CHANGES IN CARBON DIOXIDE TENSION AND HYDROGEN ION CONCENTRATION OF THE BLOOD FOLLOWING MULTIPLE PULMONARY EMBOLISM.

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INTRODUCTION.

In an effort to explain the cause of the extraordinarily accelerated respirations which result from multiple experimental embolism of the arterioles and capillaries of the lungs (1) it seemed important to observe what changes occurred in the blood in respect to its carbon dioxide tension and hydrogen ion concentration. The relative importance of these two factors in the control of respiration has been much discussed in the literature of late years, and opinion has emphasized first one, then the other. It is probable that both the pressure of carbon dioxide and the hydrogen ion concentration of the blood (or of the respiratory center itself) play an important rôle in the chemical regulation of respiration. The characteristic breathing of acidosis, due to the retention of non-volatile acids, such as is seen in diabetic coma, is hyperpnea, or a deep, labored, slow type of breathing. This, too, is the character of respiration which results from inhalation of gas mixtures rich in carbon dioxide (5 to 10 per cent). As far as we know, rapid and shallow breathing has not been definitely related to a retention of carbon dioxide, nor to an increase in the concentration of hydrogen ions. In at least one clinical condition (bronchopneumonia) (2), however, an increased content of carbon dioxide in the blood has been described, and we know that in this condition the respiratory rate may be elevated. That the accelerated respirations which we were attempting to explain resulted from an increased carbon dioxide tension or a fall in pH seemed unlikely from the outset. Still we considered it necessary to make actual measurements of these changes

in relation to the changes in respirations before ruling them out as of importance. Especially was this true in view of the observation made by Dunn (3) that the inhalation of 10 per cent carbon dioxide by goats, breathing rapidly as the result of multiple pulmonary emboli, caused a reduction of the respiratory rate. In the light of our own observations, it seems probable that the cause of this reduction was probably an increased depth of respiration stimulated by the carbon dioxide in the inspired air. Such an increased depth would lead to an increase in alveolar oxygen tension and hence a decrease in the anoxemia. Anoxemia has been shown (1) to be a contributing factor to the rapid and shallow breathing resulting from multiple embolism of the pulmonary arterioles and capillaries, though not its cause.

EXPERIMENTAL.

The experimental procedure was a simple one. Dogs were anesthetized by the intravenous injection of barbital-sodium. A cannula was inserted into the left femoral artery, from which samples of blood were drawn for analysis, and into the right external jugular vein into which suspensions of potato starch cells were slowly injected. The blood was drawn without exposure to air and kept in sampling tubes over mercury. Analyses of carbon dioxide content were made in duplicate on the separated plasma or serum by the method of Van Slyke and Neill (4). The pH was determined on serum by the colorimetric method of Hastings and Sendroy (5). From these analytical data and from the following formula (6) the partial pressure of carbon dioxide expressed in mm. Hg was calculated, assuming pk' to be 6.115:

$$pCO_2 = \frac{[CO_2]}{0.031 \times (1 + 10^{pH - 6.115})}$$

where CO_2 content is given in terms of millimols per liter. In some experiments the tidal air and minute volume of pulmonary ventilation were measured by securing a tightly fitting mask to the dog's muzzle and collecting the expired air by means of flutter valves in a Tissot spirometer. In other experiments the respiratory rate was simply counted by observing the animal's thoracic movements. In most of the experiments, anoxemia was prevented by permitting the animal to breathe oxygen. It was soon learned that the rapid and shallow breathing which comes on after a certain volume of starch suspension has been injected, is usually associated with an increase in the carbon dioxide tension of the plasma and an accompanying fall in pH. But subsequent observations revealed the fact that these changes do not necessarily occur, and sometimes follow rather than precede, the onset of abnormally accelerated respirations.

To test the effect of the experimental conditions *per se*, without starch injection, on the carbon dioxide tension and hydrogen ion concentration, these measurements were made on a dog at approximately hourly intervals over a period of 3 hours. The results showed a fall in pCO_2 and a rise in pH, or a change in the opposite direction from that usually encountered following embolism. These facts are shown in Table I.

In the following three experiments (Nos. 4, 7 and 9) the accelerated respirations following starch embolism were accompanied by a marked

TABLE I.

Experiment 6. Effect of Barbital-Sodium Anesthesia on pCO_2 and pH of Dog's Blood and on Respiratory Rate.

Time	Respiratory rate per min.	CO_2 content	pCO_2	pH
		mM	*mm.Hg*	
2.47	38	23.37	46.20	7.30
4.00	34	22.02	38.20	7.36
5.00	36	21.67	36.80	7.37

TABLE II.

Experiment 4. Effect of Intravenous Starch Suspension Injection on Respiratory Rate, CO_2 Tension and pH of the Blood.

Time	Procedure	Respiratory rate per min.	CO_2 content	pCO_2	pH
			mM	*mm.Hg*	
4.04		16	21.17	47.50	7.23
4.12–4.32	Injection of starch suspension				
4.33		52			
4.35		51	22.28	60.68	7.15

increase in CO_2 tension (from 5 to 13 mm.) and a definite fall in pH (from 0.07 to 0.09). In each instance characteristic rapid and shallow breathing occurred, the rate increasing from an average of 18 to the minute to an average of 46, and the depth decreasing accordingly. The experimental data are brought out in Tables II to IV. It is to be noted that the actual change in CO_2 content expressed in millimols may be slight when the change in CO_2 tension is considerable.

Examination of Table III will bring out the following facts: In a

TABLE III.

Experiment 7. Effect of Intravenous Starch Suspension Injection on Respiratory Rate and Depth and on CO_2 Tension and pH of the Blood.

Time	Procedure	Respiratory rate per min.	Tidal air	Min. volume	[CO_2]	pCO_2	pH	Arterial blood		
								O_2 content	O_2 capacity	Per cent saturation
			cc.	*liters*	*mM*	*mm. Hg*		*mM*	*mM*	
12.12	Dog breathing room air	17	174	2.96	23.60	37.56	7.40	7.46	8.70	85.8
12.22	" "									
12.45–12.51	Injection of starch suspension									
12.53	Room air	46			25.10	40.82	7.39	7.26	8.96	81.1
1.00	" "	50	130	6.48	23.25	44.00	7.32	6.81	8.80	77.4
1.13	Dog breathing 95 per cent O_2									
1.20		50	123	6.18						
1.26					23.52	45.52	7.31	8.87	9.36	94.8

TABLE IV.

Experiment 9. Effect of Intravenous Starch Suspension Injection on Respiratory Rate and Depth and on CO_2 Tension and pH of the Blood.

Time	Procedure	Respiratory rate per min.	Tidal air	Min. volume	[CO_2]	pCO_2	pH	Arterial blood		
								O_2 content	O_2 capacity	Per cent saturation
			cc.	*liters*	*mM*	*mm. Hg*		*mM*	*mM*	
11.59	Breathing 95 per cent O_2 throughout experiment									
12.05		21	150	3.16	23.10	34.36	7.43			
12.17–12.26	Intravenous injection of starch suspension									
12.29		37	124	4.62	22.75	39.46	7.36	9.00	8.42	107

dog anesthetized with barbital-sodium, the intravenous injection of a suspension of potato starch grains resulted in an increase in respiratory rate from 17 to 50 per minute. This was associated with a decrease in tidal air amounting to 44 cc., or a 25 per cent decrease, and a resulting increase in the volume of pulmonary ventilation from 2.96 liters to 6.48 liters per minute. This change occurred while the animal was breathing room air and was accompanied by a drop in the oxygen saturation of the arterial blood from 85.8 per cent to 77.4 per cent. Accompanying this the pCO_2 rose from 37.56 mm. to 44.00 mm., with practically no change, however, in the CO_2 content of the serum as expressed in millimols. The hydrogen ion concentration, however, increased, as shown by the drop in pH from 7.40 to 7.32.

At this point oxygen was administered to the animal, with the result that the arterial oxygen saturation rose to 94.8 per cent, or the normal level, without, however, affecting the rate or depth of breathing, which still remained rapid and became even shallower than it had been. Nor was there a return of the pCO_2 or pH to the former level.

From these experiments it can be concluded that embolism due to intravenous starch suspension leads to rapid and shallow breathing, which is accompanied by a fall in the percentage oxygen saturation of the arterial blood, a rise in the pCO_2 and a fall in pH.

Restoring the blood to its normal oxygen saturation affects neither the respiratory rate or depth nor the carbon dioxide tension or hydrogen ion concentration. Similar results, as far as changes in pCO_2 and pH are concerned, were observed in Experiment 9, in which the animal was permitted to breathe oxygen throughout, so that the arterial blood remained completely saturated with oxygen. In this experiment the respiratory rate rose from 21 to 37 following starch injection, the tidal air falling from 150 cc. to 124 cc. A slight drop in the millimolecular concentration of CO_2 occurred, from 23.10 mM to 22.75 mM, but with a fall in pH from 7.43 to 7.36, the pCO_2 may be calculated to have risen by slightly more than 5 mm. These changes are brought out in Table IV.

Thus far no conclusions can be drawn as to whether the observed changes in pCO_2 and pH are the cause of the accelerated respirations or whether they result from the same condition which gives rise to rapid and shallow breathing.

To observe the effect on respiration of increasing the partial pressure of CO_2 in the serum without the disturbing influence of pathological changes in the lungs, such an increase was produced by permitting a dog to inhale from a Douglas bag containing a 10 per cent CO_2-90 per cent oxygen mixture. In this experiment (No. 12) in which the CO_2 tension of the serum was raised by CO_2 inhalation there was naturally an increase in the hydrogen ion concentration, both changes being consonant with those observed in the starch experiments. Instead of the development of rapid and shallow

TABLE V.

Experiment 12. Effect of Inhalation of 10 Per Cent CO_2-90 Per Cent O_2 Mixture on pCO_2, pH of the Blood and on Pulmonary Ventilation.

Time	Procedure	Respiratory rate per min.	Tidal air	Min. volume	$[CO_2]$	pCO_2	pH
			cc.	*liters*	*mM*	*mm.Hg*	
12.29	Breathing 95 per cent O_2	25.0	170	4.26			
12.35	" 95 " " "				26.21	40.76	7.41
12.38	" 95 " " "	30.4	194	4.90			
1.56	" 95 " " "	21.4	175	3.74			
2.03	" 95 " " "				26.28	42.82	7.39
2.05	" 95 " " "	21.4	180	3.86			
2.13–2.42	Breathing {10 per cent CO_2 / 90 " " O_2						
2.30		42.0	390	16.42			
2.40					30.63	67.45	7.24
2.42		42.4	383	16.24			

breathing, however, the respirations, though they accelerated, more than doubled in depth. The average rate before CO_2 inhalation was 24, with a tidal air of 180 cc., compared to a rate of 42 after, with a tidal air of 383 cc. This was associated with a rise of CO_2 tension of nearly 25 mm., and a drop in pH from 7.40 to 7.24. These changes are exhibited in Table V.

This experiment (No. 12) is included simply for the purpose of demonstrating the well known effect of increasing the CO_2 tension and the hydrogen ion concentration, on the respirations. The significant difference from the starch effect is the marked increase in

depth. In many instances breathing high concentrations of CO_2 will increase the depth of respirations with little effect on rate.

Since, from the foregoing three experiments (Nos. 4, 7 and 9) it was impossible to say whether the changes in pCO_2 and pH antedated the onset of accelerated respirations, it was planned to draw the blood for analysis immediately after acceleration had begun. By this maneuver it was hoped to determine which change occurred first, *i.e.*, the change in CO_2 tension and pH or the change in rate and depth

TABLE VI.

Experiment 14. The Effect of Intravenous Starch Suspension Injection on Respiratory Rate and Depth, and on CO_2 Tension and pH of the Blood.

Time.	Procedure	Respiratory rate per min.	Tidal air	Min. volume	$[CO_2]$	pCO_2	pH
			cc.	*liters*	*mM*	*mm.Hg*	
11.43	Dog breathing 95 per cent O_2 throughout experiment	23.6	107	2.52			
11.49					24.40	51.48	7.27
11.52		23.2	120	2.78			
12.00–12.09	65 cc. 2 per cent starch suspension injected intravenously						
12.15		42.4	95	3.96			
12.21					23.58	49.75	7.27
12.24		47.6	89	4.24			
12.50					24.44	51.55	7.27
12.53		66.6	77	5.14			
1.09		73.0					

of respirations. It was found, in fact, that *accelerated respirations may occur before any measurable increase in CO_2 tension or hydrogen ion concentration.* From this the conclusion seems justified that the changes in CO_2 tension and pH are not the cause of rapid and shallow breathing which arises after embolism of the pulmonary arterioles and capillaries.

In Experiment 8 the respiratory rate, before starch injection, was 12 to the minute. At this time the pCO_2 was 66.95 mm. and the pH 7.23. After starch injection the rate had risen to 47 but the

pCO_2 was 63.42 mm. and the pH 7.25. Similarly with Experiment 14, in the control period the respiratory rate was 23 per minute and the average tidal air 113 cc. Starch injection resulted in a rate of 48 to the minute with a decrease in depth to 89 cc. No significant change, however, had occurred in the CO_2 tension or hydrogen ion concentration. The facts of this experiment (No. 14) are supplied in Table VI and in the appended protocol.

Protocol of Experiment 14. (*See Table VI.*)

Female, mongrel hound. Weight 12.2 kilos.

9.55. 3.36 gm. barbital-sodium, dissolved in 25 cc. distilled water, injected into the left leg vein.

10.05. Dog quiet, snoring. 10.30. Dog quiet, insensitive. Cannulated right jugular vein and right femoral artery.

11.00. Respirations 27. Pulse 205. Rectal temperature 38.4°C. Corneal reflex present.

11.08. Additional 5 cc. 5 per cent solution of barbital-sodium.

11.25. Respiratory mask adjusted to muzzle. 11.30. Breathing 95 per cent O_2 from Douglas bag. 11.41. Connected with Tissot spirometer.

11.43. First respiratory period. Expired air collected for 5 minutes. Total volume 12.6 liters. 118 respirations.

11.49. 25 cc. bright red arterial blood drawn from right femoral artery.

11.51. Second respiratory period. Expired air collected for 5 minutes. Total volume 13.9 liters. 116 respirations.

12.00. Injection of 2 per cent starch suspension begun. Respirations continuously counted.

12.01. Respiratory rate 26.

12.03. Total of 50 cc. starch suspension injected.

12.04. Respiratory rate 24.

12.09. Total of 65 cc. starch suspension injected. Respiratory rate 35.

12.14. Third respiratory period. Expired air collected for 5 minutes. Total volume 19.8 liters. 211 respirations.

12.21. 25 cc. bright red arterial blood drawn from right femoral artery.

12.23. Fourth respiratory period. Expired air collected for 5 minutes. Total volume 21.2 liters. 238 respirations.

12.46. Respiratory rate 61 per minute.

12.50. 25 cc. bright red arterial blood drawn from right femoral artery.

12.52. Fifth respiratory period. Expired air collected for 5 minutes. Total volume 25.7 liters. 333 respirations.

1.00. Rectal temperature 38°C.

1.01. Respiratory rate 72.

1.09. Respiratory rate 73.

At this time the experiment was brought to a conclusion and the animal used for another purpose.

SUMMARY AND CONCLUSIONS.

1. The production of multiple emboli of the pulmonary capillaries and arterioles results in rapid and shallow breathing which may be associated with anoxemia, but is not dependent for its occurrence upon anoxemia.

2. Similarly there may occur an increase in the partial pressure of CO_2 in the blood as well as an increase in hydrogen ion concentration.

3. These changes must be regarded as the result of the impaired pulmonary function.

4. They are not, however, the cause of the rapid and shallow respirations, since the abnormal type of breathing may occur without the attendant blood changes.

5. The characteristic type of response to increase in CO_2 tension is an increased rather than a decreased depth of respiration.

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