Arterial–Alveolar CO_2 Gradient after Cardiac Resuscitation in the Dog

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Arterial–alveolar carbon dioxide tension gradients ($a\text{-}AD_{CO_2}$) were studied in six dogs before, during, and after the heart was resuscitated from cardiac arrest produced by KCl infusion. The $A\text{-}AD_{CO_2}$ was 9.2 mm Hg five minutes after the heart had been resuscitated, compared with the mean value of 1.6 mm Hg in the control period. During the next hour, this gradually decreased to 3.2 mm Hg. Several possible explanations for the increase in $a\text{-}AD_{CO_2}$ are discussed, and it is provisionally concluded that pulmonary blood flow is uneven for a period after circulatory arrest. Increase in Pa_{CO_2} after cardiac resuscitation, however, may be due partly to the increased release of CO_2 from the tissue, caused by metabolic acidosis.

INCREASE in the arterial–alveolar P_{CO_2} gradient ($a\text{-}AD_{CO_2}$) or alveolar deadspace have been found in several experimental and clinical conditions. They may be caused by administration of inhalational anesthetics such as cyclopropane, halothane, and nitrous oxide,[1, 2] and may occur during deliberate hypotension,[3, 4] positive-pressure ventilation,[5, 6] or shock.[7, 8] Such an increase generally has been interpreted as indicating that pulmonary perfusion in relation to ventilation becomes more uneven in these conditions, the efficiency of carbon dioxide elimination from the lung being decreased.[9, 10, 11, 12]

The present study indicates that an increase in $a\text{-}AD_{CO_2}$ also occurs when the heart is resuscitated from experimental cardiac arrest. It was prompted by the observation that the patient occasionally experiences a high Pa_{CO_2} even with a presumably-sufficient degree of minute ventilation when resuscitated from cardiac arrest. This was recently reported in the literature also.[13] Analysis of the experimental data indicates that the residual effect of cardiac arrest on the distribution of pulmonary blood flow may be a cause of the high Pa_{CO_2}.

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Methods

Six mongrel dogs weighing 9 to 17 kg (mean 11.4 kg) were anesthetized with thiopental sodium (pentothal), 20 mg/kg. Anesthesia was maintained with chloralose, 100 mg-kg, given as a constant infusion of 0.2 per cent solution in 0.85 per cent saline solution during the next hour. Both femoral arteries were cannulated with polyethylene catheters, which were used for arterial blood pressure recording and blood sampling. Ventilation was maintained by means of an oral endotracheal tube using a Harvard constant-volume respirator. Gallamine, 20 mg/kg, was injected intramuscularly. Respiratory rate was maintained at 20/min, while tidal volume was adjusted to achieve moderate hyperventilation (table 1). Small amounts of oxygen were added to the inspired air to maintain Pa_{O_2} in the normal range during thoracotomy. The oxygen concentration of the inspired gas was constant for each dog, varying from dog to dog, but never exceeding 40 per cent throughout the study. Alveolar gas was sampled continuously at a rate of 200 ml/min via a polyethylene catheter placed in the endotracheal tube. The sampling site was at the tip of the endotracheal tube. Esophageal temperature, monitored by means of an electric thermometer, was maintained between 35.0 and 38.5° C using an electric blanket. A third catheter was introduced into the left ventricle through the right common carotid artery: correct position was achieved by monitoring the pressure recording. This catheter was used for injection of KCl solution to produce cardiac arrest.

TABLE 1. Results of Arterial Blood and Alveolar Gas Analyses, Six Dogs

	Condition	pHa	P_{aCO_2} (mm/Hg)	P_{aO_2} (mm/Hg)	P_{ACO_2} (mm/Hg)	a-AD_{O_2} (mm/Hg)
Dog 1	control	7.34	23.0	93.0	21.6	1.6
	5 min	7.20	30.0	95.0	22.6	7.4
	10 min	7.23	32.7	84.5	27.2	5.5
	15 min	7.23	26.5	73.0	22.1	4.4
	30 min	7.38	24.4	70.4	20.1	4.3
	60 min	7.45	23.4	78.9	20.1	3.3
Dog 2	control	7.45	22.5	87.2	22.6	0.1
	5 min	7.01	35.2	98.4	28.5	6.7
	10 min	7.06	32.6	92.5	28.2	4.4
	15 min	7.12	28.6	122.0	25.1	3.5
	30 min	7.21	25.8	115.0	23.7	2.1
	60 min	7.32	25.2	102.0	24.2	1.0
Dog 3	control	7.28	29.6	143.8	26.0	3.6
	5 min	7.02	45.6	83.8	36.0	9.6
	10 min	7.14	36.0	85.2	28.1	7.9
	15 min	7.15	35.6	88.1	28.0	7.6
	30 min	7.16	32.8	101.0	25.5	7.3
	60 min	7.28	31.4	132.0	25.8	5.6
Dog 4	control	7.40	30.6	84.0	28.4	2.2
	5 min	7.09	47.6	93.5	35.2	12.4
	10 min	7.13	44.0	93.5	31.4	12.6
	15 min	7.22	40.8	111.5	29.2	11.6
	30 min	7.24	35.3	104.0	27.7	7.6
	60 min	7.29	31.9	85.5	27.5	4.4
Dog 5	control	7.40	24.4	125.0	24.8	0.0
	5 min	7.15	31.4	92.5	22.5	8.9
	10 min	7.14	27.8	115.0	23.2	4.6
	15 min	7.14	28.8	106.2	25.4	3.4
	30 min	7.23	27.4	105.7	25.2	2.2
	60 min	7.30	28.0	90.3	26.1	1.9
Dog 6	control	7.40	31.0	101	29.2	1.8
	5 min	7.03	45.9	92	32.0	13.9
	10 min	7.05	42.3	100	31.2	11.1
	15 min	7.12	40.1	107	29.0	11.1
	30 min	7.21	35.1	96	27.4	7.7
	60 min	7.37	31.0	99	26.2	4.8

The dog was then turned to the right lateral position and the left thorax opened through the fourth intercostal space to permit manual cardiac massage and electrical defibrillation. Care was taken to minimize blood loss during the procedure. None of the dogs lost significant amounts of blood and none were in shock.

After surgical preparation, two deep breaths were given using double the tidal volume by occluding the expiratory portion of the respirator. After 30 minutes, allowed to obtain a steady state, control measurements of expired CO_2 and arterial blood sampling were made. Three to five ml of 7.5 per cent KCl solution (1 mEq/ml of potassium) were then injected into the left ventricle, resulting in cardiac arrest. Three minutes were allowed to pass; cardiac arrest always changed spontaneously to fibrillation during this time, after which manual cardiac massage was begun. When fibrillation became stronger, an electric shock was given using a 100-volt alternating current. Resuscitation generally required less than a minute. When more than two minutes,

or more than three electric shocks, were required, the experiment was discarded. In one dog, normal sinus rhythm appeared after manual massage alone, without electrical defibrillation. After resuscitation the chest was closed, and measurements were repeated at 5, 10, 15, 30 and 60 minutes.

Arterial blood gases were analyzed using a glass electrode for *p*H, a Severinghaus electrode for P_{CO_2}, and a modified Clark electrode for P_{O_2} (Instrumentation Laboratory, Model 113) at 37° C. Values were corrected to the temperature of the dog with appropriate correction factors.[14] Expired CO_2 concentration was determined by means of an infrared analyzer (Beckman–Spinco LB-1).

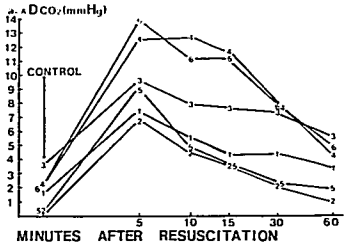

FIG. 1. Changes in a-AD_{CO_2} during control period and after resuscitation from three minutes of cardiac arrest. Mean control value of 1.6 mm Hg increased to 9.8 mm Hg five minutes after resuscitation. Abscissa is a logarithmic scale.

Results

Results are shown in table 1 and figure 1. Mean a-AD_{CO_2} was 1.6 mm Hg before cardiac arrest. This increased to 9.8 mm Hg five minutes after cardiac resuscitation, decreasing gradually thereafter. At 60 minutes it had improved to 3.5 mm Hg. Though quantitatively different from one dog to another, the trend was essentially the same for all.

In figure 2, arterial *p*H and Pa_{CO_2} values are plotted on a *p*H–log P_{CO_2} graph. The slope of the curves is entirely different from the slopes of the standard *in vitro* curve of Siggaard-Andersen[15] and the *in vivo* buffer curve,[16] indicating accumulation of organic acids of metabolic origin. That the 60-minute value is not far from the control may be interpreted as indicating that the so-called metabolic acidosis caused in such experimental conditions may well be taken care of by the body during a 60-minute period. Interestingly enough, most of the curves appear somewhat concave upward.

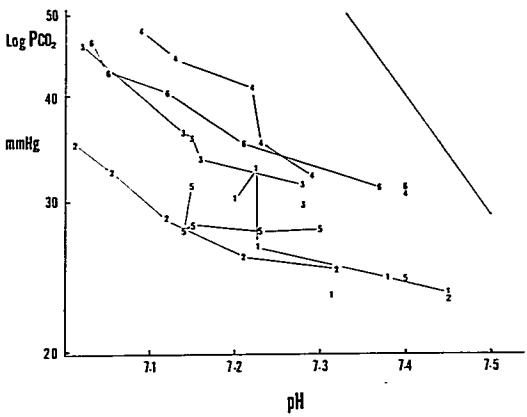

FIG. 2. Acid–base changes on *p*H–log P_{CO_2} graph. The slope of the curves is different from the normal equilibration curve (heavy line at upper right). Curves seem to be slightly concave upward. For explanation, see text. Points connected by solid lines were obtained at 5, 10, 15, 30 and 60 minutes, respectively, reading from left to right. Points not connected to the curves indicate the control values.

Discussion

An increase in a-AD_{CO_2} has been interpreted as indicating unevenness of pulmonary perfusion in relation to ventilation. Utilizing this as a parameter, poorly-perfused alveoli (alveolar deadspace) are reflected far better than poorly-ventilated alveoli (alveolar shunt), because the CO_2 dissociation curve is fairly linear in the physiologic range and because the mixed venous-to-arterial CO_2 tension difference ($P\bar{v}_{CO_2}$–Pa_{CO_2}) is normally only about 6 mm Hg. In other words, an increase in a-AD_{CO_2} generally indicates the presence of poorly-perfused alveoli or alveolar deadspace.[11]

Such increases in a-AD_{CO_2} may be attributed to any of several physiologic consequences that might follow temporary cessation of pulmonary blood flow.

The first possibility is that cardiac arrest and the resuscitation maneuver simply create more uneven distribution of pulmonary blood flow. It is conceivable that when flow is re-established some vessels remain closed, therefore those alveoli are unperfused or poorly perfused. This is especially likely because hypoxia and high concentrations of hydrogen ions, both of which accompany cardiac arrest, are powerful pulmonary vasoconstrictors.[17] Norepinephrine and serotonin may be released at the time of cardiac arrest, and may work as pulmonary vasoconstrictors.[17]

The second possibility is that this is a reflection of a decrease in pulmonary blood flow. Although cardiac output was not measured in this study, and the arterial blood pressure after cardiac resuscitation was always higher than the control (in the range of 150/100 mm Hg in the control period; increased to more than 250 mm Hg systolic, 150 mm Hg diastolic after resuscitation), the possibility of a decrease in cardiac output cannot be denied. If unevenness of pulmonary perfusion had existed in the control period, a-AD_{CO_2} might have increased with the decrease in the total pulmonary blood flow even though the relative distribution remained unchanged.[12] Even if such a decrease existed, however, it does not explain the increase in a-AD_{CO_2} by more than five times (from 1.6 to 9.2 mm Hg). This factor is now under investigation by measurement of pulmonary blood flow during the post-resuscitation period.

The third possibility is that the mixed venous-to-arterial carbon dioxide tension gradient increased and caused a larger a-AD_{CO_2}, even with the same degree of pulmonary perfusion. This cannot be ruled out because mixed venous sampling was not done systematically in this study, although it seems unlikely that an increase in a-AD_{CO_2} by more than five times can occur solely as a result of this factor.

The fourth possibility is that three minutes' cessation of pulmonary blood flow may have caused microthrombi, sluding or erythrocytic aggregation. These may, at least theoretically, create the increase in a-AD_{CO_2},[18] although small pulmonary thrombi are known not to cause an increase in a-AD_{CO_2} in clinical conditions.[19] With reservations, therefore, we temporarily conclude that the increase in a-AD_{CO_2} was caused mainly by increase in the unevenness of pulmonary flow distribution by the first or the fourth mechanism mentioned. The second and third possibilities, however, may have been contributory.

Comparison between the results of this study and results of studies of apneic oxygenation[20] suggests an interesting problem. It was stated that, "Within one hour of completion of the one hour period of apneic oxygenation all CO_2 retained was exhaled, the mean $P_{A_{CO_2}}$ 60 minutes after apneic oxygenation was 0.2 mm Hg less than the mean pre-apneic value." Our data indicate that in the fifth minute of resuscitation after three minutes of circulatory arrest both Pa_{CO_2} and $P_{A_{CO_2}}$ was definitely higher than the control values. Although part of this rise in Pa_{CO_2} was the result of decreased CO_2 elimination from the lung, this does not explain the rise in $P_{A_{CO_2}}$. In the face of constant ventilation, this can be explained only by increased CO_2 elimination from the body. Although increase in metabolic CO_2 production may not be denied, the more likely mechanism is the release of stored CO_2 from the body by the development of metabolic acidosis. When metabolic acidosis occurs, the carbon-dioxide-combining power of blood and the tissues decreases. A larger amount of CO_2 will be released and transported by the blood, and the $P\bar{v}_{CO_2}$ rises. Combined with the decreased efficiency of CO_2 elimination from the lung (increase in a-AD_{CO_2}), this is reflected as

a further increase in Pa_{CO_2}. Therefore, increased Pa_{CO_2} could have resulted from two factors, increased CO_2 release in peripheral tissues and blood, and decreased efficiency of CO_2 elimination from the lung.

Most of our dogs had normal control arterial *p*H values even with the moderate degree of hyperventilation. This was quite unexpected. The cause of this acid–base abnormality remains to be elucidated, but it might have been due to the saline solution given with chloralose in the amount of 500 ml (so-called dilution acidosis[21]).

The concavity of the *in vivo* *p*H–log P_{CO_2} curve was also unexpected. Although the exact mechanism of such nonlinearity remains to be investigated, it is explicable if CO_2 is excreted first from tissues with high buffering capacity and later from those with low buffering capacity. CO_2 would first have been excreted from the blood, which has a higher buffering capacity than any other tissue except bone, then from other tissues, the buffering capacity of which is lower.[22]

Summary

The distribution of pulmonary blood flow after resuscitation following circulatory arrest was studied in six dogs using $a\text{-}AD_{CO_2}$ as the indicator. The study was prompted by the observation that patients after cardiac resuscitation occasionally experienced high Pa_{CO_2} even with presumably-sufficient degrees of minute ventilation. Circulatory arrest was produced by injection of KCl into the left ventricle. The dog was resuscitated by manual massage and electrical defibrillation. The $a\text{-}AD_{CO_2}$ increased to 9.8 mm Hg five minutes after the heart was resuscitated, compared with the mean value of 1.6 mm Hg in the control period. In the course of the next hour, this gradient gradually decreased to 3.2 mm Hg. Several possible explanations for the increase in $a\text{-}AD_{CO_2}$ were discussed and it was provisionally concluded that the pulmonary blood flow is uneven for a period after circulatory arrest occurs. The mechanism through which such unevenness occurs is either pulmonary vasoconstriction or erythrocytic aggregation.

Increase in Pa_{CO_2} after cardiac resuscitation, however, may be due partly to the increased CO_2 release in the peripheral tissue caused by metabolic acidosis.

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Drugs

BARBITURATES AND ANTICOAGULATION Bleeding reactions occurred during anticoagulant therapy in 67 patients. In 14 patients, enzyme induction appeared to be a factor, and two of these patients died. The records of 52 patients admitted for myocardial infarction and treated with anticoagulants were reviewed. Forty patients had received barbiturates; they showed more erratic control of anticoagulant effect (and a shorter prothrombin time in spite of larger dose of warfarin sodium) than patients not receiving barbiturates. Barbiturate interference with anticoagulant activity of coumarin drugs in animals by enzyme induction is well documented. Circumstantial evidence suggests that it also occurs in man. Awareness of this type of drug interaction and close attention to proper anticoagulant dose based on frequent prothrombin determinations can prevent some of the problems that occur during anticoagulant treatment. (*MacDonald, M. G., and Robinson, D. S.: Clinical Observations of Possible Barbiturate Interference with Anticoagulation, J.A.M.A. 204: 97 (April) 1968.*)

PUPILLARY EFFECTS OF NARCOTICS Morphine, but not codeine, produces a definite degree of miosis when applied locally to the conjunctival sacs of human volunteers. Locally applied nalorphine may also produce miosis by direct action, but this drug appears to be absorbed more readily than morphine and its systemic effects largely mask its local effects. Locally applied nalorphine antagonizes miosis produced by locally produced morphine. (*Nomof, N., and others: The Local Effect of Morphine, Nalorphine, and Codeine on the Diameter of the Pupil of the Eye, Clin. Pharmacol. Therap. 9: 358 (May) 1968.*)

PENTAZOCINE ISOMERS Relative respiratory depressant potencies of d- and l-isomers of pentazocine were determined in a crossover study in man. In doses of 30 to 60 mg, the l-isomer was a potent respiratory depressant, whereas the d-isomer was not. The presently used pentazocine is a racemic mixture. (*Bellville, J. W., and Forrest, W. H.: Respiratory and Subjective Effects of d- and l-Pentazocine, Clin. Pharmacol. Therap. 9: 142 (March) 1968.*)