The Antagonistic Action of Carbon Dioxide and Adrenalin on the Heart.

By S. W. Patterson, M.D., Beit Memorial Research Fellow.

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(From the Institute of Physiology, University College, London, and the Physiological Institute of the University, Berlin.)

Although a great volume of work on asphyxia has been published, it is only comparatively recently that attempts have been made to dissociate the influence of various factors in the production of the phenomena observed. Kaya and Starling (1) were the first to differentiate the effects of lack of oxygen and excess of carbon dioxide in the spinal animal; and their work was elaborated by Mathison (2, 3), in whose papers a full discussion of the previous literature will be found. He found that during nitrogen administration no increased output of the heart is seen in the early stages of asphyxia, and attributed the increase in output noticed in ordinary asphyxia to the presence of increased tension of CO_2 in the blood, which Jerusalem and Starling (4) had shown to increase the systolic output of the cat's heart. He also observed an acceleration of the heart beat about the time of the primary blood pressure rise in asphyxia, which occurred even after removal of the upper part of the spinal cord. Since the work of v. Anrep (5) and Itami (6), a third factor, variations in the secretory activity of the suprarenal glands, must be taken into consideration; and the present paper contains an account of an investigation of the action of carbon dioxide and adrenalin on the heart isolated from the nervous system.

Methods.

The experiments reported in this paper were carried out mainly on dogs, a few on cats, the animals being anæsthetised by inhalation of chloroform and ether mixture, in the case of dogs after a preliminary hypodermic injection of morphine.

The isolated heart-lung preparation was made as described by Knowlton and Starling (7). The systemic blood was taken off by a cannula in the brachiocephalic artery after ligation of the left subclavian artery and the aorta beyond; and was returned to the heart by a cannula tied in the superior vena cava after ligation of the azygos vein. The mean blood pressure was recorded by a mercury manometer connected to the side of the innominate cannula, and the side pressure of the blood from the venous return by a water manometer connected with a cannula tied in the inferior vena cava close to its entrance into the right auricle. To the top of the water

manometer a small piston recorder was attached for graphic records; 0·1 grm. of hirudin was added to the blood to prevent clotting.

In the case of cats, the systemic schema (consisting of the arterial resistance and venous reservoir) used was that described by Knowlton and Starling; while the other experiments were made at various times with the different modifications of method which have marked the evolution of the systemic schema, and which have been reported in the communications from the University College laboratory during the last two years. References to these will be made in the discussion of results, as the separate points brought out are considered.

In all cases the systemic output was measured directly into a graduated vessel by means of a stop-watch, and is recorded in cubic centimetres per 10 seconds, the output per minute being this observed figure multiplied by 6.

When the heart volume was recorded, a glass plethysmograph on the ventricles was used similar to that described by Henderson (13), and the cardiometer was connected by air conduction with various recorders.

In some experiments the mean pressures in the left auricle were recorded from a water manometer connected with a small cannula tied in the appendage of the left auricle.

The adrenalin (Parke, Davis and Co.) was mixed with the blood in the venous reservoir, while the carbon dioxide was administered from a gas bag. The figures given of the percentages of CO_2 in the gas bag can only approximately show the percentage in the air at the trachea, as various types of artificial respiration apparatus were used, and were connected to the trachea by sometimes considerable lengths of piping, and as the side slot of the tracheal cannula was more or less open.

Results.

In the heart-lung preparation, as in the intact animal, there are three circles of blood from one side of the heart to the other, one from the right ventricle to the left auricle through the lungs and two from the left ventricle to the right side of the heart, one of which passes through the schema and represents the systemic circulation in the whole animal, and the other passes through the coronary circulation. The total output of the left ventricle consists, therefore, of the systemic output, which was measured directly in our work, together with the output through the coronary vessels; so the question of the relation of the coronary output to the systemic output under normal conditions and under the influence of carbon dioxide and adrenalin must first be considered.

Relation of Coronary Sinus Flow (as Index of Total Coronary Output) to

Systemic Output.—Evans and Starling (8) found a constant relation between the flow from the coronary sinus and the total coronary output in the proportion of 3 : 5; Markwalder and Starling (9) proved that the coronary flow depended on the arterial pressure, and, using the above figure as a basis for calculation, showed that the total output from the left ventricle was constant for a given venous inflow and independent of the arterial resistance within very wide limits. They have confirmed also the observations (10) made previously, that adrenalin causes an increased coronary flow.

Table I* contains the results of an experiment carried out on the heart-lung preparation in which a Morawitz cannula was introduced into the coronary sinus, and the blood flow through the coronary sinus and that through the systemic part of the schema were measured at the same time. The figures in column 10 (Total coronary circulation) were obtained by multiplying the observed coronary sinus flow by the factor 5/3. It will be seen that in the two series with the normal heart, the coronary output depends on the aortic pressure, while the total output is independent of the arterial resistance within wide limits and is conditioned only by the venous inflow. During the period of administration of carbon dioxide the coronary flow was the same as in the normal condition; but it was increased markedly during the recovery period from carbon dioxide, while the heart was returning to its normal state. This increase was probably due to the accumulation of 'metabolites' in the heart during the action of CO_2.

Adding adrenalin to the circulating blood caused a great rise in the coronary flow, and this occurred also when adrenalin and carbon dioxide were given together.

We have thus a guide to the interpretation of the results obtained in other experiments where the systemic output only was measured.

Systemic or Effective Output with Carbon Dioxide and Adrenalin. Experiments on Dogs.—The figures in column 7 of Table I show that the administration of CO_2 may cause a marked falling-off in the output per minute. This diminution may be small with low percentages of CO_2, but I have never observed an increased output during the administration. The diminution becomes more marked as the percentage of CO_2 is increased; so that if the CO_2 is strong, or a moderate percentage is administered for a

* In this and the other Tables, the following abbreviations are employed :—A.R. = pressure in mm. Hg in air chamber surrounding the thin rubber tube forming the arterial resistance. B.P. = mean arterial pressure in mm. Hg as measured in the cannula in the innominate artery. I.V.C. = pressure in inferior vena cava in mm. H_2O. V.S. = venous supply. =, +, − = maintained constant, increased or diminished. Systemic output = output in c.c. per 10 secs. as measured on the venous side of the artificial peripheral resistance.

Table I.—Dog, 9·8 kgrm. Heart, 142·5 grm. Heart-lung preparation, with Morawitz cannula in coronary sinus.

Temp.	A.R.	B.P.	I.V.C.	V.S.	Rate 10 secs.	Output. Systemic in 10 secs.	Per beat.	Coronary sinus 10 secs.	Total coronary 10 secs.	Total output 10 secs.	
						c.c.	c.c.	c.c.	c.c.	c.c.	
36° C.	40	68	18		23 (alt.)	72·5	3·15	3·2	5·3	77·8	
	80	112	20	=	12 (2 : 1)	64	5·3	5·25	8·7	74·7	
	120	150	24	=	12 (2 : 1)	67	5·5	7·6	12·7	79·7	
	162	192	24	=	23 (alt.)	59	2·56	11·6	19·3	78·3	
	40	74	10	=	24	68	2·84	3·9	6·5	74·5	
	40	83	24	+	25	204	8·15	5·25	8·7	212·7	
	80	112	24	=	25	216	8·65	7·25	12·1	228	
	120	156	34	=	25 (alt.)	184	7·35	14·7	24·5	208·5	
	160	192	200–100	=	25	103	4·1	20	33·4	136·4	
	40	90	26	=	25	210	8·4	6·6	11·0	221	
	40	86	60	=	20	193	9·65	6·7	11·1	204	
	80	110	210	=	21	85	4·05	7·25	12·1	97	8 per cent. CO_2.
	80	120	50	=	22	—	—	14·7	24·5	—	
	80	118	28	=	23	203	8·7	12·2	20·4	223·4	Recovery.
	80	116	28	=	22	198	9·0	8·5	14·2	212	3 mins. later.
	Adrenalin 0·1 mgrm.										
	80	114	0	=	36	182	5·05	15·9	26·5	208·5	
	120	166	10	=	35	178	5·1	27·8	54	232	
	164	210	10	=	35	167	4·76	42·5	70·7	230·7	
	Adrenalin 0·1 mgrm.										
34°	40	92	4	=	35	200	5·7	17·8	29·8	229·8	
	40	90	2	=	30	196	6·5	20	33·4	229·4	
	80	112	6	=	30	183	6·1	27·8	54	237	
	120	158	10	=	29	172	5·9	38·5	64	236	8 per cent. CO_2.
	160	200	25	=	27	108	4·0	47·5	79	187	
	160	196	40	=	27	—	—	—	—	—	
	40	78	10	=	32	184	5·75	20·8	34·7	218·7	Recovery.
	40	74	56	=	15 (irreg.)	187	12·5	9·2	15·1	202	25 mins. later.
	80	120	40	=	20	182	9·1	13·3	22·2	204	
	120	160	50	=	20	159	7·95	24·6	41	200	

considerable time, the output of the heart may almost cease. With recovery from the effects of CO_2 the output per minute is above normal, but this occurs only after the CO_2 is removed and ordinary air respired. Since the coronary output has been found not to be increased during administration of CO_2, the total output of the left ventricle is proportional to the observed output and is thus never increased but suffers more or less diminution.

After adding adrenalin to the blood circulating through a good heart, the systemic output is observed to be about the value obtained before, unless the heart was failing; but since the coronary flow is markedly raised, the total output of the left ventricle is usually increased. Adrenalin sometimes can improve the condition of a heart that is working badly, or make the heart better able to work against a greater resistance; but with some hearts adrenalin is incapable of bringing about an improvement.

When adrenalin and CO_2 are combined in suitable proportions, the systemic output has been found to be increased; and, since there is also increased coronary flow, the total output of the heart may be greatly increased.

Examples of such findings are given in the protocols of Table II.

In Experiment 1, 5 per cent. CO_2 reduced the systemic output from 130 to 96 c.c. in 10 seconds, 0·1 mgrm. adrenalin also reduced the output to 103 c.c. per 10 seconds, while with combination of the two together the systemic output was 125 c.c. In Experiment 5, combining CO_2 and adrenalin increased the systemic output to more than normal. Experiment 2 shows the greater effect of larger percentages of CO_2 in reducing the output; while Experiment 3 shows that the same percentage of CO_2 has a more marked effect when the arterial resistance is high and the load on the heart consequently greater.

The constancy of the output with constant venous inflow, even in the presence of varying rate and arterial resistance, has been insisted on in previous papers from this laboratory. How then is it possible for the output to be increased or diminished by CO_2, or adrenalin, with constant venous inflow? The clue to the interpretation of the results is given in the effect of CO_2 and adrenalin on the venous pressures (see below). The question is one of the diastolic pressure and diastolic filling of the heart. The higher the diastolic pressure, the smaller is the inflow under a given head of pressure; and it will be seen that CO_2 raises the venous pressure, while adrenalin usually lowers it.

Pressures in the Inferior Vena Cava and Left Auricle.—These pressures represent (i) the side pressure of the blood flowing into the right and left ventricles, (ii) the damming back (Stauung) of the blood in the auricles during the ventricular systole. These two factors are present in the normally acting heart; but there may be also (iii) a more marked abnormal

Table II.—Systemic Output.

B.P.	I.V.C.	V.S.	Rate 10 secs.	Output 10 secs.	Output beat.		
					Calculated.	Observed.	
Experiment 1 (10.4.13).							
				c.c.	c.c.	c.c.	
132	60	=	28	130	4·65		
128	150	=	21	96	4·5	—	5 per cent. CO_2.
140	25	=	30	113·6	3·8		
1 c.c. adrenalin.							
134	18	=	45	103	2·3		
136	30	=	44	116	2·6		
140	30	=	35	125	3·5	—	6 per cent. CO_2.
Experiment 2 (30.4.13).							
88	30		27	59·5	2·2		
90	35		25	56·8	2·27	—	1 per cent. CO_2.
92	32		25	56·8	2·27	—	5·2 per cent. CO_2.
94	30		29	59·5	2·05	—	Normal.
94	40		25	53·1	2·12	—	7·5 per cent. CO_2.
62	90		17	7·7	0·46	—	
0·5 c.c. adrenalin 1/10,000.							16 per cent. CO_2.
90	35		27	51·3	1·8	—	
90	35		33	51·3	1·5	—	
90	36		43	48·3	1·1	—	Recovery.
Experiment 3 (16.4.13).—Heart 87 grm.							
140	10		17	31·3	1·8		
112	120		12	0	0	—	9 per cent. CO_2.
140	20		13	38·5	3·0	—	Recovery.
96	12		17	37	2·1		
92	15		12	17·2	1·4	—	9 per cent. CO_2.
60	10		16	38·5	2·4		
50	10		12	25·0	2·0	—	9 per cent. CO_2.
156	10		17	51·7	3·0		
144	100		15	23	1·5	—	5 per cent. CO_2.
108	10		18	55·5	3·1		
92	150		13	14·3	1·1	—	5 per cent. CO_2.
46	10		17	53·6	3·1		
44	14		13	51·7	4·0	—	5 per cent. CO_2.
132	15		18	53·6	3·0		
1 c.c. adrenalin.							
132	50		28	55·5	2·0		
96	55		28	60	2·2		
50	35		27	51·7	1·9		
150	55		26	51·7	2·0		
192	50		25	51·7	2·05		
124	35		24	27·3	1·05		
108	25		19	5·5	0·3	—	CO_2.
1 c.c. adrenalin.							
140	45		18	47	2·6		
128	45		30	36·6	1·2	—	CO_2.

Table II.—*continued.*

B.P.	I.V.C.	V.S.	Rate 10 secs.	Output 10 secs.	Output beat. Calculated.	Output beat. Observed.	
Experiment 4 (10.2.14).—Dog 4·65 kgrm., heart 52 grm.; cardiometer on ventricles. 36° C.							
				c.c.	c.c.	c.c.	
88	60		26·5	109	4·1	4·0	
86	80		25	103	4·1	4·0	8 per cent. CO_2.
86	120		24	100	4·2	4·5	8 per cent. CO_2.
86	60		26	111	4·25	5·5	
86	60		26	108·5	4·15	4·5	
0·5 c.c. adrenalin.							
86	90	=	32·5	102	3·15	4·0	
94	130	+	34	223	6·5	6·5	
104	150	+	34	333	9·8	8·75	
106	180	full	34	333	9·8	8·75	
0·5 c.c. adrenalin.							
106	60	=	33	333	10·1	8·5	8 per cent. CO_2.
102	230	=	26·5	313	11·8	10·0	8 per cent. CO_2.
(1′) 108	180	=	32	333	10·2	11·5	
(2′) 106	190		35	313	8·9	6·5	
Experiment 5 (29.1.14).—Dog 6·45 kgrm., heart 44 grm.; cardiometer on ventricles. 36·3° C.							
106	190		25	190	7·6	7·0	
0·5 c.c. adrenalin.							
110	40	=	35	—	—	5·0	
106	30		35·5	189	5·3	6·0	
108	40	=	34·5	200	5·8	7·25	8 per cent. CO_2.
104	40		38	—	—	6·0	

damming back through the failure of the ventricle to pass on the blood which it receives in diastole.

CO_2 causes a rise of venous pressure, which is proportional to the increase of percentage of CO_2, and which is an expression of the slower rate of inflow into the heart, and of the greater damming back due to the slowed relaxation. With large percentages of CO_2, the third factor also comes in as an expression of the heart failing to pass on the venous blood it receives.

The addition of adrenalin to a heart in good condition lowers the venous pressures (fig. 1). Both the contractile process and relaxation are more rapid, the heart is relatively longer in a relaxed condition and offers less resistance to the inflowing blood; the heart also passes on the blood better, and the side pressure of the faster venous inflow falls. In good hearts adrenalin is able to diminish, or even counteract, the effect of the CO_2 when the two are employed together.

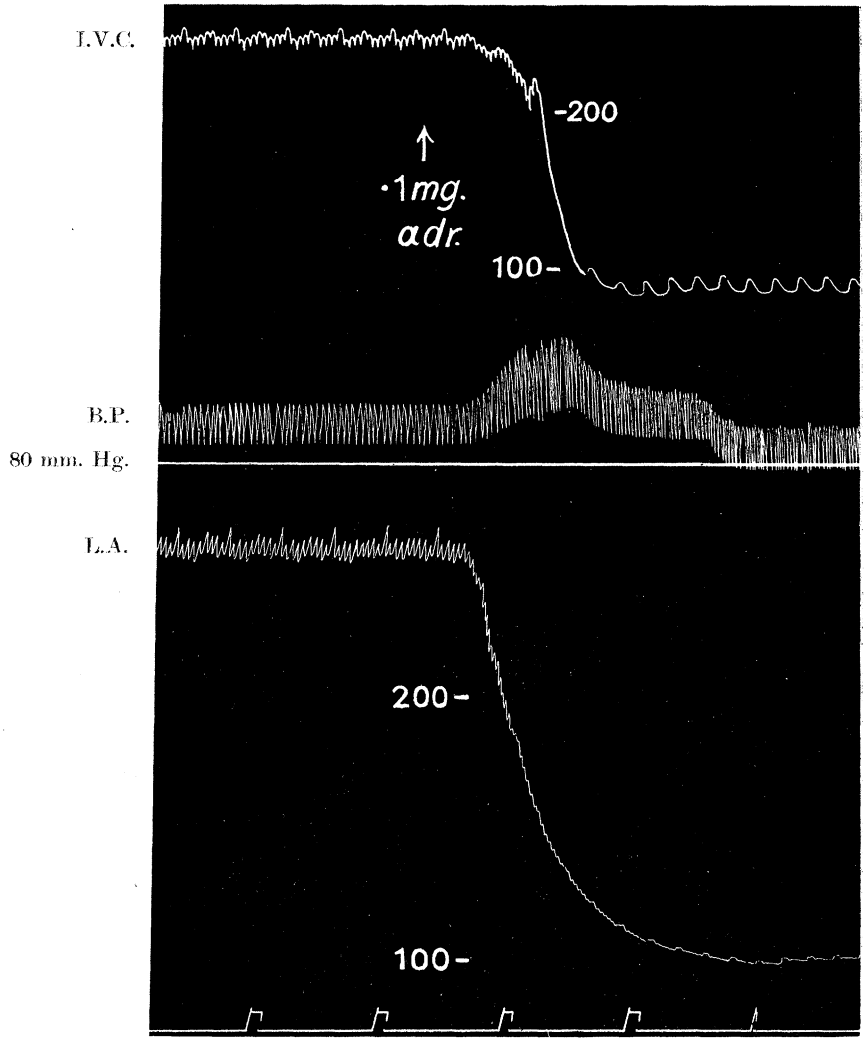

FIG. 1.—Effect of Adrenalin on Inferior Vena Cava and Left Auricle Pressures. I.V.C. pressure reduced from 260 mm. H_2O to 80 mm., and L.A. from 250 to 100; rate of heart increased from 22 beats in 10 secs. to 40 in 10 secs.

Adrenalin can improve a heart that is not doing well, so that it is then able to work better. In Table I, adding adrenalin enabled the heart to keep up its output against a higher arterial resistance than before. But if the heart muscle is doing its work badly, or if the "contractile substance" is used up, so that the heart has lost the material with which it can respond, adding adrenalin may have no good effect, and the venous pressures remain high (see Experiment 5 in Table III).

Table III.—Venous Pressures.

Temp.	B.P.	I.V.C.	L.A.	Rate 10 secs.	Output 10 secs.	Output beat.	
					c.c.	c.c.	
Experiment 1 (23.10.13).—Dog. 6·1 kgrm., heart weight 55 grm.							
35° C.	126	260	500	22	189	8·6	
	1 c.c. adrenalin, 1/10000.						
	162	18	45	34	232	6·8	
	132	14	11	37	207	5·6	
	130	10	18	37	192	5·2	
	130	20	40	34	189	5·5	5 per cent. CO_2.
	1 c.c. adrenalin + 8 per cent. CO_2.						
	135	16	30	38	200	5·2	
Experiment 2.—Dog, 7·2 kgrm., heart weight 60 grm.							
35·5° C.	92	200	54	32	313	9·75	
	1 c.c. adrenalin, 1/10000.						
	92	200	14	41	263	6·4	
Experiment 3.—Dog, 6·45 kgrm., heart weight 44 grm.							
36·3° C.	106	190	—	25	172	6·9	
	0·5 c.c. adrenalin, 1/10000.						
	106	30	—	35·5	190	5·3	
	108	40	—	34·5	200	5·8	8 per cent. CO_2.
Experiment 4.—Dog, 5·5 kgrm., heart weight 46·5 grm.							
35·2° C.	95	10	—	28	110	3·9	
	95	40	—	22·5	106	4·7	11 per cent. CO_2.
	95	10	—	26	106	4·0	
	0·5 c.c. adrenalin, 1/10000.						
	94	0	—	37·5	98	2·6	
	94	40	—	26·5	100	3·8	20 per cent. CO_2.
Experiment 5.—Dog, 3 kgrm., heart weight 33·5 grm.							
33° C.	130	330	—	15	85		
	1 c.c. adrenalin, 1/10000.						
	130	330	—	24	77	3·2	
	125	380	—	21	62	2·95	7 per cent. CO_2 on.

Experiments with Cats.—Various difficulties were encountered in making the experiments on cats, the main ones being due to the sensitiveness of the lungs. The blood of several cats had to be used in order to get sufficient to fill the tubes of the schema, and it seemed that the foreign blood was liable to cause œdema of the lungs, which soon brought the experiment to a conclusion. A typical example of the results obtained in a good experiment is given in Table IV, from which it will be seen that with various percentages of CO_2 no increase in the output per minute was obtained, while the heart rate is reduced considerably by the larger percentages. In other experiments, using the suck and thrust pump devised

by Hans Meyer, and using a cardiometer attached to various forms of recorder, it was found that the output as measured was not increased, although in some instances the recorder showed an increased amplitude of stroke. Since the output through the coronary system is not increased, the difference between these results and those of Jerusalem and Starling (4) probably lies in the inadequacy of the volume recorder used by them, which responded to the slower rhythm by a greater throw.* On the other hand, cats are remarkably tolerant of CO_2 as compared with dogs; and it is of interest to note that, in the only experiment with dogs recorded by these authors, the output was much reduced by administering CO_2.

Adrenalin alone reduced the systemic output, but when adrenalin and CO_2 were used together the effective output was in some cases higher than in the normal preceding period.

Table IV.—Cat. Heart weight, 12 grm.

Temp.	B.P.	I.V.C.	Rate 10 secs.	Output 10 secs.	Output beat.	
				c.c.	c.c.	
36° C.	73	5	37	20	0·54	
	73	8	28	20	0·71	5·5 per cent. CO_2.
	72	4	36	21·5	0·58	
	72	10	30	20·4	0·68	10·5 per cent. CO_2.
	70	5	34	20·8	0·61	
	70	20	22	19·2	0·87	17·5 per cent. CO_2.
34°	108	8	33	14	0·425	
	0·8 c.c. adrenalin, 1/10000.					
	100	18	47	7	0·149	
	105	24	45	13	0·29	
	104	18	40	13·1	0·32	17 per cent. CO_2.
	104	28	49	13	0·26	
	104	12	39	13	0·33	18 per cent. CO_2.
	105	20	46	13·5	0·29	
	106	15	34	14·3	0·42	20 per cent. CO_2.

Heart Rate.—With all percentages of CO_2 in the inspired air there is a slowing of the heart rate, and this retardation becomes more marked as the percentage of CO_2 is increased. The slowing sometimes lasts for a time after the CO_2 is taken off and ordinary air respired again.

Adrenalin causes, under all conditions, a quickening of the heart rate. With inhalation of CO_2 combined with the injection of adrenalin, the algebraical sum of the above effects is noticed. Sometimes during the

* Ketcham, King, and Hooker (11) found no increased output in the isolated cat's heart.

administration of CO_2 and adrenalin the ventricle drops to half its previous rate, due to heart block.

Volume Changes in the Heart.—During the administration of CO_2 the mean volume of the heart is shifted towards the diastolic side, while adrenalin causes a diminution in the mean volume. This is shown in fig. 2 from curves obtained by the method described in a paper by Führer and Starling (12); the protocols are given below.

Table V.—Mean Heart Volume.

Dog, 16·4 kgrm. Heart, 128 grm.

Time.	Temperature.	B.P.	I.V.C.	Rate 10 secs.	
min. secs.					
—	35·5°	94	50	20	
1 30	—	88	65	17	11 per cent. CO_2.
1 0	—	86	75	17	
1 0	—	96	55	21	
1 0	—	92	48	23	
2 c.c. adrenalin, 1/100000.					
1 0	—	94	42	35	

During the administration of 11 per cent. CO_2, this heart, weighing 128 grm., increased 50 c.c. in capacity.

Fig. 3 is taken from an experiment in which the cardiac volume was recorded by a plethysmograph attached to an Albrecht piston recorder of brass with vulcanite piston. It shows that the systolic volume is first increased, followed by increase in the diastolic volume during the same beat, the excursion being the same as before. The heart does not contract to its previous volume, but takes a new increased length. It may come to an equilibrium in the position of increased mean cardiac volume; but usually in our experiments the course shown in the figure is taken and the heart continues to dilate; the excursions become smaller as the systolic volume increases more rapidly than the diastolic volume, so that the output per beat is diminished and may even cease. The dilatation is greater, the larger the amount of CO_2 in the air breathed. When the CO_2 is removed and air respired, the heart resumes its normal mean volume gradually, and as the systolic volume now decreases more rapidly than the diastolic volume, the excursion of the recording lever (output per beat) is increased, and may for a time be above normal.

When 1 c.c. of a 1 in 10,000 solution of adrenalin was added to the blood in the experiment (Table V), bringing the concentration in the circulating

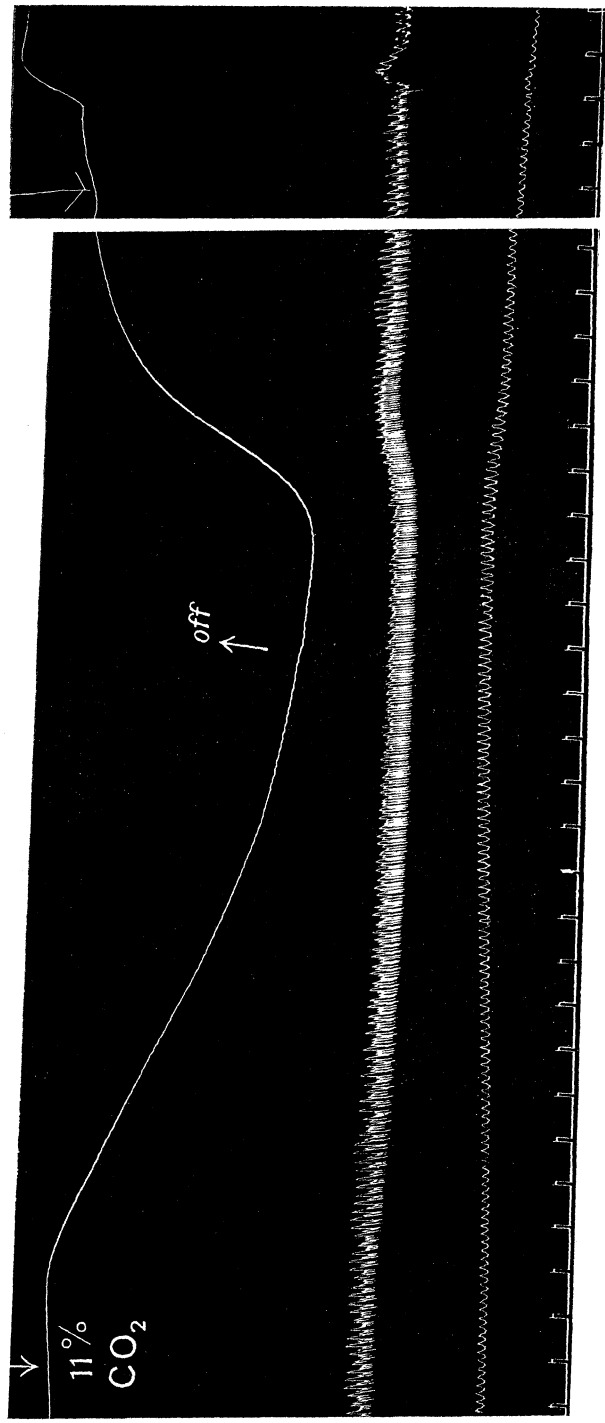

FIG. 2.—Effect of Carbon Dioxide (I) and Adrenalin (II) on Mean Heart Volume. Read from left to right. Protocols in Table V. Increase of cardiac volume caused fall of lever.

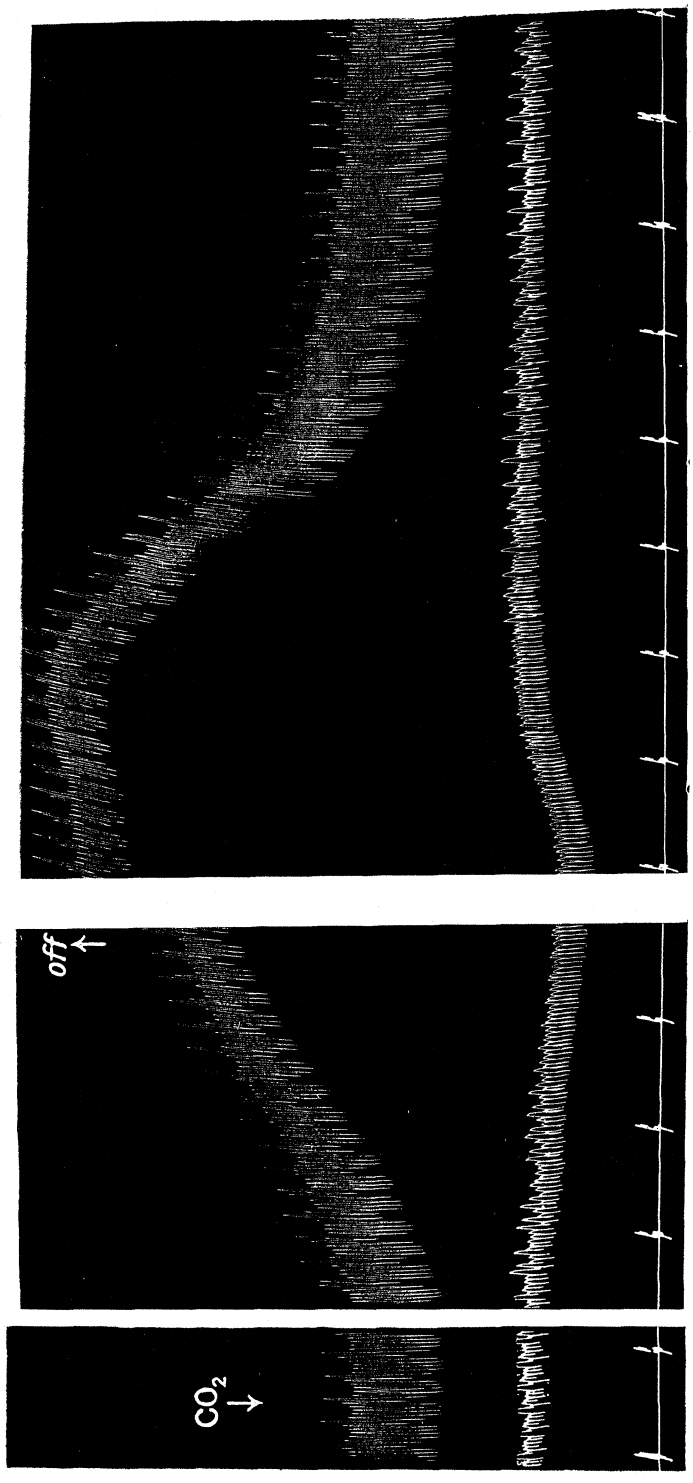

FIG. 3.—Effect of CO_2 on Heart Volume and Blood Pressure. Read from left to right; Systole downwards; increase of cardiac volume caused rise of lever. Intervals 20 secs. Upper tracing, cardiometer; lower tracing, blood pressure.

blood to about 1 in 3,500,000, the mean heart volume diminished 17·5 c.c. This takes place by the diastolic volume decreasing owing to lessened time between each beat for filling with the increased rate of the heart; and as the diastolic volume diminishes more rapidly than the systolic (fig. 4) the output

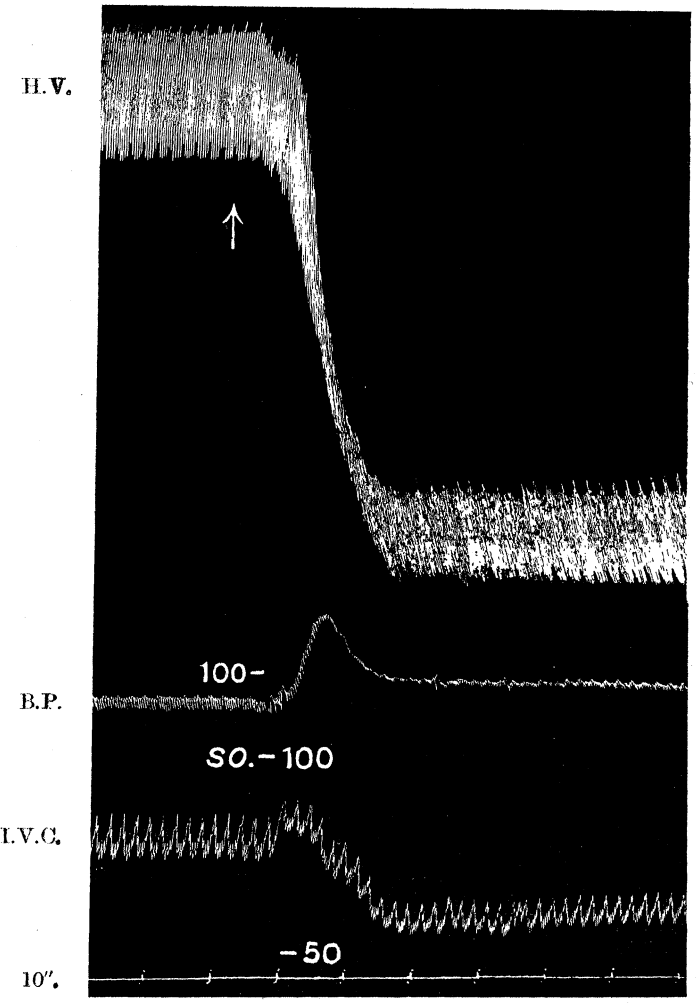

Fig. 4.—Effect of Adrenalin on Heart Volume, Blood Pressure, and Venous Pressure. 0·1 mgrm. adrenalin added at the arrow. Read from left to right. Systole downwards; decrease of cardiac volume caused fall of lever.

per beat is less. With recovery from adrenalin, the mean heart volume is greater than before its administration. A heart working badly and not dealing well with its venous inflow, so that the venous pressure is high, or a

heart working against a high arterial resistance, may dilate even in the presence of adrenalin.

Combining the administration of CO_2 and adrenalin in proper proportions may keep the mean heart volume constant, usually in a position shifted to the diastolic side; and the increased excursions of the lever (fig. 5) correspond with the increased output per beat and output per minute described above.

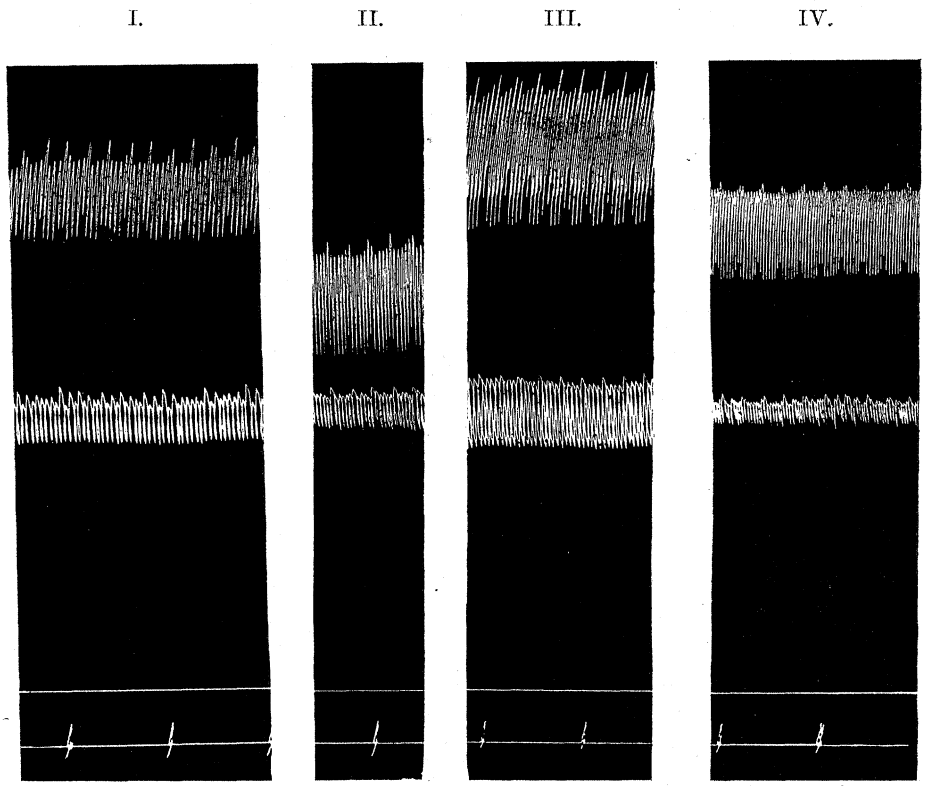

FIG. 5.—Cardiac Volume and Blood Pressure, showing effect of combining CO_2 and Adrenalin. (I) Normal; (II) adrenalin; (III) CO_2 and adrenalin; (IV) CO_2 off, recovery. Read from left to right. Intervals 2 mins. Systole downwards; increase of heart volume caused rise of lever.

Form of the Heart Volume Curves.—These curves were obtained by means of a glass plethysmograph on the ventricles, the movements being carried by air transmission to the brass piston recorder with vulcanite piston made by Albrecht. The movements of the piston were arranged to write in a vertical plane and recorded on smoked paper (fig. 6).

Normally, the form obtained by this method consists of a rounded curve, reaching its minimum usually with two points at which the curve changes to

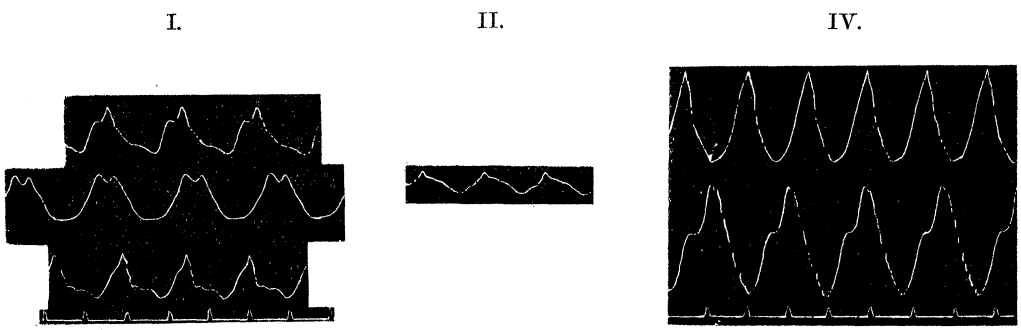

FIG. 6.—Ventricular Volume Curves. Read from left to right. Systole downwards. Time 1/5 second. (I) Medium venous inflow, normal, CO_2, adrenalin; (II) small venous inflow, adrenalin; (III) full venous inflow, adrenalin, adrenalin with CO_2.

be more convex to the abscissa, as the blood is driven out more slowly towards the end of systole. Diastole sets in rapidly and continues till, after about two-thirds of its course, it becomes less rapid, and then rises again parallel to its original curve to the maximum diastolic position, when the curve turns sharply into the downstroke of ventricular systole. With greater or smaller filling, the shape of the curve is steeper or more gradual; but only with hearts abnormally slowed by vagus stimulation is there a diastolic portion running nearly parallel with the abscissa; the part appearing to run parallel with the abscissa for an instant and interrupting the usual diastolic curve being probably due to the ventricles being drawn up slightly through the movable elastic diaphragm of the cardiometer by the contracting auricles.

When CO_2 is administered, the systolic downstroke is less steep, while the diastole is lengthened so that the next auricular systole occurs at the time that the heart volume has reached the maximum diastolic position.

With adrenalin the systolic downstroke is steeper than normal, and then reaches the minimum gradually, while the diastolic expansion is interrupted by the next auricular systole before the maximum dilatation is reached. In many cases, with small venous inflow, the heart volume curve presents a flat top, the systole continuing after the ventricle has expelled the blood in it. This is especially marked in curves obtained with small venous inflow after injection of adrenalin, when the major part of the output per beat is ejected in the first part of systole.

With full venous supply after adrenalin the systolic and diastolic parts of the curve are smooth and rapid;* but when CO_2 is administered at the same

* The smoothness of the curve with adrenalin, however, is probably due to the period of the recorder being too slow; for using the recorder designed by Piper (14), in Berlin, which turns the volume changes into pressure changes and records these by a beam of

time the systole of the ventricle is slower, and the next auricular systole shows as a well marked interruption of the diastolic part.

Endocardiac Pressure.—The curves were obtained in Berlin on the heart-lung preparation by means of the small manometers designed by Piper (15) according to Frank's specifications, and recording photographically. Figs. 7 and 10 (1) show the effect on the form of the intraventricular pressure curve of

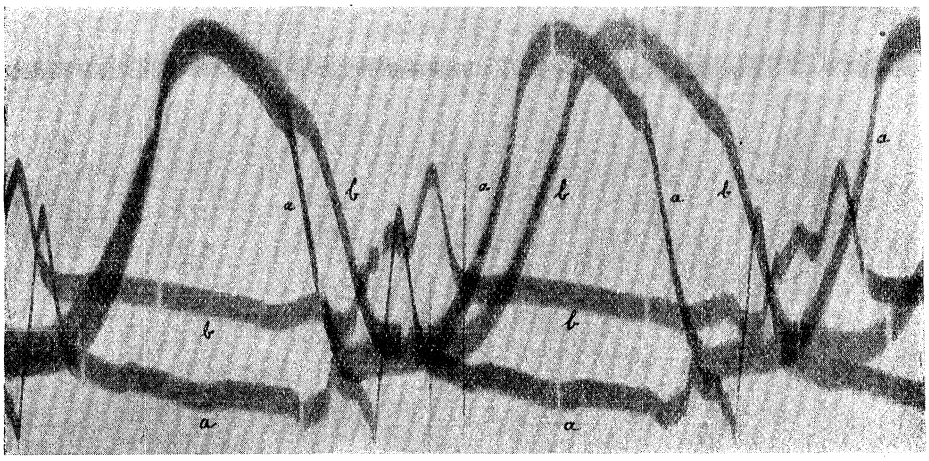

FIG. 7.—Effect of 12 per cent. CO_2 on Left Auricle and Ventricle. Read from right to left. Experiment 3, *a*, Table VI.

(*a*) Normal, T. 34·2, B.P. 102, I.V.C. 12, O.P. 101 c.c. in 10 secs.
(*b*) 12 per cent. CO_2, T. 34·2, B.P. 102, I.V.C. 30, O.P. ?

small percentages of CO_2 in the air breathed; the isometric period is not so steep as in the normal curve, the ventricle taking a longer time to develop the same amount of pressure (see Table VI, 1, 2, 3, 5, 8). The total length of systole is longer, and relaxation is slower; but it is a delay of the whole process of the heart cycle, and the proportion of systole to diastole remains about the same as in the normal beat. The maximum pressure exerted by the ventricle is usually a little less, 108 mm. Hg, as against 117 mm. in the normal, with the same venous supply and same arterial resistance (Table VI, Experiment 3).

After adrenalin the ventricle more rapidly reaches a certain tension in the isometric period,* and relaxation is also rapid; but the total diastolic time is proportionally longer than normal. For instance, in Experiments 6 and 7, Table VI, the diastole represented 52 per cent. of the total heart cycle,

light reflected from a mirror, we found the interruption due to auricular systole well marked, even with full venous supply after adrenalin.

* Wiggers (16) has already noted this in the right ventricle.

Table VI.—Rate and Force of Contraction and Relaxation.

	Heart rate 10 secs.	As-Vs interval.	Duration of heart cycle.		Systole.*		Diastole.*		Isometric period.		Maximum pressure in ventricle.
			Time.	Per cent.	Time.	Per cent.	Time.	Per cent.	Time.	Pressure.	
Experiment 1.—Dog, 7·5 kgrm., heart ? ; cannulæ in left auricle and left ventricle.											
			sec.		sec.		sec.		sec.	mm.	mm. Hg.
Normal	25	—	0·440	100	0·170	38·7	0·27	61·4	0·040	50	100
CO_2	21	—	0·490	100	0·188	38·5	0·302	61·5	0·047	50	102
CO_2 and adrenalin	34·5	—	0·285	100	0·090	31·6	0·195	68·4	0·013	50	80
Experiment 2.—Dog, 5·5 kgrm., heart 63 grm. ; cannulæ in left auricle and left ventricle.											
Normal	30	0·070	0·318	100	—	53·0	—	47·0	0·038	120	200
CO_2	25	0·085	0·398	100	—	49·0	—	51·0	0·041	120	225
Adrenalin	37	0·056	0·270	100	—	42·5	—	57·5	0·023	120	194
CO_2	26·5	0·091	0·376	100	—	47·0	—	53·0	0·041	120	220
CO_2 and adrenalin	36	0·062	0·277	100	—	39·0	—	61·0	0·029	120	225
Experiment 3.—Dog, 10·5 kgrm., heart 84 grm. ; cannulæ in left auricle and left ventricle.											
a Normal	24	0·093	0·415	100	0·215	51·8	0·200	48·2	0·060	75	117
a CO_2	22	0·093	0·455	100	0·243	53·5	0·212	46·5	0·080	75	108
Normal (V.S.+)	24	0·078	0·415	100	0·230	55·4	0·185	44·6	0·032	40	159
Adrenalin	37	0·068	0·272	100	0·107	39·4	0·165	60·6	0·015	40	156
Adrenalin	37	0·068	0·272	100	0·109	40·0	0·161	60·0	0·013	35	136
Adrenalin and CO_2	31	0·069	0·322	100	0·109	34·0	0·213	66·0	0·016	35	146
Experiment 4.—Dog, 8·5 kgrm., heart 66 grm. ; cannula in left ventricle and cardiometer.											
a Normal	26	—	0·388	100	0·185	47·7	0·203	52·3	0·052	75	130
a CO_2	25	—	0·400	100	0·195	48·8	0·205	51·2	0·058	75	130
b CO_2 and adrenalin	24·5	—	0·405	100	0·144	35·3	0·261	64·6	0·028	75	152
c Adrenalin	31	—	0·320	100	0·118	36·8	0·202	63·1	0·022	75	141
c Adrenalin and CO_2	25	—	0·400	100	0·135	33·8	0·265	66·2	0·028	75	170

Experiment 5.—Dog, 7·5 kgrm., heart 62 grm.; cannula in right ventricle and cardiometer.

a Normal	28	—	0·355	100	0·142	40·0	0·213	60·0	0·042	15	25
a CO_2	26	—	0·480	100	0·160	42·0	0·220	58·0	0·046	15	16·4
b Normal	26·5	—	0·377	100	0·138	36·6	0·239	63·5	0·042	15	17·2
b Adrenalin	43·5	—	0·228	100	0·090	40·0	0·187	60·5	0·020	15	34·5
c Adrenalin and CO_2	40	—	0·250	100	0·089	35·5	0·161	64·5	0·022	15	39

Experiment 6.—Dog, 7·5 kgrm., heart 75 grm.; cannulæ in left auricle and left ventricle.

Normal	24·5	0·110	0·410	100	0·197	48	0·213	52	0·050	75	116
Adrenalin	38	0·063	0·262	100	0·097	37	0·165	63	0·014	75	314

Experiment 7.—Dog, 8·5 kgrm., heart 85 grm.; cannulæ in left ventricle and left subclavian.

Normal	26·5	—	0·550	100	0·257	46·8	0·293	53·2	0·063	65	126
Adrenalin	40	—	0·383	100	0·146	38·1	0·237	62	0·021	65	172

Experiment 8.—Dog, 9·5 kgrm., heart 70 grm.; right ventricle and pulmonary artery.

a Normal	—	—	0·505	100	0·216	42·8	0·289	57·2	0·056	40	
a CO_2	—	—	0·538	100	0·288	53·5	0·250	46·5	0·064	40	
b Normal	—	—	0·513	100	0·235	45·8	0·278	54·2	0·054	40	48
b Adrenalin	—	—	0·380	100	0·166	43·6	0·214	56·3	0·039	40	67·5
c Adrenalin	—	—	0·380	100	0·146	38·4	0·234	61·0	0·0345	40	60
c Adrenalin and CO_2	—	—	0·415	100	0·169	40·7	0·246	59·3	0·046	40	63

* Systole = beginning of contraction to closure of aortic or pulmonary valves; diastole = remainder of heart cycle.

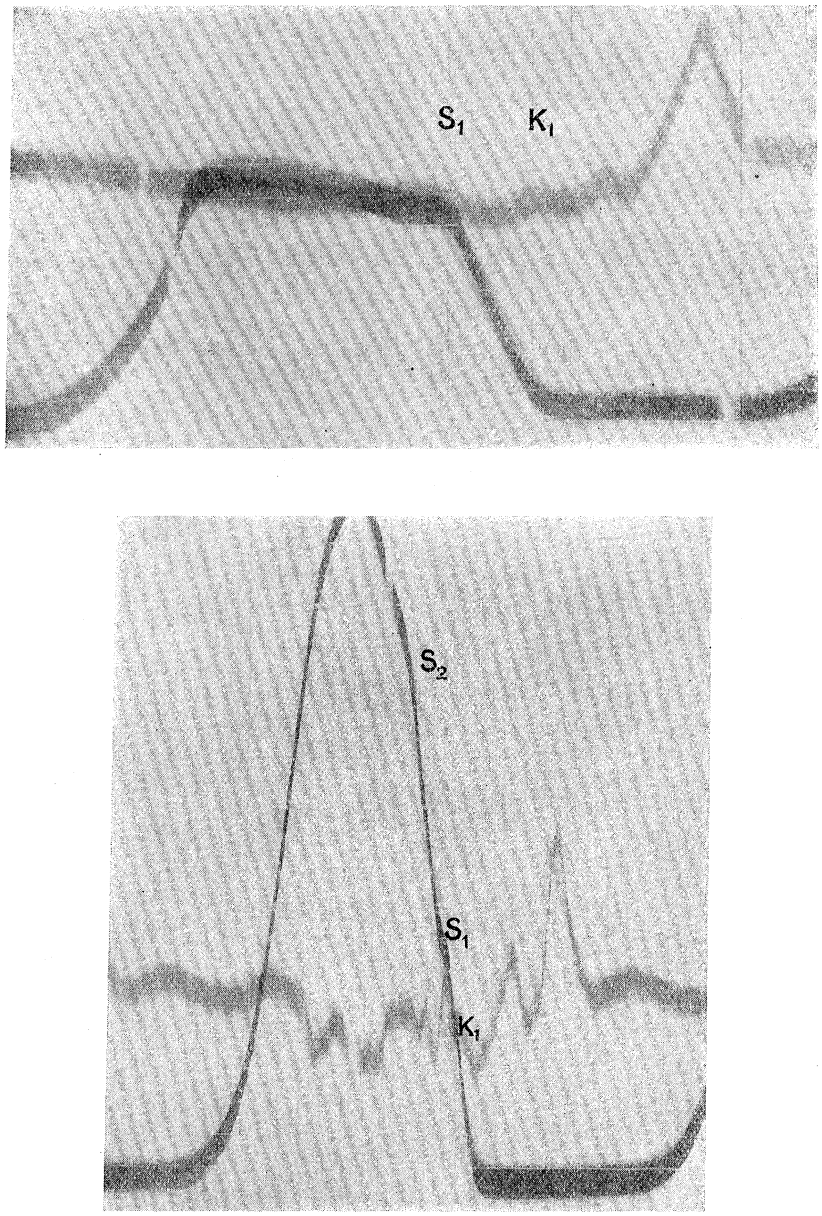

FIG. 8.—Left Auricle and Ventricle before and after Adrenalin. Read from right to left. Experiment 6, Table VI.

(*a*) T. 35·5, B.P. 84, I.V.C. 20, O.P. 194 c.c. in 10 secs., rate 24·5 in 10 secs. (normal).

(*b*) T. 36·4, B.P. 84, I.V.C. 10, O.P. 194 c.c. in 10 secs., rate 38 in 10 secs. (after 0·1 mgrm. adrenalin).

and after injecting adrenalin, diastole was 63 per cent. of the total heart cycle. The shortening of the time of the contractile period is so great that, even with the increased rate of heart-beat, the heart is in a state of contraction for 3·7 seconds in 10 seconds, as against 4·8 seconds in 10 seconds in the preceding normal period. In the heart cooled by cooling the inflowing blood, the proportion of diastole to total cycle is 50 per cent. Evans and Ogawa (17) have found the metabolism of the heart to be increased by about three times after injecting adrenalin. Since the time per 10 seconds during which the heart is in a state of contraction is shorter than in the normal period, adrenalin seems to have a specific effect in mobilising the "contractile substance," or in exaggerating the changes taking place on the "active surface" of the muscle fibres during contraction. That the heart behaves in quite another manner after injecting adrenalin is shown in fig. 8, the protocols of which are given in Table VI, 6 and 7. They show the more rapid development of tension in the isometric period, the great rise of maximum pressure (116 to 314 mm. Hg) as the blood is shot violently out of the ventricle, and the relatively short duration of the whole contractile process. For a similar effect on the right ventricle, see fig. 10 (2), protocols in Table VI, 5.

When CO_2 and adrenalin are administered together, there is a slightly lengthened time to get up a certain tension in the isometric period; the maximum pressure in the ventricle attains a greater height than before; and there is marked lengthening of the diastolic period, thus allowing time for greater filling before the next systole begins [figs. 9 and 10 (3)].

Output per Beat.—During the inhalation of CO_2 in percentages from 3 to 11, the output per beat is equal to, or even greater than, before; but with percentages of 12–20, or more, the output per beat is diminished, and there may be no flow of blood at all. When the CO_2 is removed and ordinary air breathed again, the output per beat is greater than before the CO_2, since the efficiency of contraction of the heart recovers before the rate again becomes normal.

With adrenalin, the output per beat is diminished. Inhalation of CO_2 combined with addition of adrenalin, gives an output per beat, if the dosage is adjusted, equal to, or greater than, the normal (fig. 5).

As–Vs *Interval.*—Adrenalin shortens the *a–v* interval. Small percentages of CO_2 in the air breathed cause little or no alteration in the interval, but with larger percentages (above 12 per cent.) the interval is lengthened; when combined with adrenalin, CO_2 still has not much effect; but sometimes with large amounts of CO_2 the heart rate drops to half, and a 2 : 1 heart-block is set up. Lewis and Mathison (18) found heart-block to be of regular occurrence

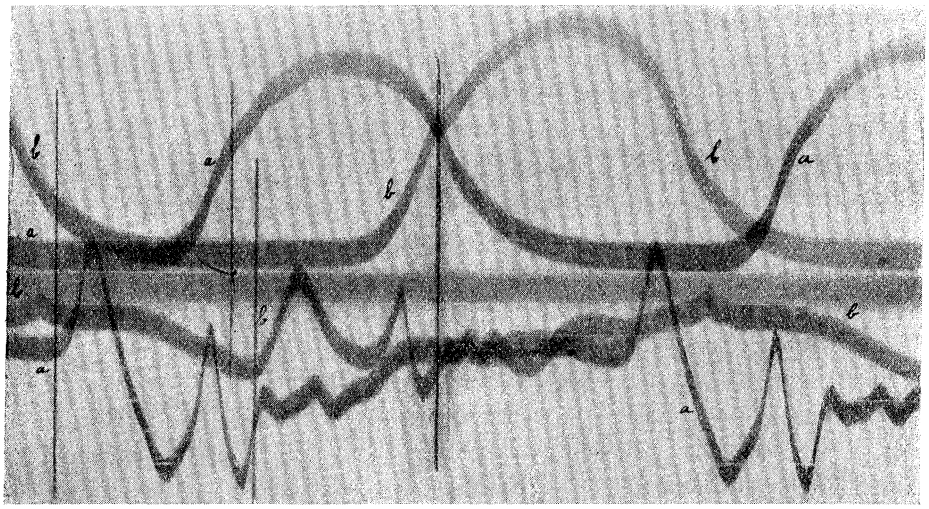

FIG. 9.—Effect of Adrenalin, and Adrenalin combined with CO_2, on Left Auricle and Ventricle. Read from left to right. Experiment 2, Table VI.

(*a*) T. 35, B.P. 96, I.V.C. 70, O.P. 100 c.c. in 10 secs. (after adrenalin).

(*b*) T. 35, B.P. 96, I.V.C. 70, O.P. ? (adrenalin and CO_2).

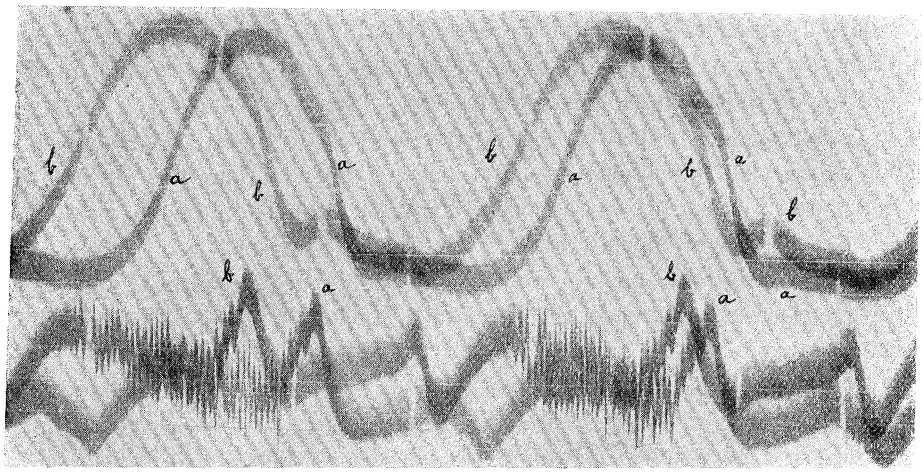

FIG. 10 (1), (2), and (3).—Right Ventricle and Pulmonary Artery. Read from right to left.

Fig. 10 (1).—Effect of CO_2, Experiment 8, *a*, Table VI.

(*a*) T. 36·5, B.P. 92, I.V.C. 22, O.P. 106 c.c. in 10 secs. (normal).

(*b*) T. 36·5, B.P. 92, I.V.C. 90, O.P. ? (6 per cent. CO_2).

(2)

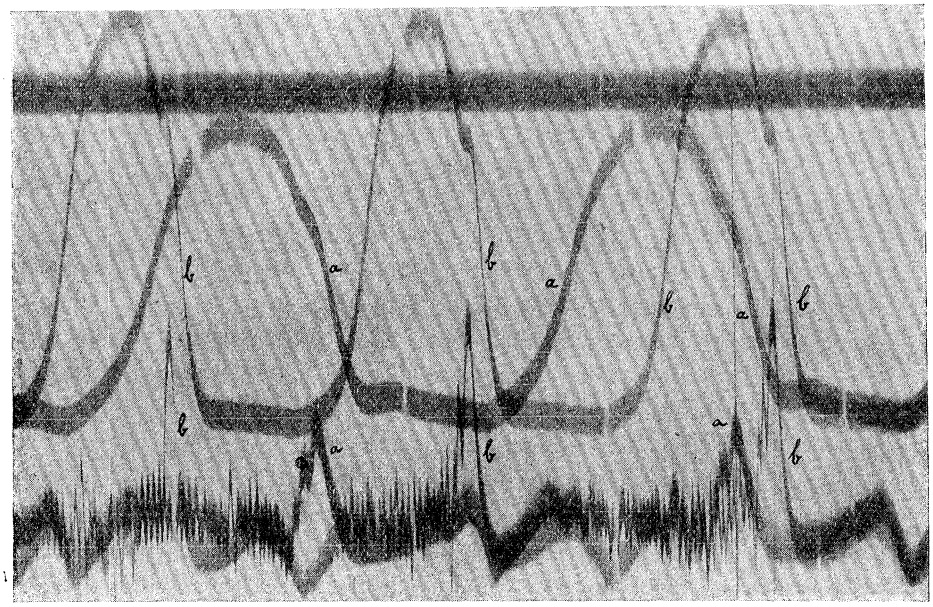

Fig. 10 (2).—Effect of adrenalin, Experiment 8, *b*, Table VI.

(*a*) T. 26·6, B.P. 92, I.V.C. 38, O.P. 128 c.c. in 10 secs. (normal).

(*b*) T. 36·6, B.P. 92, I.V.C. 12, O.P. ? (after 0·1 mgrm. adrenalin).

(3)

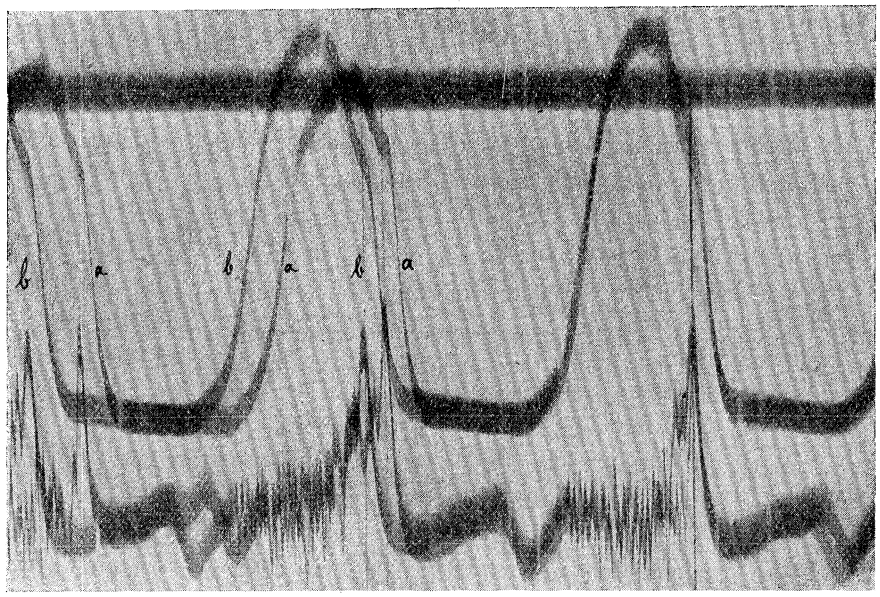

Fig. 10 (3).—Adrenalin and CO_2, Experiment 8, *c*, Table VI.

(*a*) T. 36·6, B.P. 92, I.V.C. 12, O.P. ? (adrenalin alone).

(*b*) T. 36·7, B.P. 96, I.V.C. 22, O.P. 124 c.c. in 10 secs. (adrenalin with 6 per cent. CO_2).

in asphyxia and independent of inhibition; and Mathison (19) found the cause to be due to lack of oxygen rather than excess of CO_2 in the spinal animal; but observed that heart-block may occur with large doses of CO_2 even in the presence of sufficient oxygen.

Summary and Discussion of Results.

Recent work on contraction of skeletal muscle has tended to establish more and more the view that the phenomena of contraction can best be described by reference to alterations of the surface energy of the muscle elements, and the length of the muscle fibres is a measure of the surface of action. In the heart the mean volume is the guide we have to the length of the muscle fibres, and it has been shown (20) that the heart reacts to increased work by increasing its mean volume, whether the increased work is evoked by greater diastolic inflow or greater arterial resistance.

It will be seen, from the results given above, that CO_2 in all doses appears to have a depressant action on the functions of the heart; the contractile stress is developed more slowly, the heart taking a greater mean volume to carry out its work, but if the CO_2 is continued, the observed output diminishes. Since the coronary circulation is unaltered this indicates a diminution of total ventricular output, and the venous pressure rises owing to the damming back of blood in the veins.

Adding adrenalin to the blood circulating through a heart which is capable of responding, causes increased rate of contraction and rate of development of contractile stress; the heart can develop the requisite tension more easily and from a position of shorter initial length, so the mean heart volume is shifted to the systolic side. Adrenalin seems to have a specific action in mobilising the "contractile substance" and increasing the energy changes taking place at the surface of the muscle fibres during contraction. The result is that the ventricle contracts violently and the blood is expelled under great pressure into the aorta. The coronary perfusion is greatly increased and the nutrition of the heart improved. Relaxation takes place rapidly, and since there is no resistance to the inflowing blood the venous pressure falls; but the onset of the next systole comes so early that the filling of the heart, and consequently the output per beat, are less than normal, but the total output of the ventricle per minute is equal to or greater than normal.

With CO_2 and adrenalin combined in proper doses we still obtain greater rate of contraction and relaxation, but the whole diastolic period is lengthened; thus there is time for greater filling, and there is increased output per beat and per minute. This increased observed systemic output

is accompanied by an increase in the coronary output, so that the total ventricular output is above normal. The slower contraction is also more effective in driving a mass of blood into the aorta instead of firing it out suddenly.

Cannon (21) has recently summarised the evidence of the significance to the organism of the function of the adrenal medulla in times of great emergency. We have found that the heart muscle is not only better nourished by increased coronary supply, but the contractile process is also strengthened in a specific manner. We have probably obtained in the heart-lung schema with maximum venous inflow and proper proportions of CO_2 and adrenalin, the conditions occurring in short severe muscular exercise, where the muscles of the arms and abdomen are contracted, while the legs are active, all aiding the venous return to the chest, the increased depth of respiration also assisting the venous return. The small excess of CO_2 is both the call to the secretion of the adrenals, which dilates the coronary vessels and strengthens the cardiac contraction, and the cause of the lengthened diastole and time for greater filling, so that the maximum output of the heart can be obtained.

Conclusions.

1. Carbon dioxide alone depresses all the functions of the isolated heart.
2. Adrenalin, besides dilating the coronary vessels, has a specific action in increasing the rate and strength of ventricular contraction.
3. The effect of carbon dioxide and adrenalin combined is still to allow of more rapid and stronger contraction and rapid relaxation, and also to lengthen the diastolic period. Thus greater filling of the heart takes place and the heart is in a better condition for putting out a maximal output.

I have much pleasure in recording my thanks to Prof. Piper, of Berlin, for his assistance with the endocardiac pressure tracings, and to Prof. Starling, of London, for the initiation and successful carrying out of the whole work.

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The Influence of Salt-Concentration on Hæmolysis.

By W. W. C. Topley, M.B., M.R.C.P., Bacteriologist to Charing Cross Hospital.

(Communicated by Dr. F. W. Mott, F.R.S. Received November 25, 1914.)

(From the Bacteriological Department of Charing Cross Hospital.)

The question of the effect of salt-concentration on the phenomena involved in hæmolysis has already received a considerable amount of attention.

Nolf originally showed that the presence of certain salts, in definite concentrations, inhibited hæmolysis, and his observations have been repeatedly confirmed.

Markl, working with acid sodium phosphate, showed that the introduction of this salt into a hæmolytic mixture caused complete inhibition of hæmolysis when a certain concentration was reached. He was also able to show that the presence of this salt did not prevent the combination of the antibody with the red cells. He therefore concluded that its action consisted in so influencing the osmotic relations of the cell membrane that the complement could not be fixed upon it. He found that this action was not specific for acid sodium phosphate, but could be observed with other salts, notably with hypertonic solutions of sodium chloride itself.

These results were confirmed by Ehrlich and Sachs; but these authors, interpreting their findings in the light of the side-chain theory, believe that the action of the increased saline concentration is produced by preventing the chemical union of the amboceptor and complement, and not by any change in the osmotic relations of the cell membrane.

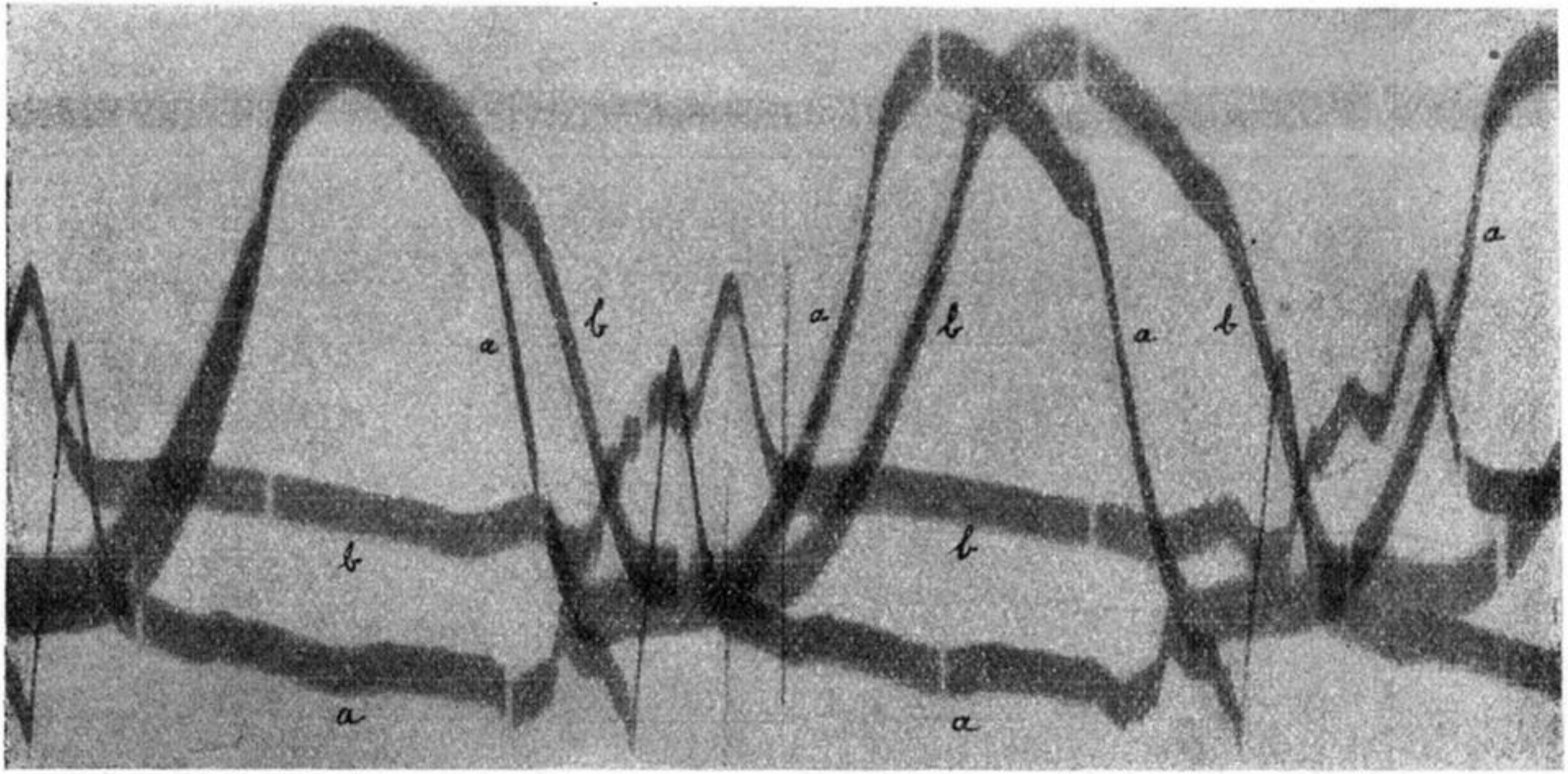

FIG. 7.—Effect of 12 per cent. CO_2 on Left Auricle and Ventricle. Read from right to left. Experiment 3, *a*, Table VI.

(*a*) Normal, T. 34·2, B.P. 102, I.V.C. 12, O.P. 101 c.c. in 10 secs.
(*b*) 12 per cent. CO_2, T. 34·2, B.P. 102, I.V.C. 30, O.P. ?

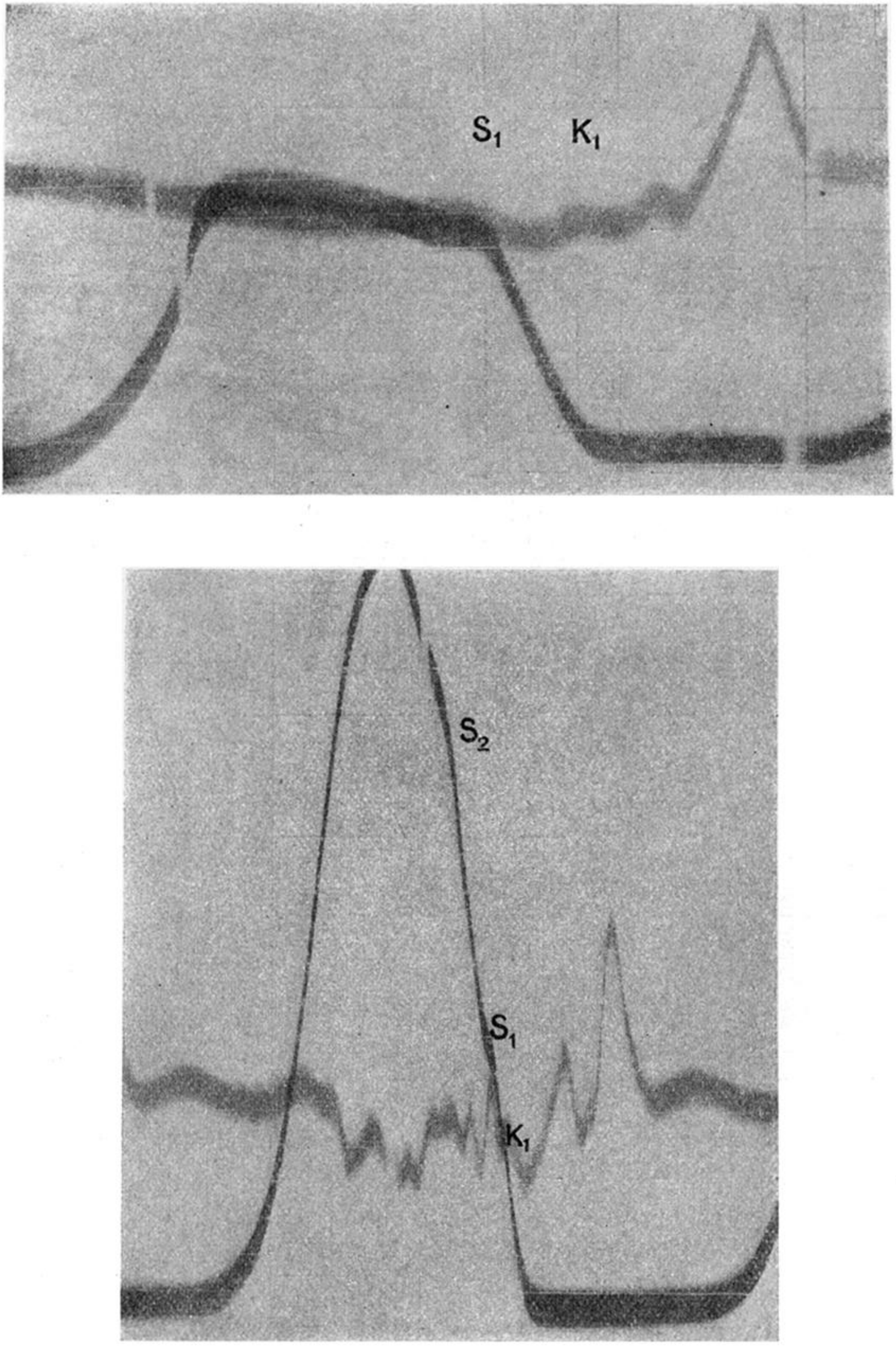

FIG. 8.—Left Auricle and Ventricle before and after Adrenalin. Read from right to left.
Experiment 6, Table VI.

(*a*) T. 35·5, B.P. 84, I.V.C. 20, O.P. 194 c.c. in 10 secs., rate 24·5 in 10 secs. (normal).

(*b*) T. 36·4, B.P. 84, I.V.C. 10, O.P. 194 c.c. in 10 secs., rate 38 in 10 secs. (after 0·1 mgrm. adrenalin).

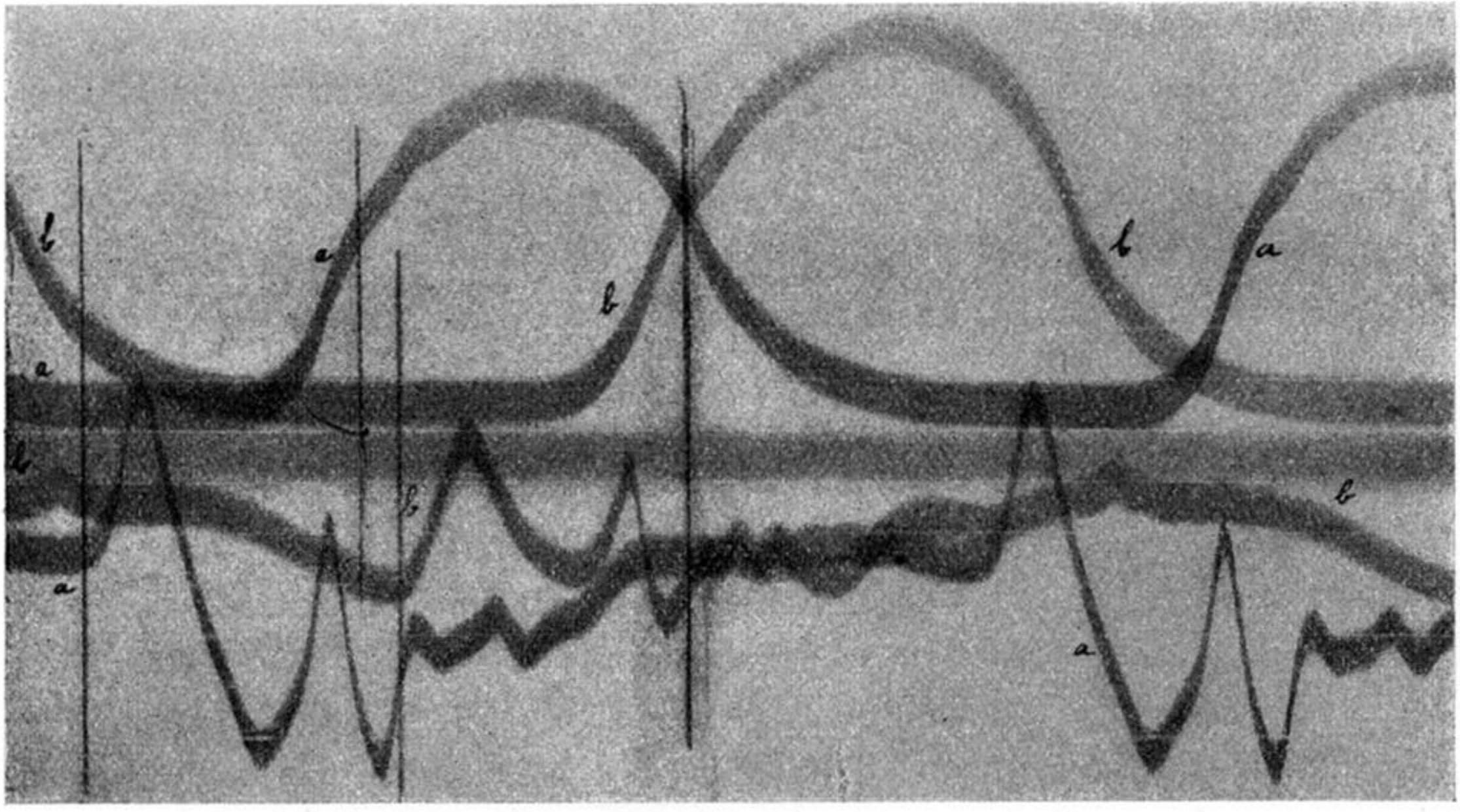

FIG. 9.—Effect of Adrenalin, and Adrenalin combined with CO_2, on Left Auricle and Ventricle. Read from left to right. Experiment 2, Table VI.

(*a*) T. 35, B.P. 96, I.V.C. 70, O.P. 100 c.c. in 10 secs. (after adrenalin).
(*b*) T. 35, B.P. 96, I.V.C. 70, O.P. ? (adrenalin and CO_2).

I(1)

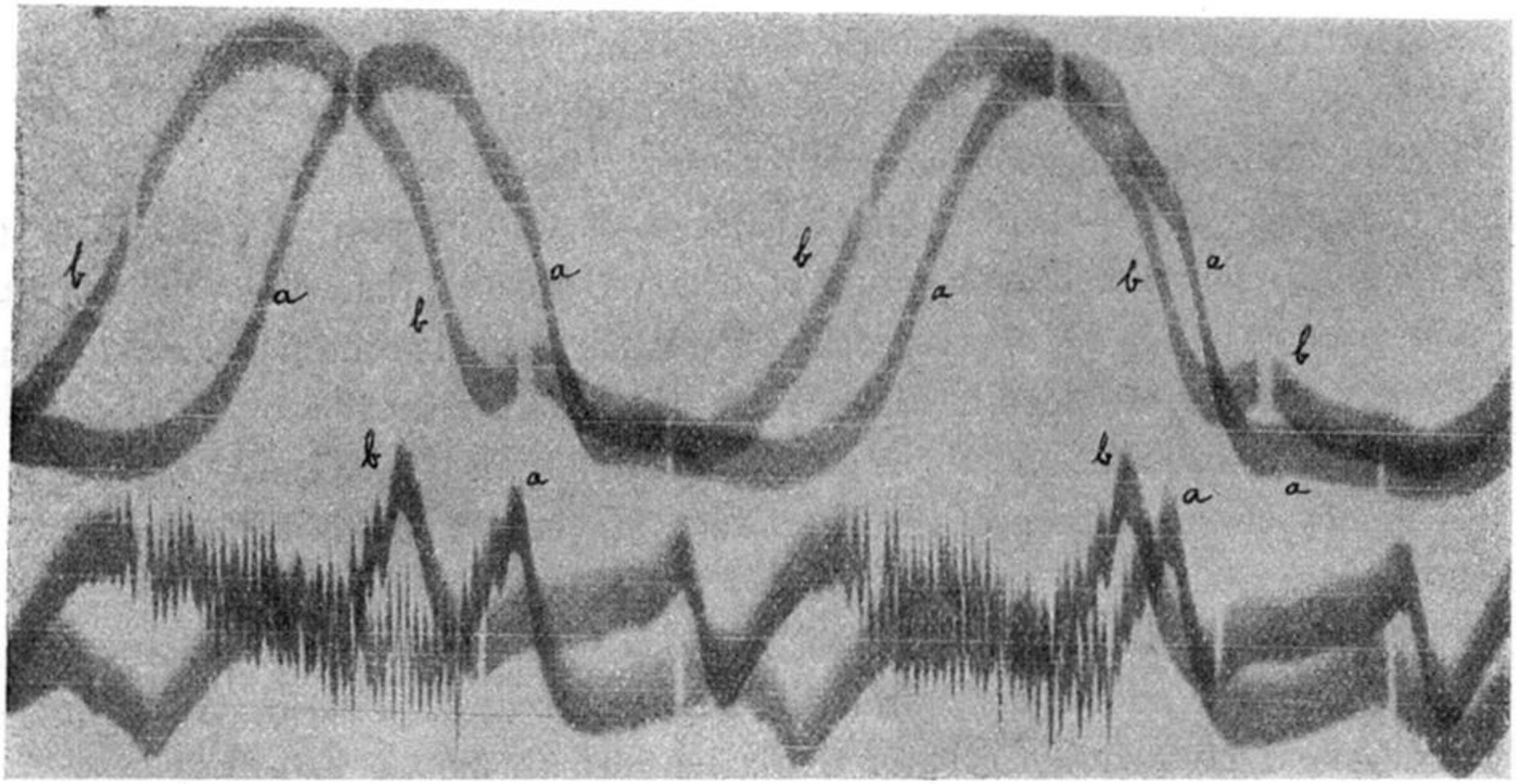

Fig. 10 (1), (2), and (3).—Right Ventricle and Pulmonary Artery. Read from right to left.

Fig. 10 (1).—Effect of CO_2, Experiment 8, *a*, Table VI.

(*a*) T. 36·5, B.P. 92, I.V.C. 22, O.P. 106 c.c. in 10 secs. (normal).

(*b*) T. 36·5, B.P. 92, I.V.C. 90, O.P. ? (6 per cent. CO_2).

(2)

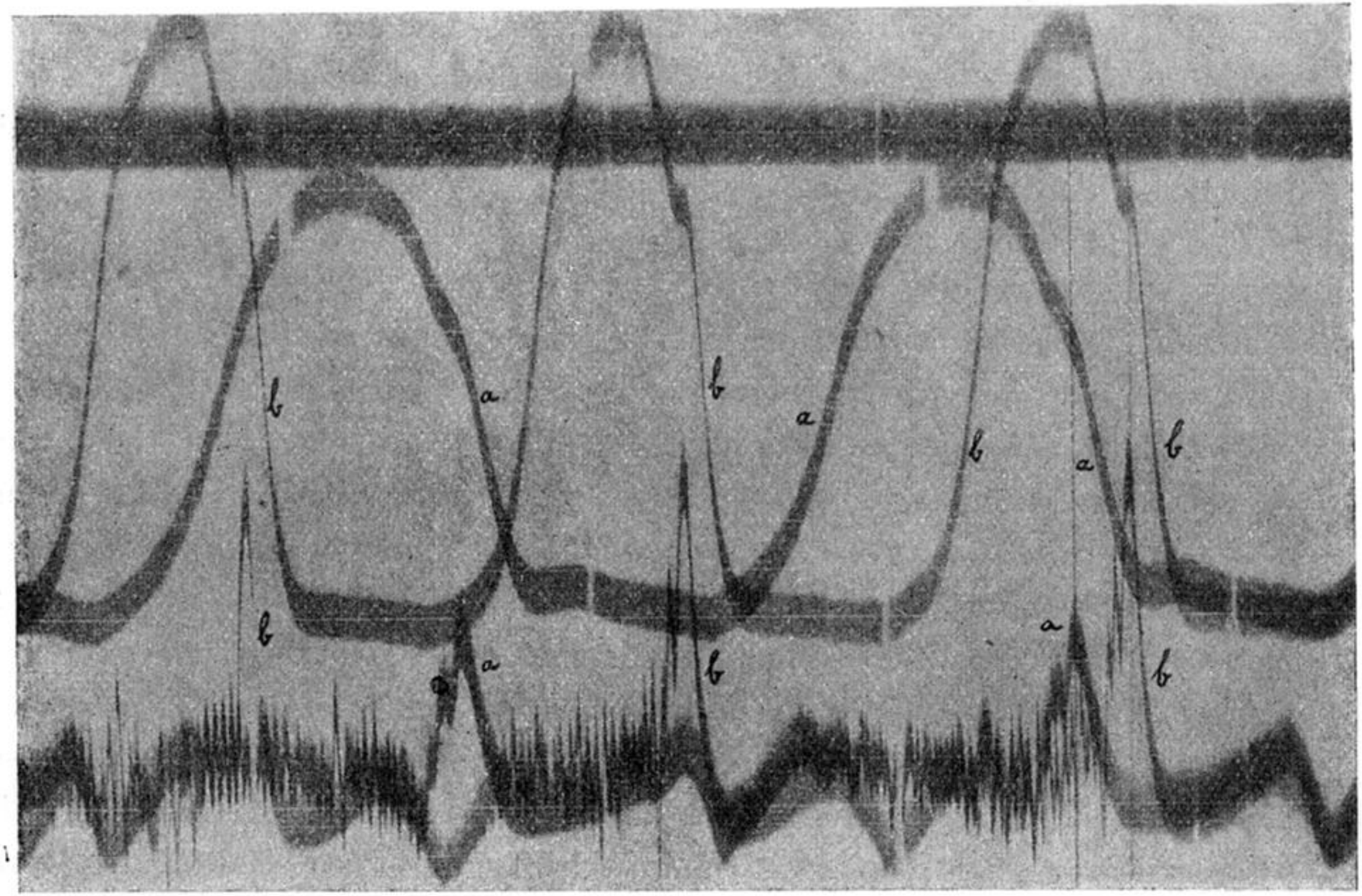

Fig. 10 (2).—Effect of adrenalin, Experiment 8, *b*, Table VI.

(*a*) T. 26·6, B.P. 92, I.V.C. 38, O.P. 128 c.c. in 10 secs. (normal).

(*b*) T. 36·6, B.P. 92, I.V.C. 12, O.P. ? (after 0·1 mgrm. adrenalin).

(3)

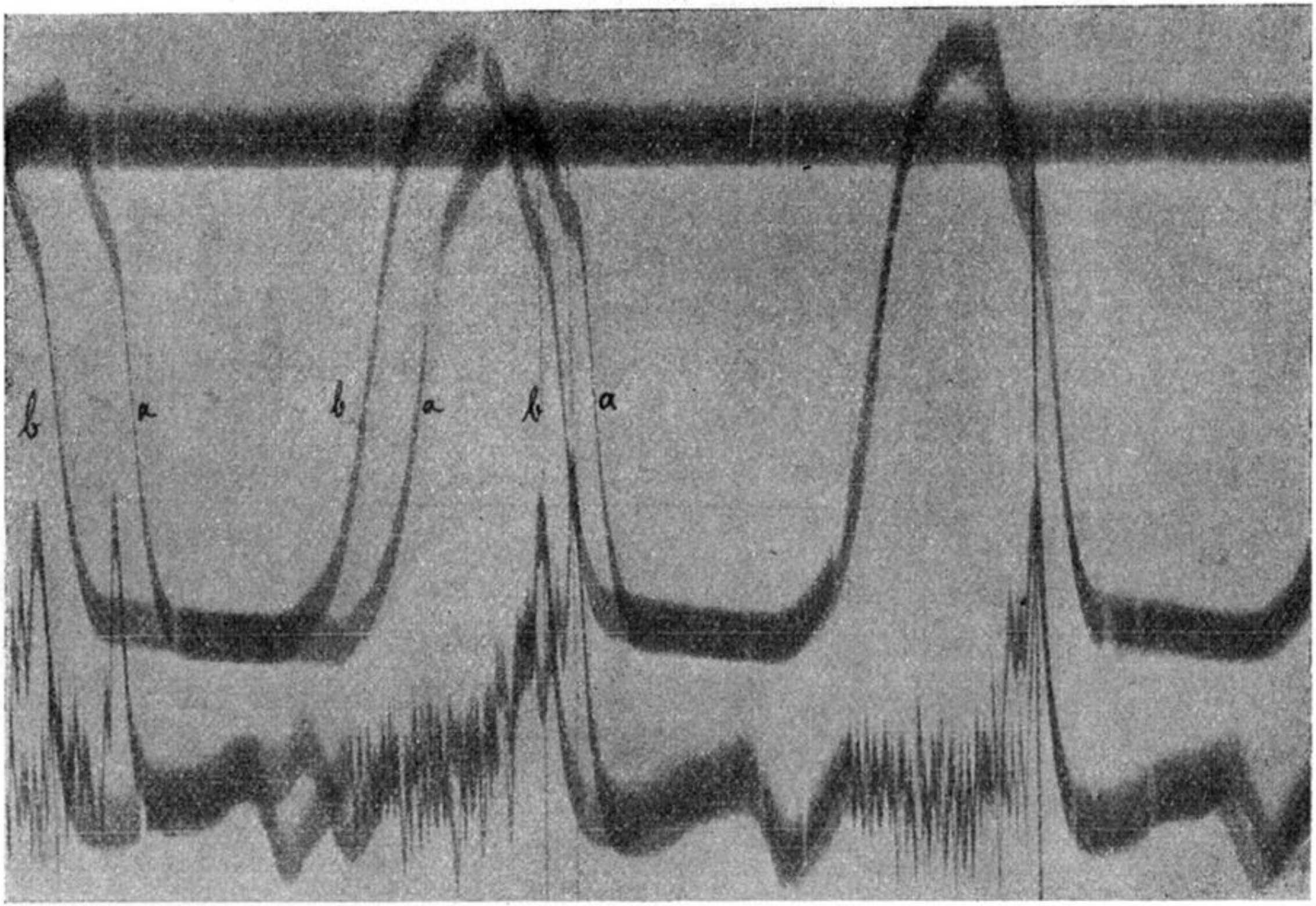

Fig. 10 (3).—Adrenalin and CO_2, Experiment 8, *c*, Table VI.

(*a*) T. 36·6, B.P. 92, I.V.C. 12, O.P. ? (adrenalin alone).

(*b*) T. 36·7, B.P. 96, I.V.C. 22, O.P. 124 c.c. in 10 secs. (adrenalin with 6 per cent. CO_2).