THE EFFECT OF ADRENALIN ON THE GASEOUS METABOLISM OF THE ISOLATED MAMMALIAN HEART.

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The effect of adrenalin on the gaseous metabolism of the mammalian heart was referred to by Barcroft and Dixon(1) who found that the oxygen consumption was much increased when adrenalin was given in such doses as to accelerate the heart. The effect of adrenalin on the oxygen usage of the heart was also the subject of an investigation by Rohde, in conjunction with one of us (S. O.(2)); it was shown, as a result of this work, that although the acceleration of the rate of the heart beat was accompanied by a large increase in the oxygen absorption, yet the oxygen usage per beat and per mm. of "pulse pressure" under isometric conditions were not much if at all increased.

In the present investigation, we have sought to find what were the effects of adrenalin on the respiratory quotients of the isolated heart. There were several reasons which made this information highly desirable, such, for example, as the relation of adrenalin to carbohydrate metabolism. It has been shown by one of us (E.) that when glucose is added to the circulating blood, the heart commences to utilise it and the respiratory quotient is raised accordingly; if, therefore, adrenalin plays the part of "mobilisation of carbohydrate of the tissues" which is often ascribed to it, then we should expect that the respiratory quotient would be raised by the addition of adrenalin. According to Wilenko(3) the addition of adrenalin to the circulating blood or perfusion fluid did increase the utilisation of sugar, but Patterson and Starling(4) attribute this increase to the largely increased work which the heart performs under these circumstances, and not to any specific effect of the adrenalin. According to other work of Wilenko(5), adrenalin has little effect on the respiratory quotient in the intact animal, although in the presence of glucose the respiratory quotient is

lowered by previous administration of adrenalin. The inference from this was that adrenalin diminished the capacity of the organism to burn sugar.

Fuchs and Roth(6) from experiments made on patients concluded that the effect of adrenalin was to raise the total respiratory exchange and the respiratory quotient, but since the experiments were made by the Zuntz method, and the adrenalin administration caused some respiratory disturbances, the results are not quite free from objection. Hári(7) also finds that adrenalin introduced intraperitoneally causes a rise of respiratory quotient due to diminution of oxygen intake which, he says, indicates that there is an increased consumption of carbohydrate. La Franca(8) finds that adrenalin does not alter the respiratory quotient, although the total gaseous exchanges are raised.

We have studied the effects of adrenalin on the gaseous interchanges of the isolated heart in two distinct ways, since it was expected that these might give different results. In one series of experiments we have added small amounts of adrenalin and observed the effect which these doses had upon the metabolism of the organ. In other series of experiments the adrenalin was added continuously to the blood, and a state of equilibrium, as judged by the pulse rate, was as far as possible maintained.

1. *The effect of single doses of adrenalin.*

Method. The heart-lung preparation was made by Starling's method (9), the apparatus being of the closed type figured by Starling and Evans(10) (Fig. 3), with the exception that we did not use the coronary cannula there depicted. The adrenalin solution was run in by means of a burette connected with a fine nozzle which passed through the bung by which the venous reservoir was closed in. The strength of the adrenalin stock solution from which the dilutions were subsequently made was determined by the colorimetric method described by Folin, Cannon and Denis(11), and a dilution of this containing one part of adrenalin in 10,000 parts of normal saline solution was generally employed. After having taken the respiratory exchanges of the preparation for periods of about half an hour or an hour, the adrenalin solution was added in small amount, usually about 1 c.c. of the 1 : 10,000 dilution. The volume of blood circulating in the apparatus was generally about 300 c.c., so that the concentration of the adrenalin in the circulating blood was thus about one part in three million.

Exp. 1. Dog. Heart 64·5 grams. One lung tied off. Arterial pressure 80 mm. Temp. 36·7 ± ·2° C. Gaseous volumes not corrected for lung metabolism.

Duration of period, mins.	Rate of heart per min.	Output of heart, l. per hr.	Work of left ventricle, kgm. per hr.	Per hour: Oxygen, c.c.	Per hour: Carbon dioxide, c.c.	R.Q.			Remarks	c.c. O_2 per kgm. of work
21	125	12·4	12·9	218	176	·8	Mean			17·0
20	125	11·9	12·4	219	165	·75	= ·775			17·6
20	204	13·6	14·2	309	239	·77	Mean	Mean = ·775	1 c.c. adrenalin 1 : 10000 at beginning	21·8
20	150	10·3	10·7	191	91	·48	= ·625			17·9
20	162–200	10·8	11·2	317	292	·92	Mean		Do.	28·3
21	177–200	9·7	10·1	337	293	·87	= ·895		Do.	33·3
20	150	8·1	8·4	249	198	·79				29·7
10	185–223	—	—	413	233	·57	Mean = ·895		Do.	—
11	177	—	—	283	352	1·24				—
10	134	5·5	5·7	256	224	·88				45·0

This experiment shows that the addition of adrenalin has a decided effect on the total exchanges and on the respiratory quotient. The disturbance of the respiratory quotient is best seen in the last three periods which are of ten minutes duration only. It is there seen that the first effect is to increase the oxygen intake much more than the carbon dioxide output, so that the first quotient is very low indeed. In the next period, however, the CO_2 production has outstripped the oxygen intake, which has indeed fallen off by this time; the R.Q. is accordingly a high one. In the last period the CO_2 and O_2 are both less and the quotient has fallen to ·88. The average of the three quotients for these last periods is ·895 and represents the mean quotient during a period of 31 minutes. It is seen to be identical with that obtained for periods 5 and 6, which represents the quotients obtained over a period of 41 minutes, during which two doses of adrenalin were given. In the last period, the action of the adrenalin cannot be considered to have passed off, as is indicated by both the pulse rate and the oxygen intake.

The mean of periods 3 to 7 is ·775 which is identical with the mean for the first two normal periods. This mean represents the R.Q. during a period of 100 minutes, in which three doses of adrenalin were given, 41 minutes being allowed to elapse between the administration of the last dose and the termination of the period. It is therefore clear that when a dose of adrenalin is given to the heart there are temporarily profound changes in the respiratory quotient, but the changes are such that the average quotient, representing the changes which ensue until the action of the drug has ceased, is not different from the normal one.

The following experiment is a similar one, and shows very clearly the time relations of the oxygen intake and CO_2 production.

EXP. 2. Dog. Heart 58·5 grams. One lung tied off. Temp. of ingoing blood 36° in all periods. Arterial pressure 100 mm. Hg. Gases not corrected for lung metabolism.

Period No.	Duration of period, mins.	Rate of heart per min.	Output of heart, l. per hr.	Work of left ventricle, kgm. per hr.	Per hour O_2 c.c.	Per hour CO_2 c.c.	R.Q.		Remarks	C.c. O_2 per kgm. of work
1	20	143	10·9	14·2	203	165	·81			14·3
2	20	148	10·7	13·9	199	164	·82	Mean		14·3
3	20	145	10·3	13·4	202	159	·79	= ·81		15·0
4	20	—	—	—	206	168	·81			—
5	10	236	10·3	13·4	804	396	·49		1 c.c. 1 : 5000	60·0
6	10	222	—	—	558	546	·98	Mean = ·84	adrenalin added at beginning of period	—
7	10	197	—	—	430	447	1·04			—

Here again it is seen that the oxygen intake increases much more quickly than does the CO_2 production, but the mean R.Q. in this case is almost the same as that for the normal periods preceding the addition of adrenalin. There seems little doubt then that the metabolism of the heart muscle is not changed qualitatively by the presence of small amounts of adrenalin. A mobilisation of the glycogen of the heart muscle, other than that which would occur under any other conditions which called for great activity of the tissue, is not indicated.

Experiments made in this laboratory have shown that the respiratory quotients of the hearts of diabetic animals are much lower than those of the normal heart. Yet it is clear from the above experiments that doses of adrenalin of the order of those here used do not result in any permanent lowering of the respiratory quotient. It follows from this that whatever the cause of "adrenalin diabetes" may be, it cannot be in any way connected with qualitative changes in the metabolism of the tissues, nor with a direct action of the adrenalin on them.

With regard to the difference in the times at which the oxygen is taken up and the carbon dioxide formed in increased amount, there may be two causes for this interesting phenomenon. Thus, a simple explanation would be that the oxygen can pass into the blood or to the tissues much more readily than the carbon dioxide can pass in the reverse direction, owing to purely physical reasons. But this would be opposed to all previous experience, and, in fact, a simple calculation by the use of the formula of Loewy and Zuntz[12] will show that even under extreme conditions this explanation will not suffice. Let us assume that the difference in the partial pressures of oxygen in the

alveolar air and in the venous blood ($p_1 - p_2$) is 35 mm., and that the corresponding difference in the case of the carbon dioxide is as little as 2 mm. The tension difference in the case of carbon dioxide would certainly be greater than this, if the oxygen difference were 35 mm., so that by making this assumption we are taking an extreme case, and giving the oxygen a great advantage over the carbon dioxide[1] in making our calculation.

Then, according to the formula of Loewy and Zuntz:

$$v = \frac{a\,(p_1 - p_2)\,c}{760\sqrt{m}\,.\,d},$$

where a is the absorption coefficient,

m the molecular weight of the gas,

c the diffusion factor (which is ·139 for the lung tissue),

d the thickness of the alveolar membrane (·004 mm.),

and v the velocity of diffusion, *i.e.* the number of c.c. of the gas which passes 1 sq. cm. of the surface in 1 minute, we have for the case of the oxygen,

$$v = \frac{\cdot 024 \times 35 \times \cdot 139}{760 \times 5 \cdot 66 \times \cdot 004} = \cdot 00676,$$

and for carbon dioxide it is $v = \dfrac{\cdot 6 \times 2 \times \cdot 139}{760 \times 6 \cdot 63 \times \cdot 004} = \cdot 00827.$

Since, even under these conditions the carbon dioxide still has a decided advantage over the oxygen as regards their respective tendencies to diffusion, it is evident that if the carbon dioxide were present in the blood it would effect its exchange with the alveolar air more rapidly than the oxygen would. We are bound to conclude, therefore, that the oxygen passes into the tissues before the carbon dioxide leaves them, and this deduction provides us with an explanation of the phenomenon, which seems much more probable than the one which has just been considered. Our hypothesis is that a definite interval of time elapses between the moment when oxygen is taken up by the tissues and the time when, the oxidative processes being completed, the full quantum of carbon dioxide is yielded to the blood. And for this reason, if the oxidations in the tissue are increased in any way, as is the case here, without the metabolism being qualitatively

[1] To this statement the objection may possibly be made that it has been shown that the blood leaving the lungs does not differ in tension of CO_2 from the air in the alveoli by more than a small fraction of a millimetre. We would point out, however, that these statements refer to *arterial* blood, and this fact affords perhaps a better proof than our calculation can do that the carbon dioxide passes out far more readily than the oxygen passes in, since it practically attains equilibrium during its brief transit through the lung capillaries, which the oxygen does not.

altered, this interval, which is occupied with the processes of intermediary metabolism, will make itself apparent in the way we have seen. We think that it is necessary to lay great stress on the fact that in dealing with the respiratory quotients of isolated organs such as the heart, we are dealing with quantities which are in a state of dynamic equilibrium, the ratio between which may therefore be readily disturbed. This hypothesis seems to be quite a suitable one on which to explain the fact, previously observed by one of us (C. L. E.(13)) that if the total oxidations of the heart be increased in other ways, as for example by increasing the temperature or by raising the arterial pressure, the respiratory quotient is temporarily lowered.

The following experiment (3) shows essentially the same facts as those given above. The time relations of the oxygen intake and carbon dioxide production are not so clearly seen as in exps. 1 and 2, but it shows that there is no marked alteration of the respiratory quotient after the addition of the adrenalin when sufficient time is allowed after the administration of the drug for a condition of equilibrium to be restored.

When the heart is under the influence of adrenalin, its power of abstracting the oxygen from the blood is well seen if an analysis of the blood gases be made. The results of some analyses made by Barcroft's method are given in the following table, which shows the difference between arterial blood circulating in the apparatus and the venous blood drawn from the coronary sinus in normal hearts before and after the addition of adrenalin.

EXP. 3. Dog. Heart 37·5 grams. One lung off. Arterial pressure 80 mm. Temp. 37° ± ·2° C.

No. of period	Duration of period, mins.	Rate of heart per min.	Output of heart, l. per hr.	Work of left ventricle, kgm. per hr.	Gaseous exchanges per hour: O_2 c.c.	Gaseous exchanges per hour: CO_2 c.c.	R. Q.		Remarks	C.c. oxygen per kgm. of work
1	30	122	14·4	15·0	184	163	·88			12·3
2	10	218	18·0	18·8	452	268	·59		1 c.c. 1 : 10000	24·0
3	10	168	17·1	17·8	256	234	·92	Mean	adrenalin	14·4
4	10	167	17·1	17·8	210	164	·78	= ·79		11·8
5	20	150	15·6	16·1	156	134	·86			9·7
6	20	261	14·7	15·3	278	232	·83		0·5 c.c. do.	18·1
7	20	172	11·6	12·1	222	137	·62			18·3
8	15	217	14·4	15·0	400	182	·46	Mean	0·5 c.c. do.	26·7
9	20	167	13·1	13·7	188	214	1·14	= ·89		13·7
10	21	134	5·6	5·8	122	191	1·56			21·0

Percentages of oxygen in arterial and venous blood.

Rate of heart	% of oxygen in arterial blood	% of oxygen in sinus blood	% difference of oxygen	Remarks
—	15·0	5·3	9·7	Before adrenalin.
—	15·0	9·3	5·7	
—	13·7	8·0	5·7	
—	14·8	1·5	13·3	4 mins. after adding 1 c.c. of 1 : 10000 adrenalin.
230			2·9	Before adrenalin.
244			8·3	10 mins. after 1 c.c. adrenalin.
131			1·4	Before adrenalin.
—			3·5	
238			12·7	5 mins. after 1 c.c. of 1 : 10000 adrenalin.
—	Analyses by differential method		3·7	Before adrenalin.
—			3·5	
—			3·5	
—			7·5	5 mins. after 1 c.c. 1 : 10000 adrenalin.
120			3·9	Before adrenalin.
207			13·2	1 min. after 1 c.c. 1 : 10000 adrenalin.
173			4·1	12 mins. later.

It will be seen from these figures that the difference between the oxygen content of the arterial and venous blood is often increased four-fold, and that the blood of the coronary sinus frequently contains not more than one or two per cent. of oxygen, an amount which approaches closely to that which is present in asphyxial blood[1]. If we bear

[1] Although the blood of the coronary sinus shows such a deficit of oxygen as compared with the arterial blood, this fact does not diminish the probability of our statement that the tension difference between the blood carried to the lungs and the alveolar air does not greatly exceed 35 mm. Hg. For, as shown by Starling and Evans[10] the blood flow through the coronary vessels is about 60 % of the weight of the heart per minute, and this rate of flow is not more than doubled after the addition of 1 c.c. of 1 : 10,000 adrenalin to 300 c.c. of blood. Now, in exp. 3 of this paper for example, about 245 c.c. of blood leaves the aorta per minute, while assuming that the coronary flow is of the above mentioned order, there would be 45 c.c. of blood passing along the coronary circuit per minute. The total output of the right ventricle would thus be 290 c.c. per minute. Of this 245 c.c. would consist of arterial blood containing, say, 18 % of oxygen, and 45 c.c. of it would be venous blood containing, suppose, only 1 % of oxygen. The mean oxygen content of this blood which was carried to the lung would therefore be 15·4 % which would represent 84 % of full saturation, and the oxygen tension which this would exert in the presence of normal tensions of carbon dioxide (say 40 mm.) would be about 60 mm. A tension difference of 35 mm. would thus prevail if the oxygen tension in the alveoli were about 95 mm., and in view of the rapidity with which oxygen is being abstracted from the air it is not likely to be much greater than this.

in mind at the same time that the coronary flow is much increased under the influence of adrenalin, we shall see with what avidity the heart tissue takes up oxygen from the blood when adrenalin is present.

2. *The relation of adrenalin to the metabolism of carbohydrate in the tissues.*

Patterson and Starling (*loc. cit.*) have shown that when hearts are treated with adrenalin, glucose disappears much more quickly from the circulating blood than it does in the case of normal hearts without such addition. Wilenko (*loc. cit.*) has obtained results which are in agreement with this, while Cruickshank(14) finds that under these conditions the heart muscle may be almost depleted of its store of glycogen. Patterson and Starling ascribe this increased consumption of glucose to the increased energy requirement of the heart, rather than to any specific effect of the drug on the power of the tissues to attack sugar.

If we take into account the amount of glycogen which the heart loses under these conditions, it seems that the glucose consumptions as determined by Patterson and Starling were commonly increased from two or three times, or in those cases where the hearts were stimulated by the addition of larger amounts of adrenalin, even more than three times.

Evidence has been advanced in a previous publication by one of us (E.(15)) to show that the isolated normal dog's heart is capable of fully oxidising the glucose which it takes from the circulating blood. The fact that the respiratory quotient of the heart is not altered by small doses of adrenalin indicates that the increased amount of glucose which is removed from the blood under these conditions is also fully oxidised. We have not given such large amounts of adrenalin in these experiments as were given by Patterson and Starling, but in exps. 2 and 4 the oxygen usage per kgm. of work at the height of the adrenalin action is nevertheless seen to be increased about four-fold, while in exps. 1 and 3 it is almost doubled. Similar relations of course hold for the carbon dioxide produced, since the respiratory quotients are not changed.

In order to find whether adrenalin favoured or retarded the oxidation of carbohydrate when the latter was present in abundance in the blood, we added glucose to the blood in some cases, and then, after the respiratory quotient had become steady (about an hour), adrenalin was added as in

the previous experiments. The results of these experiments are given in the following table.

Exp. 4. Dog. Heart 48·5 grams. Arterial pressure 88 mm. Temp. 37·5 ± 0·2° C.

No. of period	Duration of period, mins.	Rate of heart per min.	Output, l. per hr.	Work of left ventricle, kgm. per hr.	Gaseous exchanges per hr. O_2 c.c.	Gaseous exchanges per hr. CO_2 c.c.	R.Q.	Remarks	C.c. oxygen per kgm. of work
1	60	—	9·6	11·1	130	116	·89	Normal periods	5·8
2	80	143	9·9	11·4	116	102	·88	1 gram glucose added	5·1
3	20	273	9·7	11·2	236	198	·84	0·5 c.c. 1 : 10000 adr.	10·6
Exp. 5. Dog. Heart 50·5 grams. Arterial pressure 30 mm. Hg. Temp. 36·5° C.									
1	60	164	10·2	4·0	166	152	·92		41·5
2	60	158	9·8	3·8	186	171	·92	1 gram glucose added	49·0
3	60	197	9·9	3·9	235	208	·89	0·8 c.c. 1 : 10000 adr. given in four doses of 0·2 c.c.	60·0
Exp. 6. Dog. Heart 67 grams. Arterial pressure 55 mm. Temp. 36·5° C.									
1	60	154	12·0	8·7	202	177	·88		23·2
2	120	154	11·8	8·5	242	210	·87	1 gram glucose	28·5
3	75	175	10·8	7·8	270	231	·86	0·5 c.c. 1 : 10000 adr. in first half hour. Then 2 c.c. of pancreas extract.	34·5

In order to avoid the disturbing effect of large doses of adrenalin, we gave smaller doses in this case than in the previous experiments, and after the addition the respiratory quotients were taken for a fairly long period (20 mins. to one hour) in order to allow the effect to fully pass off, and for equilibrium to be re-established. The results of these experiments show that the quotient is not higher after the addition of the adrenalin, but rather a little lower. Any specific favouring effect of adrenalin seems therefore to be excluded, and the increased usage of carbohydrate which the heart shows on treatment with adrenalin is, as stated by Patterson and Starling, merely one aspect of a general increase in catabolic activity.

3. *The effect of repeated doses of adrenalin.*

In these experiments we attempted to bring the gaseous exchanges of the heart in presence of adrenalin into a condition of equilibrium by continuously adding the adrenalin to the circulating blood in such amount as to keep the pulse rate at a constant high level.

The results of such experiments are given in the table below (exps. 7, 8, 9).

Exp. 7. Dog. Heart 50 grams. Arterial pressure 108 mm. Hg. Temp. 36° C. The rate of the heart was kept up to 240 per minute by the addition of adrenalin solution 1:10,000 when necessary. The amounts added during each period are shown in the column for "Remarks."

No. of period	Duration of period, mins.	Rate of heart per min.	Output of heart, l. per hr.	Work of left ventricle, kgm. per hr.	Gaseous exchange per hr. O_2 c.c.	Gaseous exchange per hr. CO_2 c.c.	R.Q.		Remarks	C.c. oxygen per kgm. of work
1	20	152	21·4	30·1	210	174	·83			7·0
2	20	245	21·4	30·1	447	167	·37		1 c.c. adr. 1:10000	14·9
3	20	240	18·7	26·2	441	338	·75	Mean = ·717	1·5 ,, ,,	16·9
4	20	240	21·4	30·1	444	300	·67		·25 ,, ,,	14·8
5	20	240	18·7	26·2	441	312	·71		·55 ,, ,,	16·8
6	20	247	—	—	453	392	·86		·75 ,, ,,	—
7	20	240	18·7	26·2	393	333	·85		·2 ,, ,,	15·0
8	20	240	17·3	24·2	402	327	·81		·6 ,, ,,	16·7

Exp. 8. Dog. Heart 63 grams. Arterial pressure 110 mm. Hg. Temp. 36°. Smaller quantities of adrenalin were added than in the previous experiment.

1	20	141	22·5	32·2	400	280	·70	Mean = ·685		12·5
2	20	—	—	—	380	256	·67			—
3	20	214	—	—	490	342	·695	Mean = ·704	1·0 c.c. adr. 1:10000	—
4	20	218	—	—	680	472	·690		0·5 ,, ,,	—
5	20	236	—	—	852	552	·650		0·5 ,, ,,	—
6	20	253	—	—	816	635	·780		0·5 ,, ,,	—

Exp. 9. Dog. Heart 48 grams. Arterial pressure 110 mm. Hg. Temperature 36° C. ± ·3°.

1	20	125	25·6	36·6	263	267	1·01			—
2	20	240	25·0	35·8	432	322	·75		1·8 c.c. adr. in 4 doses	7·2
3	20	240	23·7	33·8	546	401	·735	Mean = ·85	1·5 ,, ,, 3 ,,	11·7
4	20	240	22·6	32·3	504	424	·84		1·5 ,, ,, 3 ,,	16·1
5	20	235	21·4	30·7	528	466	·88		1·0 ,, ,, 2 ,,	17·2
6	20	200–207	21·4	30·7	438	458	1·04		No addition	14·3
7	20	267	17·4	25·0	600	411	·685		5 c.c. in 4 doses	24·1
8	20	267	—	—	560	401	·715	Mean = ·75	3 ,, 3 ,,	—
9	20	267	—	—	460	390	·845		3 ,, 3 ,,	—

It was expected that after a preliminary fall and complementary rise, the respiratory quotient would soon acquire a normal value, and that, as in the previous experiments, the mean value of the quotient during the adrenalin period would approximate closely to the normal one. This, however, was not the case, for although the normal quotient was in some cases established during the adrenalin administration (exp. 7, periods 6 to 8 and exp. 8, periods 3 and 4) the compensatory rise was not seen in any case. The mean quotient was therefore lowered by adrenalin, except in the case of exp. 8, where it was low to begin with. In exp. 9 it is seen that the R.Q. does rise again as soon as the administration of adrenalin is discontinued (period 6), but that

when larger doses of adrenalin are given it falls still lower again (periods 7, 8 and 9).

We believe that the explanation of this effect is to be sought along the lines of the hypothesis already advanced, namely, that the oxidative reactions in the tissues require an appreciable time for their consummation. Let us suppose that we are taking the respiratory exchanges of an organ over a series of time intervals t_1, t_2, t_3, ... t_n, all of equal duration. We will further suppose that t is the time which the oxidative processes require for completion. Then oxygen taken up by the tissue during t_1 will be used in processes of intermediary metabolism during that interval and the carbon dioxide which results from the oxidative processes will be liberated during the next interval t_2; similarly during t_2 oxygen is taken in which yields carbon dioxide during t_3, and so on.

Let us suppose that the tissue is in equilibrium, and that x c.c. of oxygen are taken in during time t and y c.c. of carbon dioxide produced. The respiratory quotient is y/x. If now the oxidative reactions are doubled, during the first interval of time, $2x$ c.c. of oxygen will be taken up, but as yet only y c.c. of carbon dioxide will be formed and the respiratory quotient will be lowered ($y/2x$). In the following period the carbon dioxide will also be doubled and the R.Q. restored to what it was before ($2y/2x$). At this level the quotient will remain until there is a further quantitative change in the total oxidations. Suppose that these return to normal again. Then in the first interval after the return there will be only x c.c. of oxygen intake, but $2y$ c.c. of carbon dioxide production, *i.e.* the compensatory rise will now appear (R.Q. $= 2y/x$). In the succeeding periods the carbon dioxide and also the respiratory quotient will be restored to normal (y/x).

Another explanation of the phenomenon which might be advanced is that some of the energy-yielding constituents are not fully oxidised, or that there is an increased oxidation of fat, but these explanations do not agree so well as the one suggested above with the experiments in which single doses of adrenalin are given.

4. *The relation between the amount of oxygen used and the pulse rate.*

The experiments detailed above furnish us with data relative to the amounts of oxygen used by the heart for each beat under normal conditions and also under the influence of adrenalin. According to the work of Rohde and Ogawa (*loc. cit.*), the volume of oxygen per beat and

per mm. of increase of endocardiac pressure (under isometric conditions) is constant whether the heart be treated with adrenalin or not. Evans (13) has shown that in the somewhat similar case of acceleration of the heart by rise of temperature, the arterial pressure remaining constant, the oxygen requirement per beat under the normal conditions of contraction is unaltered.

These independent statements appear to be so similar in significance that we have calculated the oxygen usage per gram of heart per beat and per mm. of arterial pressure[1] in the present series of experiments, in order to ascertain to what extent the results of Rohde and Ogawa with the isometrically contracting heart are in agreement with ours in which the mechanical conditions of the contraction approach nearly to the normal.

The calculations are given in the table on p. 458.

In exps. 1, 5 and 6, and in some of the periods of exp. 9 the amounts of oxygen taken up after the administration of adrenalin are sufficiently near to those observed before the drug was given to justify the conclusion that the amounts are essentially the same. But in the other experiments there is such a great alteration of oxygen usage after adrenalin that the relation cannot be considered to hold at all. In these cases there was often first an increase and then a diminution in the amount of oxygen used.

It seems therefore, that in the heart when contracting in the normal manner and at constant arterial pressure, the oxygen usage before and after adrenalin is only in some cases, and then only approximately, proportional to the rate at which the heart is beating at the time.

The difference between these results and those of Rohde and Ogawa is no doubt to be explained as due to the different conditions of experiment. The tension changes set up in the heart muscle, and on which no doubt the metabolism largely depends, could be better appreciated in the conditions which obtained in their experiments than in ours.

[1] According to some experiments which we made, the arterial pressure is the chief factor which determines the endocardiac pressure in the left ventricle. Since in our experiments the diastolic endocardiac pressure is near to zero, the increase of endocardiac pressure in systole is identical with the maximum pressure produced, which as stated above is determined by the arterial pressure.

No. of Exp.	No. of period	C.c. oxygen per gram heart per beat and per mm. of arterial pressure $\times 10^{-8}$	Adrenalin
1	1	565	0
	2	565	0
	3	487	+
	4	410	
	5	570	+
	6	570	+
	7	534	
	8	655	+
	9	517	
	10	617	
2	1	405	0
	2	380	0
	3	396	0
	5	972	+
	6	717	
	7	620	
3	1	840	0
	2	1150	+
	3	843	
	4	698	
	5	578	
	6	595	+
	7	715	
	8	1028	+
	9	626	
	10	505	
4	2	318	0
	3	337	+
5	1	1116	0
	2	1300	0
	3	1310	+
6	1	590	0
	2	710	0
	3	695	+
7	1	425	0
	2	563	+
	3	568	+
	4	570	+
	5	566	+
	6	568	+
	7	505	+
	8	517	+
8	1	682	0
	3	550	+
	4	750	+
	5	870	
	6	774	+
9	1	662	0
	2	570	+
	3	715	+
	4	662	+
	5	710	+
	6	675	
	7	710	+
	8	660	+
	9	543	+

CONCLUSIONS.

(1) Adrenalin greatly increases the total gaseous exchanges of the heart. The increase in oxygen usage is roughly proportional to the increase in the pulse rate.

(2) When a single dose of adrenalin is given, the oxygen intake attains a maximum during the next few minutes. The carbon dioxide output, however, reaches its maximum some time later, when the oxygen intake has begun to diminish again. The result of these relations between the oxygen and carbon dioxide is that the respiratory quotient is first lowered and then raised, after which it returns slowly to normal.

(3) The explanation which is offered for this fact is that a definite time is required for the chemical reactions which occur in the intermediary stages of the oxidations, so that if these oxidations be quantitatively altered, the amount of oxygen alters promptly, while the carbon dioxide more slowly attains its new level.

(4) If the mean respiratory quotient be taken for a considerable time after the addition of a single dose of adrenalin, it is found to be identical with that of the heart before the addition was made.

(5) Adrenalin neither increases nor diminishes the power of the tissues to utilise carbohydrate. The observed increases in carbohydrate consumption are due to a generalised increase of catabolic activity, and not to any specific effect of the drug on carbohydrate, as distinct from other metabolism.

(6) When adrenalin is continually added to the circulating blood, in such amount as to maintain the pulse-rate at a constant high level, the respiratory quotient soon becomes constant. But the mean quotient during the addition is then lower than that of the normal heart previous to the addition of adrenalin. It is pointed out that this is really a confirmation of the statement given above (3) that the oxidative processes are not instantaneous, but require an appreciable time for their completion.

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