OBSERVATIONS ON THE EFFECT OF ANOXEMIA ON THE HEART: *I. Auriculo-ventricular Conduction*

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OBSERVATIONS ON THE EFFECT OF ANOXEMIA ON THE HEART

I. Auriculo-ventricular Conduction

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INTRODUCTION

Since anoxemia is so frequent a manifestation of many medical conditions, and particularly since in some of these abnormal states its severity may make it a prominent feature of the malady, it is of some interest and importance to inquire in how far it may affect various bodily functions. Is anoxemia to be considered merely a symptom, relatively unimportant in itself, except in indicating that the process which causes it may be a severe one; or is it to be viewed in the light of a symptom which, by virtue of its own effects, may have a serious influence on the course of the underlying condition? It is needless to point out that an impaired oxygen supply may have harmful effects on certain physiological activities, the general nature of which has been sufficiently emphasized by Haldane (1919) and Barcroft (1920).

Concerning the influence of anoxemia on the heart not a great deal is definitely known. I do not propose to enter into a detailed review of all the literature bearing on the changes in the heart produced by anoxemia, but shall confine myself particularly to the work which is directly related to the problem of the effect of anoxemia on auriculo-ventricular conduction.[1] Lewis and Mathison (1910–11) first proved

[1] In this paper, I shall use the term "conduction" only to express the transmission of an impulse from the auricles to the ventricles, without reference to the hypothetical function "conductivity," or to the mechanism by which alterations in the transmission time are brought about.

that following asphyxiation depression of auriculo-ventricular conduction took place, ultimately advancing to the degree of complete heart block. Since these events occurred after the complete removal of vagal tone, they were ascribed to a direct effect on the myocardium, and Mathison (1910–11) showed that this result was not caused by the accumulation of carbon dioxide, but rather by lack of oxygen. Later, Mathison (1910) found that the administration of a high concentration of carbon dioxide might bring about a certain degree of auriculo-ventricular block, apparently slight. More recently, Greene and Gilbert (1922) observed the effect of a more slowly induced progressive anoxemia, produced by the method of re-breathing and maintained until the animal died usually within a period of 15 to 18 minutes. Carbon dioxide was continually absorbed in the apparatus which they used, and was thus eliminated as a possible factor in the causation of the changes which took place in the cardiac mechanism. Up to a certain critical period, usually when respiration failed, there were practically no changes in the heart except slight quickening of rate and reduction of the P-R interval. Following the "crisis" however, certain alterations in the rhythm of the heart (including conduction defects) did take place, these changes occurring as a result of central stimulation of the vagus nerves by anoxemia. It was only three to five minutes after respirations had ceased and just before the death of the animal that Greene and Gilbert were able to detect a direct action on the heart by anoxemia. Essentially the same phenomena had been noted previously by Haggard (1921) on exposing animals to increasing concentrations of carbon monoxide. Greene and Gilbert reconciled the difference in the results obtained by them and those observed by Lewis and Mathison by assuming that, because of the rapid method of inducing anoxemia used by the latter, the direct effects on the myocardium appeared early in their experiments and corresponded to the late effects which they (Greene and Gilbert) observed in their own more prolonged experiments.

On the basis of the observations of Greene and Gilbert, then, one might infer that even a severe degree of anoxemia had relatively little influence on the myocardium. It seemed, however. that a more accurate idea of the effect of anoxemia on the heart muscle might be acquired if one subjected an animal to a degree of anoxemia, insufficient

to bring about its death, but maintained over a longer period of time. In this way, conditions would simulate more closely those prevailing in the ordinary clinical cases, in which a moderate or severe grade of anoxemia may be present for a comparatively long time. It was possible that the duration of time in which anoxemia was present might be a factor of some importance in determining the effect on the heart muscle. Moreover, it was conceivable that if one increased the rate of the heart during anoxemia, one might bring out a change which was latent in the naturally beating heart. Erlanger and Hirschfelder (1905) and Lewis and Oppenheimer (1910–11) have shown that when auriculo-ventricular conduction was already impaired, an increase in the heart rate exaggerated the degree of block between the auricles and ventricles.

EXPERIMENTAL METHODS

Dogs, averaging between 10 to 15 kg. in weight were anesthetized by the subcutaneous administration of pantopon, 5.5 to 6.0 mgm. per kilogram, followed within 15 minutes by giving 1 gm. urethane per kilogram by stomach tube. A steady and satisfactory anesthesia was produced, the animal remaining quiet and in good condition for as long as five hours, the longest period over which the experiments were carried out. Both vagus nerves were tied; in addition, in all but a few of the experiments full doses of atropine, usually 2 to 5 mgm., were injected intravenously every 15 to 20 minutes. No differences were noted between those animals which received atropine, and those that did not. After the insertion of a cannula in the trachea, artificial respiration was started, using intratracheal insufflation. Usually the pressure distending the lungs was 20 to 30 mm. mercury. After ligating the internal mammary arteries, the sternum was split in the midline, the sides being retracted by weights. In most of the experiments the pericardium was opened and stitched to the sides of the chest wall, and in these electrocardiographic records of the heart were taken from electrodes placed directly on the auricle. The electrodes were small glass tubes filled with a saturated solution of copper sulphate, the ends of the tubes being plugged with a paste of kaolin in normal saline solution. In other experiments, in which the pericardium was unopened, records were taken by lead II, small german silver electrodes being either sewn under the skin or held in position by bandages soaked in saline.

Anoxemia, always of the anoxic type, was produced by administering suitable mixtures of oxygen and nitrogen. Thick-walled rubber tubing leading from high pressure gas tanks fitted with reducing valves were connected to glass tubes inserted through a rubber stopper in a glass flask. The ends of the glass tubes were placed just beneath a layer of water, the gases bubbling through the water before being forced out of a side tube leading to the intratracheal catheter. Connected

with each rubber tube coming from the tanks was a mercury manometer giving the pressure of each of the gases flowing to the mixing flask; and between the mixing flask and the catheter was another manometer registering the pressure in the the lungs. The amount and proportions of the gases and the degree of distention of the lungs were regulated by varying the pressure in each of the systems. The volume of gas flowing to the lungs was about 5000 cc. per minute, insuring adequate ventilation.

The auricles were driven at desired rates by a Lewis rotary stimulator, only break shocks being used, the strength of the shock in every instance being well above the threshold value. This apparatus was connected to small fishhook stimulating electrodes which were inserted near the base of the right auricular appendage. The recording electrodes on the heart, when they were used, were placed about 1 cm. away toward the midcaval region, in line with the stimulating electrodes. In some of the experiments, two galvanometers were used, recording simultaneously on the same film, one for the stimuli, the other for the activity of the heart. Owing to a temporary disarrangement of one of the galvanometers, only one could be used in most of the observations. It was found, however, that this method was quite satisfactory, since by using sufficiently a strong stimulating current, the stimuli were clearly shown on the electrocardiographic record.

Measurements of the P-R interval were made with a Lucas comparator, the average of at least three determinations being taken as the figure for a record. The figures do not represent true P-R values since the measurements were made from the sharpest points, not necessarily the beginning of the auricular and ventricular complexes. Since the same points were used in measuring the curves of an entire experiment, the absoute figures are comparable, then, in the same but not in different animals. In most instances, the figures for a record fell within 0.003 to 0.005 second in the records taken by lead II; and within 0.002 to 0.003 second in the records taken directly from the auricle.

The degree of anoxemia was ascertained by determination of the oxygen saturation of the arterial blood (van Slyke and Stadie, 1921), which was obtained from the femoral artery and handled with the usual precautions. At first, the oxygen capacity was determined on every sample. Later, this was not done, for with sufficiently high concentrations of oxygen (50 to 100 per cent) in the gas mixtures, it was assumed (after a few control observations) that the oxygen saturation was 100 per cent.

The usual procedure of an experiment was to give a high oxygen mixture and to record the activity of the heart with the electrocardiograph during various rates of rhythmic stimulation. The time of stimulation was constant before each record was taken. The percentage of oxygen in the gas mixture was then lowered, and after several minutes records were taken at intervals, at approximately the same rates of stimulation that had been used before. Finally, in most cases, the percentage of oxygen was increased to its previous level and a further series of records again obtained.

TABLE 1

Dog 13. Pericardium unopened; fully atropinized

Oxygen saturation 96 per cent*				Oxygen saturation 89 per cent Started 12:45			
Time	Rate of stimulation	Auricular response	P-R interval	Time	Rate of stimulation	Auricular response.	P-R interval.
	per minute		*seconds*		*per minute*		*seconds*
11:55	212	1:1	0.077	12:56	212	1:1	0.078
11:58	243	1:1	0.081	12:57	243	1:1	0.081
12:00	264	1:1	0.083	12:58	261	1:1	†
12:17	285	1:1	0.087	12:59	277	1:1	0.085
12:22	323	1:1	0.097	1:00	324	1:1	0.102
12:24	367	1:1	2:1 response	1:01	370	1:1	2:1 response
12:26	428	1:1	2:1 response	1:02	422	1:1	2:1 response
12:28	476	1:1	2:1, 1:1 response alternating	1:04	475	Occasional dropped beat	2:1 with 1:1 response every third beat
12:30	516	Occasional dropped beat	2:1, occasional 1:1 response	1:06	518	Occasional dropped beat	2:1 with 1:1 response every fourth beat
12:32	572	2:1 response (rate 286)	1:1 response	1:08	580	2:1 response (rate 290)	1:1 response
12:34	640	2:1 response (rate 320)	1:1 response	1:10	658	2:1 response (rate 329)	1:1 response
12:36	768	2:1 response (rate 384)	2:1 response (rate 192)	1:12	774	2:1 response (rate 387)	2:1 response (rate 198.5)

* In this table, as in all subsequent tables, the percentage of oxygen saturation refers to the arterial blood.

† Accurate measurements could not be made.

RESULTS

The results will be presented in three groups, divided arbitrarily according to the degree of anoxemia, mild (arterial oxygen saturation above 85 per cent), moderate (70 to 85 per cent saturation), severe (oxygen saturation below 70 per cent). The effect of anoxemia on

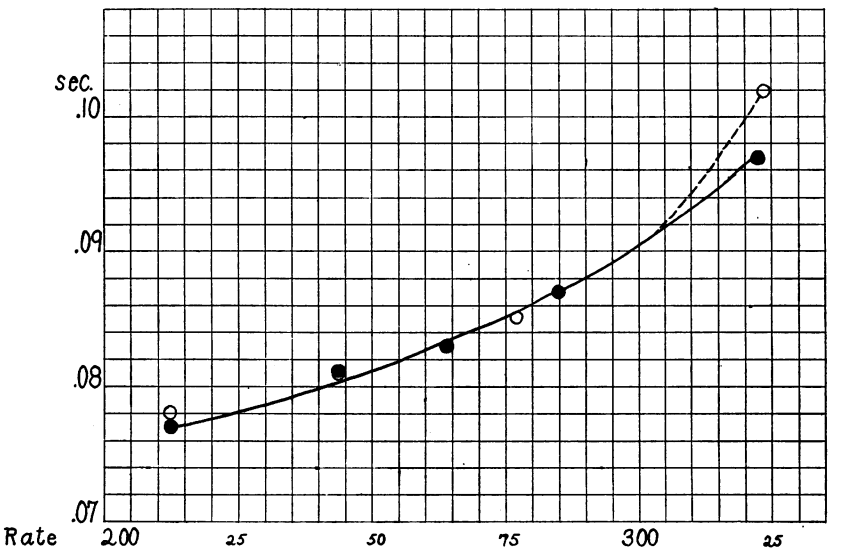

FIG. 1. DOG 13. THE P-R INTERVALS AT DIFFERENT RATES OF RHYTHMIC STIMULATION OF THE HEART

Black dots: Arterial oxygen saturation 96 per cent.

Circles: Arterial oxygen saturation 89 per cent.

The chart shows the effect of mild anoxemia on auriculo-ventricular conduction. The values for the P-R intervals during the periods of higher and lower arterial oxygen saturation lie on an identical curve, except at the rate of approximately 325 per minute. The apparent divergence of the curves at this point is probably due in part to errors of measurement (see text).

auriculo-ventricular conduction was observed in 17 animals, and since the course of events was essentially the same in the different groups, I shall give the figures only of those experiments in which the data are more complete, or which are of unusual interest.

Effect of mild anoxemia

In tables 1, 2, and 3 are given the results in three experiments. In experiment 13 (table 1), the anoxemia was of relatively short duration

TABLE 2

Dog 19. Pericardium unopened; fully atropinized

Oxygen saturation 90 per cent Started 11:40 Natural heart rate 176			Oxygen saturation 98 per cent Started at 12:37 Natural heart rate 164		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*second*		*per minute*	*second*
12:19	221	0.085	1.20	218	0.092
	260	0.092		254	0.100
	312	0.113		312	0.119
12:35	361	Occasional dropped beat	1.28	355	Occasional dropped beat

TABLE 3

Dog 24. Pericardium opened; fully atropinized

Oxygen saturation 100 per cent Natural heart rate 156			Oxygen saturation 89 per cent Started 11:38 Natural heart rate 152			Oxygen saturation 100 per cent Started 1:33 Natural heart rate 144		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*second*		*per minute*	*second*		*per minute*	*second*
11:15	227	0.092	1.28	223	0.087	2.01	224	0.091
	301	0.107		292	0.101		290	0.104
	342	Rare dropped beats		342	1:1*		338	1:1*
11:29	357	Every sixth or seventh beat dropped	1.32	364	Occasional dropped beat	2.12	358	Occasional dropped beats

* Accurate measurements could not be made.

and there was practically no change in the P-R intervals. The values are charted in Figure 1 up to the stage of auriculo-ventricular block.

There is an apparent divergence of the curves at the rate of approxi-

mately 320; but it was more than likely that the difference is due, in part at least, to errors of measurement. One would expect, if there were actually increased impairment of conduction during the anoxic period, that this defect would be enhanced at the more rapid rates. The responses remain, however, practically identical.

In the other two experiments (tables 2 and 3),[2] a decrease in the

Dog 15. Pericard

Oxygen saturation 100 per cent Natural heart rate 162			Oxygen saturation 81 per cent Started 11:47 Natural heart rate 154			Oxygen saturation 81 per cent Started 11:47 Natural heart rate 158		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*seconds*		*per minute*	*seconds*		*per minute*	*seconds*
11:33	204	0.091	11:57	210	0.089	12:30	201	0.083
	230	0.091		234	0.091		226	0.086
	257	0.096		266	0.095		256	0.090
				286	0.099		280	0.092
	301	0.099		306	0.102		307	0.096
	335	0.116		342	0.113		344	0.103
	366	0.125		372	0.123		376	0.121
	400	1:1, with periods of 2:1 response		393	1:1, with periods of 2:1 response		399	1:1 *respon
11:45	438	2:1, with 1:1 response every third beat	12:07	434	2:1, with 1:1 response every third beat	12:40	420	Periods of 2 3:1, w long peri of 1:1 sponse

* Accurate measurements could not be made.

P-R interval occurred after a somewhat longer period of anoxemia. The difference between the values of the higher and lower oxygen series is slight but definite. It represents a real change, for it occurred uniformly at the different rates of the same series of observations;

[2] Although a series of records was made during high oxygen concentration, the records were not sufficiently good for accurate measurement. The results are given primarily to show the increase in the P-R intervals following the change from the lower to the higher oxygen saturations of the arterial blood.

and, on restoration of normal oxygen saturation, as in Experiment 24, (table 3), the P-R intervals rose again and approached those originally obtained.

Experiments 13 and 24 serve also as controls on the observations to be reported below; for they demonstrate that the mere duration of an experiment produced no significant changes in the P-R interval.

3 4

pened; fully atropinized

Oxygen saturation 81 per cent Started 11:47 Natural heat rate 156			Oxygen saturation 81 per cent Started 11:47 Natural heat rate 144			Oxygen saturation 97 per cent Started 2:16 Natural heart rate 162		
me	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*seconds*		*per minute*	*seconds*		*per minute*	*seconds*
15	205	0.082				3:01	207	0.077
	220	0.082	2:01	229	0.079		222	0.079
	254	0.084		260	0.081		257	0.079
	279	0.089		282	0.085		282	0.090
	301	0.092		304	0.091		303	0.092
	337	0.100		341	0.102		330	0.096
	364	0.113		371	0.118		365	*
	400	2:1 response		396	2:1 response		380	0.119
25	432	2:1 and 1:1 response	2:15	427	Periods of 2:1, with periods of 1:1 response	3:16	424	Periods of 1:1, with periods of 2:1 response

In experiment 24, after almost three hours, the values at the different rates were practically identical.

To summarize, then, the effects of mild anoxemia on auriculoventricular conduction: there is practically no change over a short period of time; over longer durations, the P-R interval is slightly but definitely lowered at both low and high rates of stimulation. When the normal degree of arterial oxygen saturation is restored, the figures rise again to practically their original values.

Effect of moderate anoxemia

Table 4 contains the figures of an experiment in which a moderately severe anoxemia persisted over a long time. The effect was to cause a progressive lowering of auriculo-ventricular conduction time even after two hours of anoxemia. Moreover, after the re-establishment

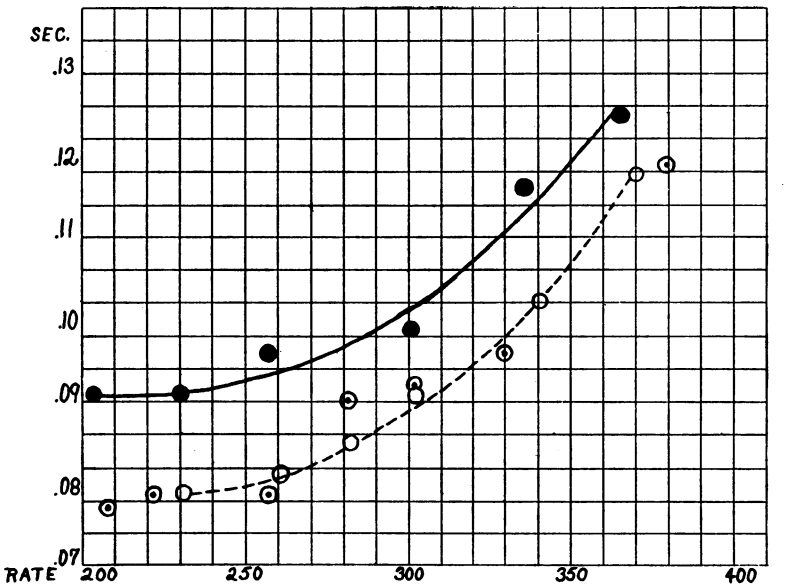

FIG. 2. DOG 15. THE P-R INTERVALS AT DIFFERENT RATES OF RHYTHMIC STIMULATION OF THE HEART

The determinations were made in the following order:

1. Black dots: Arterial oxygen saturation 100 per cent (column 1, table 4).
2. Circles: Arterial oxygen saturation 81 per cent (column 5, table 4).
3. Dotted circles: Arterial oxygen saturation 97 per cent (column 6, table 4).

This chart illustrates the decrease in the P-R interval during moderate anoxemia; and also the failure of immediate return to the normal figures when normal percentage of arterial oxygen saturation is restored after a long period of anoxemia.

of normal arterial saturation (column 6), the figures for the P-R intervals remain essentially at the level of the last series of determinations in the period of anoxemia.

Tables 5 and 6 give the summaries of two further experiments. In experiment 22 (table 5), the first series of determinations (column

3) during anoxemia showed a slight fall in the P-R values. In the second series (column 4), the auriculo-ventricular conduction time was still further shortened at the lowest rate of stimulation; as the rate of stimulation rose, however, the P-R interval increased to the normal level, and at the rate of 353 per minute, conduction defects

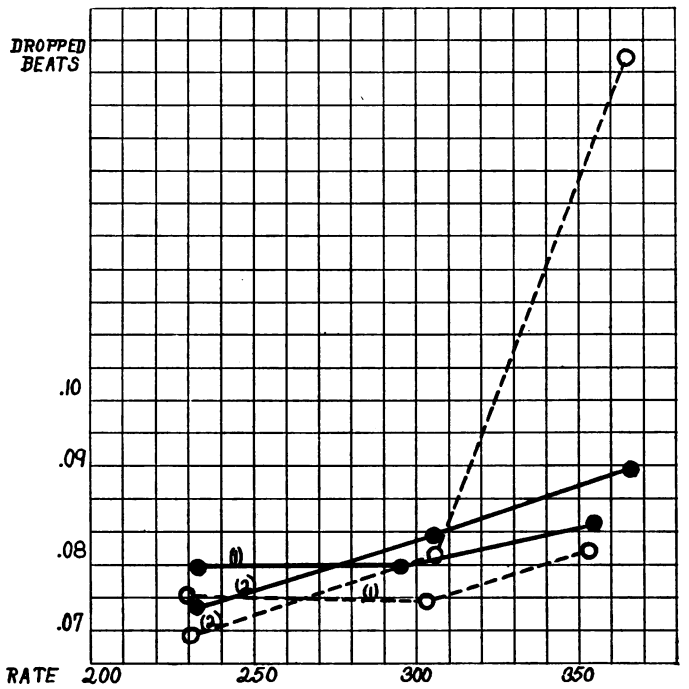

FIG. 3. DOG 22. THE P-R INTERVALS AT DIFFERENT RATES OF RHYTHMIC STIMULATION OF THE HEART

The determinations were made in the following order:

1. Black dots (1): Arterial oxygen saturation 97 per cent (column 1, table 5).
2. Circles (1): Arterial oxygen saturation 80 per cent (column 3, table 5).
3. Circles (2): Arterial oxygen saturation 80 per cent (column 4, table 5), 15 minutes after the preceding series.
4. Black dots (2): Arterial oxygen saturation 100 per cent (column 5, table 5).

The chart illustrates the early quickening of conduction during anoxemia; the later stage of impaired auriculo-ventricular conduction, brought out at the rapid rates of stimulation; and the return toward the original P-R values when normal arterial oxygen saturation is restored.

TABLE 5

Dog 22. Pericardium opened; fully atropinized

Oxygen saturation 100 per cent			Oxygen saturation 100 per cent			Oxygen saturation 80 per cent Started 11:37			Oxygen saturation 80 per cent Started 11:37			Oxygen saturation 100 per cent Started 12:03			Oxygen saturation 80 per cent Started 12:27			Oxygen saturation 80 per cent Started 12:27			Oxygen saturation 100 per cent Started 1:29		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*seeond*
11:19	232	0.078	11:32	230	0.078	11:45	230	0.075	12:00	231	0.070	12:06	232	0.073	12:39	238	0.076	1:26	226	0.070	1:45	231	0.075
11:21	295	0.078	11:34	300	0.077	11:47	302	0.074	12:01	306	0.079	12:08	306	0.082	12:40	307	0.077	1:27	302	0.077	1:47	301	0.077
11:24	354	0.083	11:35	351	0.083	11:49	353	0.080	12:03	365	*	12:10	368	0.090	12:42	363	0.082	1:28	354	0.079	1:50	354	0.083

* Every fourth or fifth beat dropped.

were definite; there were dropped ventricular beats. On return to the normal oxygen saturation, the figures tended to approach the normal again. In this animal anoxemia was again produced, this time bringing about only the stage of quickened conduction. Again, with the establishment of high arterial oxygen saturation, the figures became normal. In figure 3, the results of this experiment are shown graphically.

I am unable to account for the fact that in the first period of anoxemia, the stage of impaired conduction was brought about in slightly less than one-half hour; whereas later the same degree of anoxemia called forth only the initial stage of quickened conduction after one hour. The conditions of the experiment were apparently unchanged.

TABLE 6

Dog 16. Pericardium unopened; fully atropinized

Oxygen saturation approximately 96 per cent Natural heart rate 130			Oxygen saturation approximately 70 to 75 per cent Started 1:12 Natural heart rate 97		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*second*		*per minute*	*second*
12:50	219	0.092	1:20	216	0.115
	271	0.099	1:25	271	2:1, 1:1 response
	323	0.138			
1:10	372	Periods of 1:1 and periods of 2:1 response			

In experiment 16 (table 6), only the stage of impaired conduction was seen, without the preliminary period of quickened conduction. Moreover, this change was produced in a very short time. The explanation of this result undoubtedly lies in the fact that during the operative procedure a considerable amount of blood was lost, estimated at one-third to one-half the total blood volume. The animal was in poor condition, and, subjected to the stress of both acute hemorrhage and anoxemia, died shortly after the last record was taken at 1.25 p.m.

One may summarize the results obtained in this group of experiments by stating that moderate anoxemia first causes a decrease of the P-R interval. If the anoxemia is carried on for a sufficiently

long time, the stage of impaired conduction appears, and this impairment is most conspicuous at the higher rates of stimulation.[3] If after a period of anoxemia, normal oxygen saturation of the arterial blood is restored, there is usually a return toward the normal P-R values for the different rates. However, in some instances the recovery may not be complete even after a considerabe length of time; the state of auriculo-ventricular conduction may remain very much in the condition in which it was during the last part of the preceding period of anoxemia. The effect of anoxemia is enhanced and hastened if the general condition of the animal is poor.

Effect of severe anoxemia

Tables 7 to 10 show the results of subjecting animals to marked degrees of anoxemia. The results are quite similar to those described in the preceding group except that they appear earlier. In experiment 9 (table 7), in which anoxemia was present for a brief time, only the stage of quickened conduction is seen.

In experiment 12 (table 8), anoxemia was maintained for a slightly longer period, but still of relatively short duration. Here, there appeared within a few minutes the stage of quickened conduction. In the next series of records, however, taken but a few minutes later, the figures for the P-R interval were beginning to rise, and the stage of impaired conduction was undoubtedly making its appearance. Unfortunately, a further series of records during anoxemia was not taken.

The extreme effects of anoxemia are shown by experiment 20 (table 9). Here, a very marked grade of anoxemia produced from the first increased P-R intervals. These defects were markedly exaggerated during the rapid rates of beating, especially after the anoxic state had persisted for a time, still relatively short. It is interesting that after return to normal oxygen saturation of the arterial blood, two series of records showed practically no recovery. Figure 4 is a chart of this experiment, and it illustrates well the steepness of the curve of P-R intervals during severe anoxemia, and the failure of recovery after administration of a high oxygen mixture.

[3] In experiments other than those described in detail, conduction defects appeared at the low as well as the high rates of stimulation.

In experiment 19 (table 10), marked anoxemia was produced and maintained until the death of the animal ensued. At frequent intervals, the auricles were driven at a rate of approximately 220 per

TABLE 7

Dog 9. Pericardium opened; vagus nerves tied; fully atropinized

Oxygen saturation 96 per cent			Oxygen saturation 40 per cent Started 1: 12		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	R-R interval
	per minute	*second*		*per minute*	*second*
1:01	307	0.139	1:21	304	0.103
1:09	261	0.109	1:20	270	0.099
1:10	210	0.100	1:18	211	0.095

TABLE 8

Dog 12. Pericardium opened; vagus nerves tied; fully atropinized

Oxygen saturation 100 per cent			Oxygen saturation 62 per cent Started 12: 45			Oxygen saturation 62 per cent Started 12: 45			Oxygen saturation 100 per cent Started 1:08		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*second*
12:27	252	0.090									
12:30	282	0.092	12:48	286	0.088	1:00	279	0.091			
12:33	302	0.095	12:50	300	0.088	1.01	294	0.091	1:14	321	0.092
12:35	349	0.112	12:52	330	0.091	1:02	331	0.096	1:15	348	0.096
12:37	382	Dropped beats	12:54	369	0.104	1:03	380	0.110	1:16	392	0.118
			12:56	416	Dropped beats	1:04	422	Dropped beats	1:17	430	Dropped beats

minute. Here, again, there was first a fall, later a rise in the P-R interval.

To sum up the data of this group of experiments: practically the same events took place as had been observed when animals were subjected to moderate grades of anoxemia, the changes, however,

TABLE 9

Dog 120. Pericardium opened; fully atropinized

Oxygen saturation 97 per cent Natural heart rate 206			Oxygen saturation 45 per cent Started 11:42 Natural heart rate 203			Oxygen saturation 45 per cent Started 11:42 Natural heart rate 197			Oxygen saturation 97 per cent Started 12:08 Natural heart rate 179			Oxygen saturation 97 per cent Started 12:08 Natural heart rate 178		
Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval	Time	Rate of stimulation	P-R interval
	per minute	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*second*		*per minute*	*second*
11:32	212	0.058	11:53	208	0.070									
	234	0.057		223	0.068	12:03	222	0.068	12:19	218	0.064	12:39	217	0.064
				244	0.073		249	0.072		240	0.069		241	0.070
	263	0.064		268	0.074		271	0.077		270	0.074		270	0.075
	292	0.067		307	0.085		300	0.110		303	0.106		303	0.111
				320	0.108		326	0.137		329	0.133		322	0.128
11:40	338	0.103	12:01	348	Occasional dropped beat	12:07	352	Numerous dropped beats	12:23	353	Occasional dropped beats	12:45	358	Occasional dropped beat

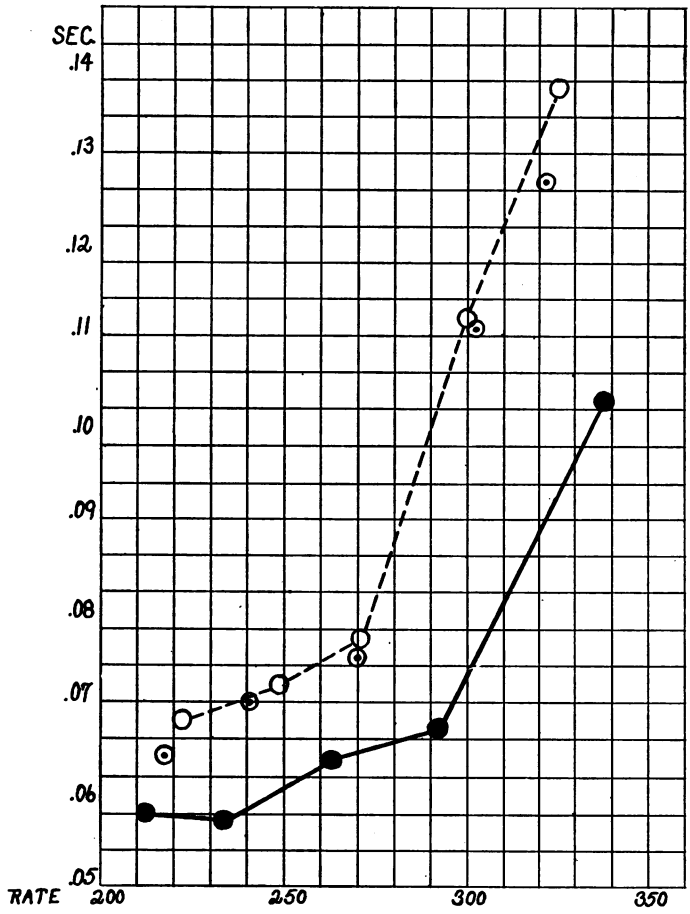

FIG. 4. DOG 20. THE P-R INTERVALS AT DIFFERENT RATES OF RHYTHMIC STIMULATION OF THE HEART

The determinations were made in the following order:

1. Black dots: Arterial oxygen saturation 97 per cent (column 1, table 9).
2. Circles: Arterial oxygen saturation 45 per cent (column 3, table 9).
3. Dotted circles: Arterial oxygen saturation 97 per cent (column 5, table 9).

The chart shows the effect of severe anoxemia on auriculo-ventricular conduction. The stage of impaired conduction appears early, the impairment being exaggerated at the higher rates of stimulation. The failure of immediate recovery is also well illustrated, the P-R values being almost identical, after one-half hour of normal arterial oxygen saturation, with the values obtained during the anoxic period.

tending to be more marked and to appear more rapidly. In these experiments, too, there was evidence that recovery may be slow after the re-establishment of normal oxygen saturation of the arterial blood.

TABLE 10

Dog 19. Pericardium unopened; fully atropinized

Normal P-R interval at rate of 218 is 0.092 second (oxygen saturation 98 per cent). Natural heart rate during normal arterial oxygen saturation is 164 per minute.

Time	Oxygen saturation 41 per cent Started 1:28		
	Natural rate	Rate of stimulation	P-R interval*
	per minute	*per minute*	*per minute*
1:30	156	218	0.086
1:31.30	158	222	0.084
1:38	157	220	0.086
1:41	158	224	0.087
1:45	161	226	0.086
1:50	163	224	0.088
1:55	155	220	0.089
2:00	152	224	0.090
2:06	135	220	0.094
2:10	114	219	0.109
2:14	108 (Sino-auricular block)	220	Intra-auricular block

* During rhythmic stimulation.

DISCUSSION

It is clear that several factors are of importance in determining the effect of anoxemia on auriculo-ventricular conduction. These are the severity and duration of the anoxemia, the rate at which the heart beats and the condition of the animal. In general, anoxemia produces first a decrease, and later an increase of the P-R interval, the latter being favored by severe anoxemia of long duration, by a rapid cardiac rate, and by deterioration of the general condition of the animal, from one cause or another. I have not investigated the influence of alterations of blood pressure. However, Mathison (1910–11) has shown that variations in blood pressure exert no direct effect on the occurrence of heart block in

asphyxia, but that an originally high pressure causes auriculo-ventricular block to appear earlier. This result he ascribed to the more vigorous action of the heart and the more rapid exhaustion of the available oxygen supply. This would also appear to be the explanation for the exaggerated effect of anoxemia at high rates of stimulation, for under these conditions the work of the heart is increased. It is conceivable that the increases in conduction time at gradually advancing rates of stimulation even during normal arterial oxygen saturation may be explained on the same basis. Barcroft, Bock and Roughton (1921–22) found that in a clinical case of paroxysmal tachycardia there was a striking diminution of the circulatory minute volume associated with an anoxemia of the stagnant type. Since the mean arterial pressure was only slightly decreased, the result of the tachycardia in this case was to increase the work of the heart, at the same time decreasing the total blood supply, and, presumably diminishing the oxygen supply to the heart, to some extent at least. If the lengthening of the P-R interval at increasing cardiac rates is due, however, to a gradually diminishing oxygen supply to the heart, one should be able to find in a series of records taken at different rates a stage in which the conduction time is shorter than it is at still lower rates, since the first effect of anoxemia is to quicken conduction. This phenomenon is not apparent in any of my experiments; that is to say, there has not been an instance in which the P-R interval shortened definitely on increasing the rate of stimulation. The absence of a stage of quickened conduction does not prove, however, that it does not exist, for owing to the fact that the initial rates of beating were relatively high on account of the removal of vagal tone, rates which were slow enough to show such a condition may not have been obtained.

The cause of impairment of auriculo-ventricular conduction in the later stages of anoxemia is definite: it is due to a direct influence on the heart muscle produced by oxygen lack, whatever may be the fundamental mechanism by which such a lack of oxygen exerts its effects. Concerning the cause of the initial quickening of auriculo-ventricular conduction, there may be some question. Vagal influence may be dismissed as a factor in the production of this change in these experiments. However, one must consider the possibility of stimula-

tion of the sympathetic nerves, for such an action is known to hasten auriculo-ventricular conduction. There is a certain amount of contradictory evidence concerning the rôle of the sympathetics in the changes in the heart caused by asphyxia, the effect being judged by alteration in the rate of the heart. Although there is some evidence indicating that the sympathetic nerves may be stimulated during asphyxial or anoxic states, there is other evidence demonstrating that an increase in heart rate may occur, when there is no possibility of sympathetic stimulation. Thus, Greene, Payne, and Siddle (1925) have found, in animals in which the vagus and sympathetic nerves to the heart have been cut, and in which the adrenals have been removed, that although with progressive anoxemia an increase in heart rate does not usually take place, a rise *may* at times occur. Moreover, Mathison (1910) has shown that in the spinal animal cardiac acceleration ensues during asphyxia even after the removal of the upper part of the cord, from which the cardiac accelerator nerves arise.

In the experiments which I performed, the following data favor the view that the decrease in the P-R interval during anoxemia was not entirely due to sympathetic stimulation. (1) The decrease of the P-R interval was not associated with those alterations of the electrocardiogram (when Lead II was used) which have been described by Rothberger and Winterberg (1910). (2) In order to obtain more definite information, I removed in one animal both stellate ganglia, in addition to tying the vagus nerves and administering full doses of atropine. In this animal, as in the others, a decrease in the P-R interval followed the administration of low oxygen mixtures.

The shortening of conduction time was definite, pointing to the conclusion that the change is due to a direct effect on the myocardium.

In view of the work of Hilton and Eichholtz (1925), it is not altogether surprising that a fairly severe and prolonged anoxemia was necessary to bring out the stage of impaired conduction. On subjecting heart-lung preparations of dogs to marked grades of anoxic anoxemia, they found that coincident with the lowering of oxygen tension of the blood, dilatation of the coronary vessels took place, so that the blood supply to the heart was increased. This augmented blood supply was usually able to compensate for the diminished amount

of oxygen available from each unit of blood to such an extent that the oxygen consumption of the heart remained normal. In some instances, however, there was evidence of an oxygen debt, that is to say, the oxygen requirements of the heart could not be fully met. At least one other factor besides the dilatation of the coronary vessels is of importance in compensating for a diminished arterial oxygen tension. The increased hydrogen ion concentration of the blood which was probably present, shifts the oxygen dissociation curve considerably to the right, the result being that at low tensions of oxygen (as would be present in the tissues) a liberation of oxygen that is greater than normal occurs.[4]

It must be remembered that while the circumstances which called forth impaired auriculo-ventricular conduction were severe, and are hardly ever encountered clinically, these observations were made on animals with normal hearts. These experiments show, indeed, that the normal myocardium can be subjected to a degree of anoxemia such as one ordinarily sees clinically, for a short period of time at least, without conspicuous change of conduction from auricles to ventricles.

[4] It is unnecessary to describe in detail the work which has been done on the pH of the blood in anoxemia. This has been adequately done by Koehler, Brunquist, and Loevenhart (1925) who showed in their own investigations that the pH of the blood during anoxemia depends on the balance of two factors: excessive ventilation tending to decrease the hydrogen ion concentration; accumulation of acid products, formed in the tissues as a result of impaired oxidation, tending to increase the acidity of the blood. They reached the conclusion that although there is an alkalosis at first, this increased pH was due to the greater effect by over-ventilation over the acidotic processes, which, however, occurred from the beginning.

In the absence of pH determinations, I cannot state with assurance the alterations that took place in the hydrogen ion concentration in the blood in my experiments. There was probably, during the periods of normal arterial oxygen saturation, an increased alkalinity of the blood due to the washing out of carbon dioxide by the large amount of gas mixtures flowing through the lungs, the amount remaining practically constant throughout an experiment (about 5000 cc.). Since the animals were unable to vary the amount of ventilation (because intratracheal insufflation was used) and so to compensate for the anoxemia by overbreathing, this element of the two factors determining the pH is eliminated. Consequently, any changes in the pH must have been toward the acid side, and Koehler, Brunquist and Loevenhart have shown that the acidity may become very great in anoxemia.

On the other hand, it is not unreasonable to assume that under anoxemia a heart which is already damaged or which, in addition to anoxemia, is laboring under some other strain such as a bacterial infection, may exhibit relatively early disturbances of function which appear late in a normal heart. This view is given some support by the results obtained in experiment 16, in which, because there had been a severe hemorrhage, conduction defects appeared after a short period of anoxemia, without the stage of quickened conduction being detected. Additional clinical evidence is afforded by the clinical cases of "asphyxial" block, in which varying degrees of impairment of auriculo-ventricular conduction are present in myocardial failure, the conduction defects disappearing with improvement of the circulatory condition.

TABLE 11

Dog 31. Vagus nerve tied; fully atropinized; both stellate ganglia removed

Oxygen saturation 100 per cent			Oxygen saturation 85 per cent Started 12: 28		
Time	Heart rate	P-R interval	Time	Heart rate	P-R- interval
	per minute	*second*		*per minute*	*second*
12:10	163*	0.103	12:38	166*	0.096
			12:36	312†	0.127
			12:45	312†	0.119

* Natural heart rate.

† Rhythmic stimulation.

SUMMARY AND CONCLUSIONS

Under the conditions in which the above experiments were performed.

1. Anoxemia (of the anoxic type) brings about first a shortening, then lengthening of auriculo-ventricular conduction time.

2. The effect of anoxemia on conduction is influenced by the degree of anoxemia, the length of time in which the heart is subjected to anoxemia, by the rate at which the heart beats, and by the general condition of the animal. There are undoubtedly other factors of importance which I have not investigated.

3. The appearance of the stage of impaired conduction is favored by the severer grades of anoxemia, acting over a long period of time,

by rapid cardiac rates, and by deterioration of the general condition of the animal.

4. The changes in conduction produced by anoxemia are due to a direct effect on the myocardium.

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