THE GASEOUS METABOLISM OF THE HEART AND LUNGS. By C. LOVATT EVANS (*Sharpey Scholar*).

(*From the Institute of Physiology, University College, London.*)

CONTENTS.

THE method described by Jerusalem and Starling(1) and further improved by Knowlton and Starling(2), for the establishment of a circulation in the isolated heart and lungs, has given to physiologists a very convenient preparation with which to study the phenomena of the isolated heart under practically normal conditions. The preparation thus offers obvious advantages over the isolated heart preparations described by Langendorff(3), in which an artificial perfusion fluid is used, and by Heymans and Kochman(4), in which the coronary circulation is alone supplied with blood, the heart doing no normal work. The heart-lung preparation should serve therefore for investigations on the normal gaseous metabolism of the heart. Such investigations have been made by previous writers, but upon isolated hearts prepared according to the methods of Langendorff or Heymans and Kochman. Thus Barcroft and Dixon(5) perfused the hearts of dogs and cats with blood from another animal according to Heymans and Kochman's method and determined the gaseous exchange by sampling of the blood at intervals and subsequent analysis. Their results are important since they give the rates of gaseous metabolism at particular moments of time. The experiments of Rohde(6) and of Gayda(7), in which suitably modified Langendorff's methods were used, were of a different nature,

since they gave integrated results during somewhat prolonged periods. The results of the present investigation are similar to these in this respect. Although the experiments of Rohde seem to be in every respect admirable, it is nevertheless of interest to investigate the metabolism of a blood-fed heart; it is also possible with the preparation now available to carry out some observations which were not possible with other methods.

In order to determine the gaseous metabolism a special form of respiration apparatus on the Regnault and Reiset principle was devised.

Since the preparation employed consists not merely of the living heart, but of the living lungs and blood also, an attempt has been made here to determine the metabolism of these tissues in order that due correction may be made if necessary for their contribution to the total gaseous exchange of the preparation.

Methods. The apparatus consisted of the heart-lung circulation apparatus as described by Knowlton and Starling(2), and of a respiration apparatus. The latter was adapted to give oxygen absorptions and amounts of carbon dioxide produced, and is constructed in the following way:

The vessels *D*, *E* and *F* (Fig. 1) are filled with acidulated water, which is caused to move up and down in the bulb *G* by means of alternate pressure and suction applied to the air in *D* by means of a Hans Meyer double action respiration pump. Before commencing the experiment the pump is allowed to work in this manner for half an hour or so in order to completely saturate the water with air. The vessel *G* constitutes the pump which is actually used, the water being the piston. Such a pump cannot leak at the piston and if the whole system be closed and air-tight, any diminution in volume in the course of an experiment (allowing for temperature changes) will represent an absorption of oxygen. Such absorption can be read off on the graduated tube *E*, which is merely a narrow portion of the pump-barrel *G*. At each ascent of water in *G* some air is driven out along *M* and through the valve *N*. It now has a choice of paths open, either through *X* into the lungs, or through the side tube and into one of the absorption tubes placed between *PP'*, *QQ'*, or *RR'*. The former path offering the least resistance, owing to the pressure of liquid in the absorption tubes, the air enters the lungs. The extent of the stroke can be varied at will by varying the stroke of the Meyer pump which works the water-piston. The amount of air left in the lungs in the expiratory position can also be varied by opening the clip on the side tube *C* momentarily while

the pump is at work and thus allowing air to enter or escape from the bulb *D*.

On the descent of the water-piston suction is exerted, which, opening the valve *O* and closing valve *N*, draws the air out of the lungs through one of the absorption bulbs, *e.g.* through *R* and *R'* and so again into the pump cylinder. The absorption bulbs each contain 20 c.c. of potassium hydrate solution, 1 c.c. of which = 5 c.c. CO_2 (25 gms. KHO per litre). After the air has been in circulation for a few minutes the absorption of oxygen and consequent diminution in volume of the system causes a slight reduction in pressure in the system in consequence of which the water-piston at the end of its downward stroke stops at a

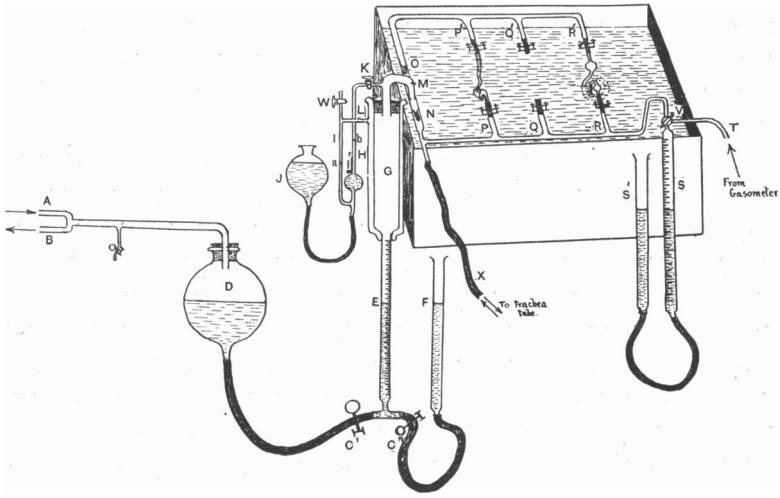

Fig. 1.

point higher up in *E* than before. Oxygen is accordingly admitted from the graduated burette *S* until the water surface attains its former amplitude of movement. In this way the oxygen tension in the circulating air is kept approximately constant throughout the experiment. In order to avoid errors arising from variations of temperature, the following precautions were taken: the absorption tubes were placed in a large galvanised tank filled with water, the temperature of which remained practically constant during the experiment. Any slight variations in temperature in the system outside the water tank were compensated by means of a thermo-barometer attachment to the bulb *G*. This vessel (*G*) is surrounded by an air-jacket *H*, which opens only at *L* and leads to the U-tube *I I'*. This is attached by rubber tubing

to the bulb J, which is filled with water. The U-tube also connects by the tap K with the tube M leading from G.

The thermo-barometer thus resembles the one used in the well-known Haldane gas analysis apparatus, and is used in the following way: C' being closed and W, K and C opened, F is lowered until the water in I' rises to a mark (b) about 3 cm. higher than (a) in I. W is now closed during the remainder of the experiment. The object of having b higher than a is obviously to have a small but constant negative pressure which shall always collapse the lungs to exactly the same extent, provided changes in elasticity of the lung tissue do not occur.

The levels of the water in the barometer having been adjusted, the level of the water in E is then observed. This having been done C'' and K are closed, and C' opened and an observation taken during a period of 20 minutes or so. At the end of this time C' is again closed, K and C'' opened, and F moved up or down until the water in I' again reaches b. If now the water in I be not exactly at a, a temperature change has occurred and must be compensated by lowering or raising J until the water again comes to the mark a. The reading in E is again taken. The oxygen consumption is given by the diminution in volume read off on E, plus the volume of oxygen which has been run in from S in the course of the period. The volume of carbon dioxide formed during the period is obtained by titrating the contents of the Winkler spirals. These are well rinsed out with water and to the contents and rinsings are added a few drops of phenolphthalein and 10 c.c. of 15% barium chloride. The titration is then made with a standard solution of sulphuric acid, 1 c.c. of which is equal to about 5 c.c. of CO_2. The values for CO_2 and O_2 may be considered as correct to the nearest cubic centimetre, that is to say, the error in the burette readings in consecutive blank experiments on dead lungs was about 1 c.c. Since the volume of the whole apparatus was about 700 c.c., the error is not large. The loss of oxygen and of carbon dioxide from the surface of the lungs is negligible provided of course that there be no holes made in the latter during the operative procedures.

Thus in the following experiments the impermeability to oxygen is shown. The circulating gas consisted of a mixture of air and oxygen and was circulated in and out of dead lungs and analysed at intervals.

Time of reading	Reading of burette	% of oxygen in circulating gas
2·10	88·0	25·8
2·40	88·0	26·0
3·0	73·5	42·8
3·30	74·4	43·4

In some half-dozen of the experiments with cats the heart-lung preparation was immersed in a bath of warm saline in order that any leaks might be detected in the lungs, but as these were never found the procedure was abandoned when dogs came to be used.

Owing to the ease with which lung œdema set in when cats were employed, the use of these animals was practically prohibited for prolonged experiments, and dogs of about 5 kg. body weight were used. The animal was first of all bled to about one half, and in order to render the blood incoagulable about ·1 grm. of hirudin in 15 c.c. of saline was added to the remaining blood. After setting up the preparation and starting the respiration pump, the heart was allowed to work for about 20 minutes until the temperature of the in-going blood became constant; this also gave opportunity for the blood gases to attain equilibrium with the air. In order to prevent change in the blood gases by contact with the air in the venous reservoir[1], this latter was kept closed by a cork through which the delivery tube from the arterial resistance passed, to dip beneath the surface of the blood in the reservoir. In many cases analyses of the blood gases were made by Barcroft's method at various periods during the experiment, but unless lung œdema had set in previous to taking the later sample very little change was found to have occurred, as the following example shows. The samples were of the blood leaving the arterial resistance apparatus.

Exp.	Time between collection of samples hrs.	mins.	Vol. of blood in apparatus in c.c.	Rate of gain or loss of blood gases per 20 mins. period, in c.c. O_2	CO_2	Oxygen p.c. At beginning	At end	Difference	Carbon dioxide p.c. At beginning	At end	Difference
1	2	12	220	+0·033	−0·17	11·4	11·5	+0·1	14·2	13·7	−0·5
2	2	30	230	−0·630	+1·06	16·0	14·0	−2·0	19·5	23·0	+3·5
3	0	50	200	−1·200	−0·48	13·2	11·7	−1·5	13·4	12·8	−0·6
4	2	0	180	+0·380	−0·27	9·8	11·1	+1·3	15·7	14·8	−0·9
5	1	30	160	−0·07	−0·29	8·2	8·0	−0·2	13·2	12·4	−0·8

The varying amounts of oxygen in the different experiments are due to varying dilution of the blood with the hirudin solution. The constancy of the blood gases indicates a very regular and sufficient air supply to the lungs.

[1] Cf. the sketch shown by Knowlton and Starling.

THE GASEOUS METABOLISM OF THE NORMAL HEART-LUNG PREPARATION.

In order to gain an idea of the extent of the normal gaseous metabolism of the heart-lung preparation, a number of experiments were carried out upon cats and dogs, but owing to the drawbacks already referred to, those upon cats were of little use. In these experiments one aimed at keeping the conditions, such as temperature, arterial pressure and venous pressure, as constant as possible. The results of some of these experiments on dogs' hearts are given in Table I and those for cats in Table II.

TABLE I. *Dogs.*

Exp.	Number of periods 20′ each	Weight of heart, grams	Mean arterial pressure, mm. Hg.	Output per hr. (litres)	Temp. of blood, °C.	CO_2 per hour, c.c.	O_2 per hour, c.c.	CO_2 per gram heart per hour, c.c.	O_2 per gram heart per hour, c.c.	R. Q.	
1	4	31·6	85	—	33·0	122·0	117·0	3·8	3·7	1·04	Mean = 0·901
2	7	68·5	90	—	35·5	189·5	222·0	2·76	3·23	·85	
3	2	32·0	80	—	35·5	139·0	187·0	4·45	5·7	·74	
6	9	50·5	100	—	32·0	102·0	111·0	2·02	2·2	·92	
7	3	—	100	—	37·0	64·0	101·0	—	—	·64	
8	5	30·0	93	—	35·0	152·0	142·0	5·1	4·7	1·07	
9	5	51·5	109	—	36·5	249·0	275·0	4·85	5·32	·91	
10	8	51·5	85	—	36·4	275·0	275·5	5·32	5·32	1·0	
11	1	23·0	65	—	35·6	91·4	96·0	3·98	4·15	·94	
12	3	23·1	64	7·2	36·5	120·7	134·1	5·22	5·8	0·9	

TABLE II. *Cats.*

I	4	13·0	58	—	35·0	49·2	70·0	3·8	5·4	0·7
II	3	14·4	76	—	36·5	29·1	—	2·01	—	—
III	1	12·0	82	—	37·2	20·6	—	1·71	—	—
IV	2	—	49	—	34·0	68·1	61·2	—	—	1·1

From Table I it may be seen that for dogs the carbon dioxide output varies from 3 to 5 c.c. per gram of heart per hour at a temperature of 33° to 36° C. The influence of temperature and pressure on the gaseous metabolism is considered in a further section. The oxygen intake has a value of about 3·5 to 6 c.c. per gram per hour under similar conditions for the dog. In the cats the values seem to be somewhat lower, viz. 1·7 to 3·8 c.c. per gram per hour for carbon dioxide. The oxygen values were not taken in the case of cats.

It is interesting to compare these results with those of other investigators. Thus Barcroft and Dixon's values for oxygen varied from ·6 to 2·7 c.c. per gram per hour, though in one case by giving adrenalin

they obtained a value of 4·98 c.c. This value however was not sustained[1]. Rohde's values for the cat for oxygen varied from 1·3 to 4·6 c.c. per gram per hour and from 1 to 4 c.c. per gram per hour for carbon dioxide (p. 227 *loc. cit.*), values which agree very well with my own experiments made by a totally different method. Gayda's results for the rabbit's heart were from 1·37 to 3·07 c.c. per gram per hour (calculated from table on p. 22). It must be borne in mind however that the experiments given in summary above were carried out with the heart and lungs. Data concerning the metabolism of the lungs are given in a further section.

The respiratory quotient in dogs had a mean value of ·90. This would indicate that the combustion of carbohydrate supplies at least some of the energy for the heart-muscle. That the heart is capable of utilising glucose was discovered independently by Locke and Rosenheim(8) and by Johannes Müller(9). Kolish(10), on theoretical grounds, threw doubt on this, but the work of Camis(11) indicated that the heart does draw upon carbohydrate from the circulating blood (in herbivora) or from the glycogen of the heart (carnivora). He was not able however to find any withdrawal of sugar from the circulating fluid in carnivora, though in herbivora the usage may be very considerable. According to this author the glycogen of the heart-muscle has its origin from protein. The researches of Rohde and of Knowlton and Starling(12) however show that the heart of carnivora can consume sugar at the rate of several mg. per gram per hour. Rohde's figures for the cat vary from 1 to 3 mg. of heart per hour (calculated from p. 227, *loc. cit.*).

The experiments of Knowlton and Starling were made under practically normal conditions upon the heart of the dog fed with blood. They found a steady usage of about 3·5 mg. of glucose per gram of heart per hour. Their demonstration that the heart of the diabetic dog uses practically no sugar, but that the sugar disappearance recommences at a normal level upon the addition of an extract of pancreas, disposes of the objections brought forward by Kolish. A consumption of 3·5 mg. of glucose would yield, if the combustion were complete, about 2·6 c.c. of carbon dioxide and would require the same amount of oxygen. From these data one is tempted to speculate as to the nature of the other

[1] In Barcroft and Dixon's experiments the ventricles were subjected to little or no internal tension since they used the coronary perfusion only. Since tension presumably has an important influence, this fact perhaps explains the low values which they obtained as a rule.

constituents which the heart-muscle uses. Thus if we take the respiratory quotient as 0·9, the carbon dioxide and oxygen as 4 and 4·4 c.c. per grm. per hour respectively, we have:

$$\begin{matrix} 4{\cdot}0 - 2{\cdot}6 = 1{\cdot}4 \text{ c.c. } CO_2 \\ 4{\cdot}4 - 2{\cdot}6 = 1{\cdot}8 \text{ c.c. } O_2 \end{matrix} \qquad \text{R.Q.} = \frac{1{\cdot}4}{1{\cdot}8} = {\cdot}78,$$

i.e. the constituents other than sugar would have a respiratory quotient of ·78. This is in good agreement with the experiments of Rohde, who found for the non-carbohydrate material a respiratory quotient of about ·74. The values of a respiratory quotient in the case of an isolated organ must be very limited as an index to the nature of the food-stuffs used, unless one knows what other stuff-metabolism is going on in the cells. v. Frey and Gruber(13), Vernon(14), Barcroft and Brodie(15), Barcroft and Dixon(16), and others, have shown that the carbon dioxide production does not always run parallel with the oxygen consumption in the case of isolated organs, and v. Frey, Fletcher(17), and Verzár(18) have shown that lactic acid is often formed in muscle under such conditions, and, as Hopkins and Fletcher(19) have shown, may disappear again when a more abundant oxygen supply is available.

By some writers the independence of oxygen absorption and carbon dioxide production is interpreted as indicating the intake of oxygen into the substance of the tissues to form the so-called intramolecular oxygen, which is subsequently used for the combustion processes of which the carbon dioxide is the end-product, and as a result of which the mechanical changes in form in muscle is brought about. Winterstein(20) has subjected this view to severe criticism and from experiments on the mammalian heart perfused by Langendorff's method, and on the isolated spinal cord of the frog(21), he concludes that the primary origin of the energy lies in non-oxidative cleavage processes and that the products so formed are subsequently removed by oxidative changes. A. V. Hill's views are similar(22), but with the further addition that in the case of muscle, the small molecules formed as a result of the excitatory process are supposed to act in a physical manner in producing the state of local tension. Verzár(18) from a study of the gaseous metabolism of striated muscle arrives at the same conclusions, namely, that the oxygen is not used during the contraction process, but for subsequent restitutive processes, the absorption of oxygen lasting long after the contraction process, just as the heat production lasts long after the contraction, as shown by A. V. Hill.

If one assumes that the liberation of oxy-acids from precursors such as amino-acids or carbohydrates, offers a mode of anærobic respiration,

and that under conditions of abundant oxygen supply these reactions may be reversed, or stopped and oxidative ones substituted, one sees that the process of tissue respiration has not merely several stages, but that it may have several phases also, phases where oxidation, deamination, hydrolysis, or synthesis may in turn take the upper hand according to circumstances. Under these conditions the respiratory quotient undergo corresponding variations.

The following experiments show that the respiratory quotient is somewhat different in different experiments and also in some cases in the same experiment. In the first two experiments given below the respiratory quotient was about unity.

TABLE III. *Exp.* 1. *Dog. Heart* 31·6 *grms.*

Temp. of blood, °C.	Arterial pressure, mm. Hg.	Gaseous exchange per hour, in c.c. CO_2	Gaseous exchange per hour, in c.c. O_2	Resp. quot.	Gaseous exchange per gram per hour, in c.c. CO_2	Gaseous exchange per gram per hour, in c.c. O_2
33·5	85	117·0	105·0	1·11	3·81	3·35
33·2	85	123·6	111·9	1·10	3·91	3·56
33·4	85	113·1	123·0	0·92	3·59	3·90
33·2	85	134·4	129·6	1·04	4·26	4·12
33·2	85	108·0	156·0	0·69	3·43	4·95
Exp. 8.	*Small dog.*	*Heart* 30 *grms.*		*Periods of* 20 *mins. duration.*		
35·3	93	139·5	140·0	1·00	4·65	4·65
35·0	93	161·4	154·2	1·04	5·40	5·12
35·0	93	120·9	97·5	1·24	4·05	3·23
35·5	93	159·0	159·9	0·99	5·30	5·30
35·5	93	180·0	165·0	1·09	6·00	5·50

In some cases the respiratory quotient is higher than unity. A similar condition was noted by v. Frey for skeletal muscle. It may perhaps mean that there is a washing out of previously accumulated carbon dioxide, or it may really indicate a different phase of tissue respiration. In those cases where it occurs late in the experiment the second possibility is indicated. In the following experiment the quotients are all below unity:—

TABLE IV. *Exp.* 9. *Dog. Heart* 51·5 *grms. Periods of* 20 *mins. duration*

Temp. of blood, °C.	Arterial pressure, mm. Hg.	Gaseous exchange per hour, in c.c. CO_2	Gaseous exchange per hour, in c.c. O_2	Respiratory quotient	Gaseous exchange per gram per hour CO_2	Gaseous exchange per gram per hour O_2
37·0	109	233·2	260·0	·90	4·53	5·02
36·5	109	259·6	296·0	·88	5·02	5·72
36·5	109	292·8	309·2	·95	5·70	6·00
36·5	109	248·0	272·8	·91	4·82	5·27
36·5	109	215·2	236·8	·91	4·17	4·60

Reference has been made above to the observations of Barcroft and co-workers (15), (16), (18) that the process of oxygen absorption may be more or less dissociated from that of carbon dioxide production. This independence of the two processes, absorption of oxygen and evolution of carbon dioxide, is well shown in some of the experiments. Generally speaking, the carbon dioxide production slowly falls off during the course of an experiment, while the oxygen intake often shows the reverse change. This was noticeable, *e.g.* in the last period of Exp. 1, but is better seen in the following experiments.

TABLE V. *Exp.* 3. *Dog. Heart,* 32 *grms.* 20 *min. periods.*

Temp. of blood, °C.	Arterial pressure, mm. Hg.	Gaseous exchange per hour, in c.c. CO_2	Gaseous exchange per hour, in c.c. O_2	Respiratory quotient
36·0	80	138·6	181·5	0·76
35·5	80	139·5	192·0	0·73
35·5	80	126·5	255·0	0·50
		Exp. 11. *Dog. Heart,* 23 *grms.*		
35·6	65	91·4	96·6	0·94
35·7	65	71·0	109·4	0·65
35·6	65	51·0	134·0	0·39

It was at first thought that these large oxygen absorptions were due to some purely mechanical error, such for example as the retention of air in the lungs in the form of froth in early stages of lung œdema. Further experiments showed, however, that the phenomenon could not be accounted for in any such simple manner, since in pronounced œdema the carbon dioxide output fell off very rapidly, while the oxygen intake did not increase very much. Moreover, a similar phenomenon was never observed in the isolated lung experiments. Probably the simplest explanation is that we are here dealing with an incomplete metabolism of the kind already referred to, induced by what is often termed "oxygen lack." Similar results have been signalled by Vernon (23) and by Thunberg (24) and others for other tissues after conditions of oxygen lack. Since the oxygen absorptions increase progressively, however, it is not quite correct to call this condition one of oxygen lack in the usual sense of the term. It is better to call it an increased oxygen usage. The condition of oxygen lack would exist only if the extra oxygen requirement were not available.

This phenomenon of increased oxygen usage has been seen in one or two cases at the beginning of an experiment, so it cannot be regarded

merely as a phenomenon of the moribund heart. Thus in Exp. 13 (p. 228) the first period shows the termination of such a period of rapid oxygen absorption which in this case lasted for some time and was very great. Afterwards, however, the respiratory quotient remained very steady.

The metabolism of the lungs and blood.

In the foregoing experiments no account has been taken of the contribution of the lungs and blood towards the total metabolism of the heart-lung preparation. In order to gain some idea of the gaseous metabolism of the lungs and blood, the apparatus shown diagrammatically in Fig. 2 was used in order to maintain a circulation through

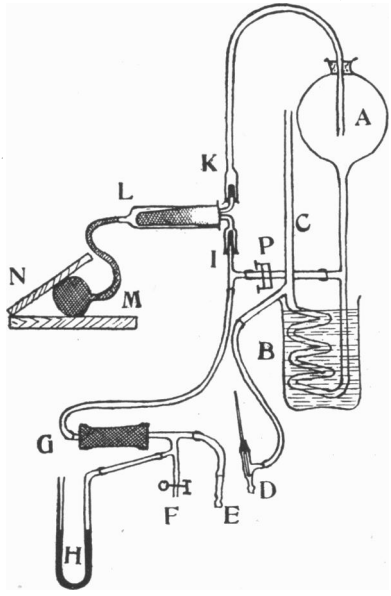

Fig. 2.

the isolated lungs, which were also connected to the apparatus shown in Fig. 1 in exactly the same way as the heart-lung preparation. The perfusion apparatus was constructed in the following way: the reservoir *A* contains defibrinated and hirudinised blood from the animal used. The blood flows along the spiral *B*, where it is warmed, and emerging by the side tube enters the pulmonary artery by the cannula *D*, which carried a thermometer to indicate the temperature of the ingoing blood. The vertical tube *C* serves as a manometer to indicate the

pressure at which the perfusion was carried out; it also acts as a trap for air bubbles which otherwise might enter with the blood stream. The blood emerging from the pulmonary vein is pumped back again into *A* by means of the pump *KLI*. This resembles the arrangement used by Locke in his new perfusion pump[1] which works on the hydraulic ram principle. For various reasons it was not possible to employ the hydraulic ram principle in this case, so the movement of the rubber finger-stall *L* was effected by a regular compression of the stout rubber bulb *M* by means of a treadle worked by a motor. *K* and *I* are rubber valves working over slits in the glass tubing. Since the bulb *M* was of stout rubber and was filled with water, considerable negative pressure was exerted in the elastic recoil and the blood could be raised to a considerable height if necessary. In order to minimise sudden variations in the negative pressure on the venous side occasioned by the working of the pump, the large thin-walled tube *G* was introduced. It consisted of a piece of inner tube of a bicycle tyre about 4 inches long.

In order further to control the extent of the negative pressure on the venous side, the short circuit, controlled by the screw clip *P*, was introduced. In this way it was possible to vary the arterial and venous pressures to any reasonable extent independently of each other. The extent of the venous pressure was given by the manometer *H*, but could be judged still better by observing the tube *G*, the pressure being so adjusted that *G* showed a slight tendency to collapse. The side tube *F* is for withdrawing samples of blood for analysis. The pump is capable of raising fluid to the height of a metre, but for the perfusion of the lungs a perfusion pressure of 10 to 15 cm. of blood should not be exceeded, otherwise pulmonary œdema soon puts an end to the experiment.

In preparing for the experiment, blood is obtained by bleeding one or more animals (three in the case of cats). The blood is defibrinated, strained, and well shaken with air before being placed in the apparatus. The animal to be used for the experiment is also bled until about half the blood is withdrawn, the chest is then opened rapidly under artificial respiration, and the cannulæ introduced into the pulmonary vessels as quickly as possible, the arterial cannula being filled with hirudin solution (·1 gram in 15 c.c. of saline). The blood is then allowed to run into the lung vessels and the pump is started. Artificial respiration was usually kept up for about 20 mins. before commencing the determi-

[1] Shown at the meeting of the Physiol. Society in Jan., 1911. Dr Locke has also kindly allowed me to inspect the apparatus privately.

nation of the gaseous exchange, in order to attain equilibrium between the gases of the air and blood[1].

An unexpected difficulty in these experiments was encountered in the fact that in many cases the lung vessels after a few minutes' perfusion constricted to such an extent that the blood-flow practically ceased. Attempts were made to discover the cause of this phenomenon but with no great success. It was not due to the influence of an alteration of temperature, or to changes in the reaction of the blood, to coagulation, to products formed in defibrination of the blood, to air emboli, to insufficient or too great pressure, nor to the hirudin solution employed. I venture to think that it was often due to a too perfect removal of carbon dioxide from the blood, since in some cases the administration of 10 p.c. carbon dioxide removed the resistance almost at once. This action of normal metabolites has already been pointed out by Barcroft and Dixon[6] in the case of the coronary vessels, and has been noticed also by the other observers quoted by them.

The results of the experiments in those cases in which a successful perfusion could be maintained were uniform. Eleven successful experiments were performed in all. Since these all showed similar results it will probably suffice to give one of them.

In the other ten experiments the gaseous exchanges were not quite so regular as in this case, but were of the same order. One must however allow for the metabolism of the blood in the circulation

TABLE VI. *Exp.* 14. *Dog*, 3·01 *kg.* *Heart*, 19·5 *grms.*[2] 30 *min. periods.*

Temp. of blood, °C.	Flow, c.c. per min.	Gaseous exchange in air per hour		Change in gases of blood per hour, c.c.		Total gaseous exchange per hour, in c.c.		R. Q.
		CO_2	O_2	CO_2	O_2	CO_2	O_2	
36·5	54·5	40·0	19·6	−20	No appreciable change	**20·0**	**19·6**	1·02
36·5	55·0 78·0	40·0	24·0	−20		**20·0**	**24·0**	0·84
36·0	96·0 96·0	27·2	22·0	− 6·8		**20·4**	**22·0**	0·93
36·7	96·0 100·0	23·6	22·6	− 3·2		**20·4**	**22·6**	0·91
36·5	100·0 100·0	20·4	28·0	0		**20·4**	**28·0**	0·73

[1] In order to keep the blood as aseptic as possible in these experiments, the apparatus was always cleaned out after use with 2 p.c. sodium hydrate solution, often followed by alcohol. The liquid was allowed to circulate for half an hour in the pump and was then washed out with several litres of water, and finally with saline solution. The apparatus was also taken down and boiled twice during the progress of the series of experiments.

[2] The weight of the lungs was of no use in any of these experiments, since they were always more or less congested and œdematous at the end of the experiment. Instead of this, the weight of the heart is recorded since it was only in relation to the heart that the results were required. The heart and lungs of some normal animals were weighed and the lungs were usually found to be from 160 to 200 p.c. of the weight of the heart. It would be possible therefore to compute roughly the weight of the lungs, were this necessary, from that of the heart.

(generally 300—400 c.c.). In Exp. 14 there were 320 c.c. of blood in the circulation. The respiration of the blood was determined by the following experiment.

10 c.c. of fresh defibrinated and well ærated blood were placed in a "sampling tube" with 47 c.c. of air and kept at 37° C. for two hours with frequent shaking.

CO_2 content of 10 c.c. of blood at beginning 2·07 c.c.

" " " " end 2·05 "

i.e. 0·02 c.c. CO_2 has been "lost" by the blood. The air had gained 0·57 p.c. CO_2, *i.e.* ·27 c.c. in the 47 c.c. of air. The total production therefore was 1·25 c.c. CO_2 per hour per 100 c.c. blood.

The 320 c.c. of blood would therefore produce 4 c.c. CO_2 per hour. Deducting this from the total we have about 16 c.c. CO_2 per hour produced by the lungs. Since the heart weighed 19·5 grams, it would be necessary in determining the metabolism of the heart to deduct from the metabolism per gram of heart per hour, about ·8 c.c. CO_2 and about ·9 c.c. oxygen, in order to allow for the metabolism of the lungs. This would be about one-fifth of the total metabolism. There may also be a further deduction of 1·25 c.c. CO_2 per hour per 100 c.c. of blood from the total metabolism of the *whole* heart, but since this is below the errors of experiment it is best neglected in experiments on the heart-lung.

THE INFLUENCE OF WORK ON THE GASEOUS METABOLISM OF THE HEART.

The amount of work performed by the heart can readily be altered when using the isolated heart-lung preparation. There are two ways in which this may be done. Firstly, if the arterial resistance be raised, the rate and output remaining practically constant, the work will be increased. Secondly, by increasing the height of the venous reservoir, the output will be increased while the arterial pressure and pulse rate remain almost unaltered, as shown by Knowlton and Starling(2). These two methods of increasing the work are not identical.

When the arterial resistance is increased we have what corresponds to an increased load in skeletal muscle. Since the heart works as an after-loaded muscle, the increase in initial tension is in this case but slight. When, on the other hand, the venous reservoir is raised and the inflow (and output) increased, the condition is not so simple. It is certain that there is a little more initial (diastolic) tension in this case but it is only slight, as the experiments of Knowlton and Starling show. But the heart is now more dilated at the beginning of systole

than before, and the muscle is contracting at a mechanical disadvantage, *i.e.* the increase in tension during the systole is relatively great in the individual muscle cells, though the endocardiac pressure may be scarcely greater than when the venous pressure was low.

Direct experiments were made in order to determine the influence of alterations in arterial pressure. The results of five experiments are given below, the results at the higher pressures being indicated in thick type[1].

In these experiments the variations in pressure have been great, so that the outflow has altered somewhat considerably in some cases. It is however clear that the heart works more economically when the arterial pressure is high than when it is low, the small increase in metabolism being quite out of proportion to the extra work done. The experiments show moreover that whilst working against a high pressure, the respiratory quotient is lowered. On changing from a high to a low pressure, the respiratory quotient rises again if the heart is in good condition, but if the heart is enfeebled by the high pressure, as shown by the diminished output, the respiratory quotient may remain low. Apparently the oxidative processes are in such a case incomplete, and cannot be carried so far as to yield the full measure of carbon dioxide. It is also possible that the metabolism may be qualitatively different, or that the results may be due to a more effective coronary circulation at the higher pressure. The gaseous exchange per kilogram-metre of work done is in the above experiments 14 c.c. to 50 c.c. CO_2, the average being about 40 c.c. at low pressure and about 25 c.c. at high pressure. The cat's heart used by Rohde(6) seemed to work even more economically: thus in Rohde's Exp. 84, the carbon dioxide per kgrm. metre was only 2·7 c.c. This low figure is of interest in view of the usual high arterial pressure which obtains in cats. Barcroft and Dixon(6) also remark that the energy set free is less for the cat than the dog, in proportion to the work done. Gayda's(7) results for the rabbit on the other hand seem to be so high, *e.g.* 45 to 510 c.c. per kilogram-metre (·000993 to ·01024 mg. per grm. cm. in one of his tables (p. 20(8))) that one accepts them with some hesitation.

The mechanical efficiency of the heart. We may take as a basis for the calculation of the mechanical efficiency of the heart three modes of calculation. We may either: (*a*) take the whole metabolism for the calculation of the energy consumption at each pressure, or (*b*) take the excess of metabolism at the higher pressure as against the lower,

[1] The values are not corrected for the metabolism of the lungs and blood.

TABLE VII. *Exp.* 12. *Dog. Heart* = 23·1 *grms. Temp.* 36·5° C.
20 *minute periods.*

Arterial pressure, mm. Hg.	Output per hour (litres)	Work per hour	Gaseous exchange per hour CO_2	Gaseous exchange per hour O_2	R. Q.	Gaseous exchange per kgm. of work, in c.c. CO_2	Gaseous exchange per kgm. of work, in c.c. O_2
64	9·22	$7·9 \times 10^5$ g.cm.	110·4	104·4	1·05	14·0	13·2
64	3·06	2·63 ,,	98·7	114·9	·86	37·5	43·6
124	**2·67**	**4·45** ,,	**128·1**	**226·5**	**·57**	**28·7**	**50·7**
64	2·59	2·23 ,,	90·6	182·1	·50	40·5	70·0
		Exp. 13. *Dog. Heart* = 45·5 *grms. Temp.* 36·5° C.					
64	5·98	$5·13 \times 10^5$ g.cm.	168·9	282·0	·6	32·8	54·9
64	5·62	4·82 ,,	168·9	213·6	·79	35·1	44·5
124	**3·27**	**5·42** ,,	**174·0**	**222·9**	**·78**	**32·2**	**41·2**
64	3·60	3·09 ,,	132·0	166·8	·79	42·6	54·0
		Exp. 15. *Dog. Heart* = 41 *grms. Temp. of* 1*st sample* 35·5, *of last* 36·4, *of rest* 36° C.					
50	4·39	$2·94 \times 10^5$ g.cm.	113·1	127·8	·87	38·3	43·3
50	4·68	3·14 ,,	106·5	124·5		33·8	39·7
110	**3·35**	**4·96** ,,	**121·5**	**155·1**	**·79**	**24·4**	**31·3**
110	**3·73**	**5·52** ,,	**129·3**	**162·6**		**23·4**	**29·5**
50	4·53	3·05 ,,	115·8	117·3	·89	38·0	38·4
50	4·4	2·95 ,,	93·0	117·0		31·5	39·7
110	**2·88**	**4·28** ,,	**113·1**	**166·8**	**·61**	**26·3**	**39·0**
110	**2·34**	**3·47** ,,	**111·9**	**207·0**		**32·2**	**59·8**
50	3·27	2·19 ,,	98·4	109·2	·90	44·8	49·5
		Exp. 16. *Dog. Heart* = 47·5 *grms. Temp.* 36° C.					
40	5·03	$2·72 \times 10^5$ g.cm.	132·0	148·2	·89	48·6	54·7
110	**4·75**	**7·03** ,,	**152·4**	**173·7**	**·76**	**21·7**	**24·7**
110	**3·89**	**5·77** ,,	**129·6**	**198·6**		**22·5**	**34·5**
40	5·15	2·77 ,,	140·1	140·4	·90	50·6	50·7
40	5·3	2·86 ,,	117·6	147·3		41·1	51·5
110	**3·13**	**4·65** ,,	**184·8**	**210·9**	**·82**	**39·6**	**45·1**
110	**3·06**	**4·54** ,,	**170·1**	**217·8**		**37·4**	**47·9**
40	3·77	2·03 ,,	98·4	147·9	·68	48·3	73·0
40	3·46	1·87 ,,	105·3	153·6		56·2	82·3
		Exp. 17. *Dog. Heart* = 76 *grms. Temp.* 36° C.					
40	7·68	$4·12 \times 10^5$ g.cm.	160·8	161·1	1·0	39·1	39·2
40	7·77	4·16 ,,	148·2	163·8	·9	35·6	39·4
110	**6·4**	**9·45** ,,	**180·3**	**213·0**	**·85**	**19·05**	**22·6**
110	**6·45**	**9·5** ,,	**180·6**	**219·6**	**·82**	**18·90**	**23·0**
40	6·55	3·51 ,,	153·6	159·0	·96	43·70	45·3
40	6·45	3·46 ,,	116·1	129·9	·89	33·5	37·3
110	**4·13**	**6·11** ,,	**189·0**	**280·5**	**·67**	**31·0**	**46·0**

and calculate the energy expenditure for the excess work done at the higher pressure as against the lower, or (*c*) determine the resting metabolism of the heart and deduct this from the total metabolism.

Let us take the results of Exp. 15 and calculate the efficiency according to methods (*a*) and (*b*).

Method (*a*). (i) At low pressures, periods 1 and 2. The total work done by the left ventricle was 3·04 kg.m. metre per hour (mean). Adding one-sixth more for the work of the right ventricle, etc., we have 3·55 kg.m. for the total work done per hour. The mean oxygen intake was 110 c.c. per hour. Deducting 28 c.c. for metabolism of the blood and of the lungs we have then 82 c.c. oxygen used per hour by the heart.

Now assuming for the sake of simplicity that glucose is the source of the energy, we have, since

1 c.c. oxygen = 1·34 mg. glucose; 1 grm. glucose = 4·1 calories;
1 cal. = 425·5 kg. metres;

the total energy expended is

$$82 \times \cdot00134 \times 4\cdot1 \times 425\cdot5 \text{ kg.m.} = 192 \text{ kg.m.}$$

$$\therefore \text{ Efficiency} = 1\cdot85\ \%.$$

(ii) Similarly at the high pressures, periods 3 and 4.

Mean work = 5·24 + 0·87 = 6·11 kg.m. per hour.
Mean oxygen intake = 159 − 28 = 131 c.c.
Energy expenditure $131 \times \cdot00134 \times 4\cdot1 \times 425\cdot5 = 307$ kg.m.

$$\therefore \text{ Efficiency} = 2\cdot0\ \%.$$

Method (*b*). Difference in work at the two pressures

$$= 6\cdot11 - 3\cdot55 = 2\cdot56 \text{ kg.m.}$$

Difference in energy consumption = 307 − 192 = 115 kg.m.

$$\therefore \text{ Efficiency} = 2\cdot23\ \%.$$

Similar calculations for the other experiments give like results. Thus for Exp. 17 by method (*a*):

Work done at low pressure = 4·83 kg.m. Energy expended = 187 kg.m.

$$\therefore \text{ Efficiency} = 2\cdot58\ \%.$$

At high pressure, work done = 11·1 kg.m. Energy expended = 246 kg.m.

$$\therefore \text{ Efficiency} = 4\cdot5\ \%.$$

By method (*b*): Difference in work done = 6·27 kg.m.

Difference in energy expended = 59 kg.m. ∴ Efficiency = 10·6 %.

This latter was the highest efficiency obtained.

Concerning method (*c*) I have made no direct attempt to determine the resting metabolism of the heart. This was done by Rohde in his experiments by bringing the heart to rest by replacing the Ringer solution used for the perfusion by one free from calcium salts. This resting heart was found by Rohde to exhibit a fairly large metabolism.

The results given above were not obtained over a sufficient range of pressures to allow of extrapolation with a view to determining the metabolism at zero pressure. Judging from the experiments of Verzár(18) on skeletal muscle, the resting gaseous metabolism of muscle is about ·27 c.c. oxygen per gram of muscle per hour. If the resting metabolism of heart muscle were of the same order, it would amount to about one-tenth to one-sixth of the total metabolism.

The figures obtained in all the above calculations show a surprisingly low efficiency when compared with the results of Barcroft and Dixon and of Rohde. The metabolism seems to be very much in excess of the requirements, but until more is known of the mechanical conditions under which the heart muscle works it is impossible to say what criterion is best to take in measuring the work done. Two factors which are not taken into account are the viscosity of the blood, and the fact that in the presphygmic interval the contraction is isometric and therefore the tension is increasing without any work being done. Now as A. V. Hill(22) has shown, the heat production of muscle (and therefore, presumably, the metabolism) depends not on the work but upon the tension. But there is a further fact to be considered: the heart muscle fibres do not exert a direct pull, as in a sartorius muscle for example,—they act more or less tangentially. If one considers the effect of two tangential components acting upon a point on the surface of a sphere, it is evident that their centrally directed resultant is very small, and that the more dilated (*i.e.* the larger) the sphere, the smaller does this resultant become[1]. What the effect of the spiral course of the fibres may be does not seem clear, but a mathematical investigation may possibly throw light upon this question.

When all the above considerations are taken into account, the low efficiency of the heart when compared with skeletal muscle is not so very surprising. The efficiency being so low in any case may perhaps explain why Barcroft and Dixon found that the oxygen intake in isotonic and isometric contractions was almost equal, an observation

[1] One may recall in this connection, by way of illustration, the well-known experiment of a smaller soap bubble emptying itself into a larger one when the two are connected by a tube.

which I have been able to confirm. Similarly Weizäcker[25] finds that in the frog's heart the rate of fatigue is the same, whether the contractions be isotonic or isometric.

Concerning the method of varying the work by means of alteration of the venous inflow, experiments have not yet been made. It is hoped to discuss this further in a later communication.

THE INFLUENCE OF TEMPERATURE.

One would expect that with an increase of temperature, there would be an increase in the gaseous metabolism as of the rate of the heart beat. The following experiments show that this is the case. In making these experiments the temperature was kept constant to within ·1 C. At the end of two periods the temperature of the water in the warming reservoir was altered and some time given for the heart to get accustomed to the new temperature and for the blood gases to get into equilibrium under the new conditions. The interval was usually 10 or 15 mins. between the periods. The arterial pressure was in all cases 50 mm. Hg, the pressure was kept low in order to prolong the experiment as much as possible.

Of very great interest is the fact that the increase in metabolism is almost exactly proportional to the increase in the rate of the heart beat, as is seen from the fact that the values of the numbers in the columns giving the consumption of oxygen and production of carbon dioxide per kg. of heart per beat are practically constant. It is also of interest to note that they are very nearly the same in the three different hearts, viz. about ·45 c.c. O_2 and ·4 c.c. CO_2 per kg. of heart per beat.

Since an increase of 7° does not increase the amount of carbon dioxide produced by each heart beat, one may perhaps infer that at the lower temperature the metabolism is already at its maximum. We have already seen from the experiments on the effect of pressure that the metabolism of the heart is far in excess of the amount of work done, that the heart considered as a machine must be regarded as a very poor one as far as mechanical efficiency goes. The experiments on the effect of temperature seem therefore in agreement with the ones on the effect of pressure.

If anything, the amounts of carbon dioxide per gram per beat are less at the higher temperatures than at the lower, that is to say, the heart at 39° seems to work somewhat more efficiently (the output and rate per minute being both increased) than at the temperature of 32°.

TABLE VIII. *Exp.* 4. *Dog.* *Heart* = 20·5 *grms.* 20 *min. periods.*

Temp. of blood, °C.	Rate of heart per min.	Output per min., c.c.	Gaseous exchange per hour, in c.c. CO_2	Gaseous exchange per hour, in c.c. O_2	R. Q.	C.c. CO_2 per kg. of heart per beat	C.c. O_2 per kg. of heart per beat
32	97	97	51·3	52·8	1·03	·430	·443
32	104	97	54·0	49·8		·425	·390
39	**162**	**97**	**—**	**81·9**		**—**	**·410**
39	**164**	**97**	**78·3**	**89·7**	**·87**	**·397**	**·445**
39	**162**	**88**	**76·8**	**87·9**		**·395**	**·440**
32	103	75	59·4	62·4	1·0	·468	·495
32	102	75	62·1	59·1		·492	·470
			Exp. 5. *Dog.* *Heart* = 16·2 *grms.*				
32	115	71	45·9	51·9	1·02	·413	·462
32	113	73	56·7	48·6		·512	·443
39	**154**	**64**	**74·1**	**71·1**	1·00	·493	·475
39	**156**	**53**	**66·0**	**68·4**		·438	·452
			Exp. 18. *Dog.* *Heart* = 47·5 *grms.*				
32	105	68	103·2	125·4	·87	·345	·422
32	107	77	105·6	115·2		·348	·377
39	**154**	**100**	**133·5**	**160·8**	**·85**	**·305**	**·366**
39	**146**	**83**	**154·8**	**177·0**		**·370**	**·425**
32	98	84	103·8	126·6	·88	·370	·450
32	102	81	109·2	115·2		·375	·395
39	**146**	**77**	**148·5**	**191·7**	**·74**	**·355**	**·461**
39	**150**	**67**	**128·1**	**186·9**		**·300**	**·438**

The figures in heavy type are observations at the higher temperature.

This is rather what one would expect to be the case, since 39° is nearer to the normal temperature of the animal than 32°. It will be noticed also that at the lower temperature the respiratory quotient is somewhat higher than at the higher temperature. This might be interpreted as indicating that the heart when cooled uses glycogen, or it may on the other hand mean that at high temperatures, as at high arterial pressures, the process of oxidation is less complete, so that less carbon dioxide results relatively to the oxygen usage. There is also the question of the tensions of these gases in the tissues altering with the temperature, and of the dissociation of carbonates in the tissues being changed. One would expect however that this would influence the result in the opposite direction.

My best thanks are due to Professor Starling for his kindness in assisting with the operative procedures.

SUMMARY.

1. A form of artificial respiration apparatus is described, with which the gaseous exchanges in the heart-lung preparation may be studied.

2. In the dog the carbon dioxide output of the heart-lung varies from 3 to 5 c.c. per gram of heart per hour. The oxygen intake similarly is 3·5 to 6 c.c. The values for the cat are somewhat lower. The respiratory quotient of the heart, on the average about ·9, is subject to decided variations and under certain conditions may be very low (·6 or less). The low quotients are due to augmented oxygen usage.

3. By means of a specially modified apparatus, the gaseous metabolism of the surviving blood-perfused lung was determined. In order to allow for the metabolism of the lungs, about ·8 c.c. should be deducted from the values found per gram of heart per hour in the carbon dioxide figures, and ·9 c.c. in the oxygen figures. A correction for the metabolism of the blood is not necessary in experiments on the heart-lung where the volume of blood is small and the total exchange high (the correction would only be of the order of one or two p.c.). But in the experiments on the isolated lung, since the total metabolism was small and the volume of blood somewhat large, the metabolism of the blood was appreciable (about 20 p.c.).

4. The efficiency of the heart considered as a machine is very low, *e.g.* from 2 to 10 p.c. The cause of this is doubtless to be sought in the peculiar mechanical conditions of the heart beat.

5. An increase in temperature of 7° C. (from 32 to 39) results in an increase in the gaseous exchanges. But this increase is almost exactly proportional to the increase in the number of beats, *i.e.* the rate of gaseous metabolism varies almost exactly as the pulse rate, the oxygen consumption and carbon dioxide production per beat being the same at both temperatures.

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Full historical references are given in the paper of Rohde.