathing bag.

Another study germa ne to the blood flow question is the relationshipof ΔPco_2 to infused liquid volume (Fig. 6 right). If the author concludes that ΔPco_2 is independent of nonrespiratory plasma pH changes, the author can assumes that the main effect of infusion of these liquids was to increase plasma volume and, with it, cardiao output. This argument implies that ΔPco_2 is independent of flow rate at high cardiac outputs.

The posture experiment, which explored the possibility that ΔPco_2 could be effected by the distribution of perfusion, showed this factor to be unimportant also. The change in posture certainly altered the balance of perfusion between the two lungs, as the change in $P\bar{v}co_2$ showed, but ΔPco_2 seemed unaffected. In summary, therefore, it appears that ΔPco_2 is unaffected by changes in the magnitude or distribution of blood flow, except at very low flow rates, when it may possibly sometimes show a marked decrease.

The increase that the author obser ed in ΔPco_2 upon acetazolamide infusion, is less than that observed by Cain and Otis(1960)[3], the difference between the two studies being about 2mm. These workers did not attempt to control $P\bar{v}co_2$, however, and it rose nearly 20mm after infusion of the drug. If the author applies the corrections for $P\bar{v}co_2$ changes derived from the respiratory acidosis experiments(Fig. 4) to the earlier data, the two studies are seen to be in close agreement.

The experiment of varying the heart-lung circulation time suggested that lack of equilibrium within the blood could not be the crucial factor in explaining the gradient. The author will consider this question in more detail in the theoretical paper.

The data on the O_2 gradient is tantalizing. It is important to consider this, as it seems only to have been reported before by De Burgh Daly et al(1968)[4] and the technique allows it to be measured with equal facility to ΔPco_2. In many cases ΔPo_2 was positive,

and was greater than could be explained by known experimental errors. When present, the gradient apparently persisted with time like ΔP_{CO_2}, though it was more variable.

The observation that ΔP_{O_2} was proportional to plasma pH in the hypercapnia experiments, while it was unaffected by infusion of acid or bicarbonate, suggests an inverse relationship between ΔP_{O_2} and $P_{\bar{v}CO_2}$ or ΔP_{CO_2}. Other evidence of physiological factors influencing this gradient, was its tendency towards negativity at low blood flow rates in some dogs. This suggests a greater extraction of O_2 from pulmonary blood at low flow rates to meet the needs of lung tissue metabolism.

The mean values of ΔP_{O_2} proved, however, to be very variable between animals, and were in many cases negative, as in the infusion of acid and bicarbonate studies(Fig. 7). Though this gradient is labile, it does not seem, however, to result from simple experimental errors; during 2 of the occlusion studies in which there were positive ΔP_{O_2} values, the author simultaneously compared blood, taken from the animal and tonometered with 2, 3 and4 % O_2 mixtures, with the gas mixture employed. The author found close agreement in the in vitro blood, gas comparison while there was a sizeable gradient in the in vivo dog measurements.

The author cannot explain the variability in ΔP_{O_2} measurements at present, and this casts a little doubt on the real existence of a positive gradient. It does appear, however, that this is a problem which should be re-examined in more detail.

Summary

Another comparison of alveolar gas pressures, in a continuously rebreathing dog lung, with pulmonary arterial (mixed venous) blood, again showed alveolar pressures to be the higher for CO_2 and usually O_2 (positive ΔP_{CO_2} and ΔP_{O_2}). ΔP_{CO_2} was almost invariably positive, it was independant of time and of plasma pH changes produced by acid or bicarbonate infusion, but proportional to blood CO_2 level. It was seemingly little affected by the distribution or magnitude of blood flow nor did it result from failure of CO_2 equilibrium within the blood, but it did rise with carbonic anhydrase inhibition. ΔP_{O_2} was more variable and sometimes negative, particularly at low blood flow rates. It seemed independant of time, and plasma pH changes, apart from an inverse relationship with that resulting from CO_2 changes. It existed despite considerable potential for gas exchange, and was unaffected by inhibition of the CO_2 reactions.

Acknowledgments

The author is indebted to many people for ideas and discussion of this work, and in particular to Dr. Arthur B. Otis, Dr. Andrew R. Guyatt and to Mrs. Berta Lutherer for technical assistance. This work was carried out while under the tenure of a fellowship awarded by the University of Florida.

References

1. Altman, P.L: Hanbook of Circulation. W.A.D.C. Tech. Report, 1959. 59-539:80.
2. Arborelius, M.J.R., S-E. Lindell and R.O. Malmborg: Zonal distribution of pulmonary blood flow during unilateral hypoxia. Acta Med. Scand. Suppl. 1967. 472:168.
3. Cain, S.M. and A.B. Otis: Effect of carbonic anhydrase inhibition on mixed venous CO_2 tension in anesthetizeddogs. J. Appl. Physiol., 1960. 15: 390.
4. Deburgh Daly, I., C.C. Michel, D.J. Ramsay and B.A. Waaler: Conditions governing the pulmonary vascular response to ventilation hypoxia and hypoxaemia in the dog. 1968.
5. Gurtner, G.H., S.H. Song and L.E. Farhi: Alveolar to mixed venous P_{CO_2} difference under conditions of no gas exchange. Respir. Physiol., In press, 1969.

反覆呼吸을 하는 犬肺에서의 肺胞와 混合靜脈血液의 CO_2 및 O_2의 傾斜度에 대한 硏究

兪 昌 濬
慶北大學校 農科大學

肺胞 gas와 肺動脈(混合靜脈血液)만의 比較實驗郡에 있어서도 亦是 炭酸 gas 張力 때로는 酸素까지도 肺胞氣體의 張力이 더욱 높았다 (positive ΔP_{CO_2} 및 P_{O_2}). ΔP_{CO_2}는 酸 또는 bicarbonate 注入으로 야기 되는 血漿 pH變化 및 時間에 따른 變異性이 없이 항상 陽性을 보였으나, 血中炭酸 gas張力의 크기에 比例하였다. 또 ΔP_{CO_2}는 血流量의 大少 및 分布에 別로 영향 받지 아니하고 血液內에서 炭酸 gas平衡의 未達로부터 오는 것도 아니었으나 炭酸脫水酵素 (carbonic anhydrase) 作用을 抑制할때 增加되었다. ΔP_{O_2}는 더욱 變異性이 컸으며 特히 낮은 血流速度에 있어서는 때때로 negative 現像을 나타내기도 하였다. ΔP_{O_2}도 또한 時間 및 血漿 pH 變化와 無關하게 獨立的인 것이었으나, 炭酸 gas 張力의 變化로 일어나는 結果와는 反比例의 關係가 있었다. ΔP_{O_2}도 gas交換이 일어날 수 있는 상당한 크기의 壓差를 주어도 存在하였고, 炭酸 gas 反應의 抑制에 依하여도 영향받지 아니 하였다.