Energy Metabolism of the Completely Isolated Mammalian Heart in Failure

By Victor Lorber, Ph.D., M.D.

Experimental cardiac failure was reinvestigated in the completely isolated mammalian heart using a simplified system in which only the left ventricle performs work and exhibits volume changes. An effort was made to assess the importance of such experimental artefacts as acapnia, altered or depleted substrate, and controlled (constant) diastolic volume. None of these factors appeared to play a determining role in the mechanism of experimental failure, which was characterized by a decline in mechanical efficiency, with little or no impairment of total energy liberation.

In the normal heart, an increase in the diastolic volume of the chambers is accompanied by a proportional increment in the work capacity of the myocardium (Starling's Law). By dilating, the competent heart can adjust work output to increased load, within physiologic limits. Beyond a point, increasing dilatation results in no further increase in work capacity, and, if continued, will ultimately lead to a decline in cardiac work. Although in the intact animal other factors modify the mechanical activity of the heart, their action is superimposed on this intrinsic cardiac mechanism.

By the same adaptive device available to the competent organ, that is, by dilating, the failing heart may adjust work output to increased load, or maintain output in the face of declining work capacity. The main distinction between the two in terms of the work-diastolic volume relationship is that at comparable diastolic volumes the failing heart operates at a lower level of work output than the normal. The finding by Starling and Vischer that under conditions of thermal and chemical constancy the oxygen utilization (energy liberation) of the heart was a function of initial fiber length (diastolic volume) gave new significance to this distinction between cardiac competence and failure. Unlike the work-diastolic volume relationship, energy liberation was found to be unimpaired in the failing heart when compared with the competent heart at comparable diastolic volumes. Thus cardiac failure in these experiments was characterized by a defect in the transformation of chemical energy to mechanical work, in the presence of a normal capacity for the liberation of chemical energy. In other words, the failing heart showed a decline in mechanical efficiency.

The concept of low-efficiency failure has received support from much additional experimental work, but has also failed of confirmation by others. An alternate view, based on the finding of a parallel fall in work and oxygen utilization and consequently no change in efficiency, regards a defect in energy liberation as the principal change in failure. No attempt will be made here to discuss the pertinent literature on the subject, since a number of well-documented reviews are available.

The present report deals with a reinvestigation of the mechanism of failure in the completely isolated mammalian heart. The apparatus employed has been refined and simplified in certain respects, to permit a clearer definition of the functions under study, and to reduce the possible contributions of systematic error to the results obtained. In addition an effort has been made to evaluate the role of certain artefacts introduced by the method employed.

In the experiments to be described, the progressive failure that occurs spontaneously in the experimentally isolated heart was charac-
terized, in the main, by marked decrements in mechanical efficiency in the presence of little or no alteration in total energy liberation.

METHODS

The isolated heart preparation was a modification of that designed by Daly and Thorpe, as adopted by Moe and Visscher for use with a closed-system spirometer, and modified by Moe and Lorber to accommodate hearts of smaller laboratory mammals (cat and rabbit). In the apparatus in current use, interchangeable fittings of appropriate size make the same basic equipment available for both large and small hearts (5 to 50 Gm.). The main components are represented diagrammatically in Figure 1.

Using the same animal as donor for heart and blood, and heparin (Connaught) as the anticoagulant, a conventional heart-lung preparation is first made. In rapid succession the left main pulmonary artery and left atrium are then cannulated, the lungs tied off with a mass ligature, and the heart-oxygenator circuit established. In the final preparation blood flows from the venous reservoir, A, to the left atrium, B. Rate of inflow can be modified by clamp C. Inflow to the superior vena cava, established during the heart-lung stage, is cut off by a clamp. The systemic output (left heart output minus the coronary flow) is pumped by the heart via tube D from the brachiocephalic artery into the jacketed tube E in which it is returned to the reservoir. Flow can be readily measured in the lower calibrated segment of tube E by means of the stop-cock just below the calibration. Aortic pressure is determined by the height above the heart of the outlet tube in E, and remains relatively fixed throughout an experiment, as long as there is an appreciable systemic flow. Aortic pressure is measured by the mercury manometer, F, attached to a cannula in the left subclavian artery. The approximately 95 per cent of the coronary flow which passes through a small gauze filter in the reservoir and receives both coronary and systemic blood. The entire heart is suspended in the reservoir and receives both coronary and systemic blood. The entire heart is suspended in the cardiometer, X, which eliminates the constriction at the A-V groove produced by the rubber diaphragm of the conventional Henderson cardiometer. Cardiac volume is recorded by the Krogh-type spirometer O. Epicardial lymph is returned to the system through the tube leading from the bottom of the cardiometer. The fluid level in this tube is held at a fixed point throughout an experiment. The venous reservoir, oxygenator, and cardiometer are immersed in a constant temperature bath controlled to within ±0.005°C. The bath is built to hold the various vessels at the desired level. The venous reservoir is maintained at an elevated level by housing it in a separate chamber which is filled from the bottom by the centrifugal pump, P, and simply overflows into the main compartments of the bath. The centrifugal pump fills not only from an inlet tube leading from the culde-sac in which the oxygenator is recessed, but also draws water through a tube (not shown in the diagram) from the chamber which houses the spirometer, VI. This assures thorough stirring in these parts of the bath. The main volume of the bath is agitated by a heavy-duty constant speed motor.

The gas is driven through the closed respiratory circuit by the oil-sealed syringe I, which is powered by a heavy-duty constant speed motor. Gas flow is directed by the low-resistance flutter valves, H. The gas passes through the fritted glass finger in the moisture bottle, III, which is immersed in the water bath, and then into the jacketed tube, E. The jacket is kept at constant temperature by means of the centrifugal pump, P. A side tube, IV, is provided so that systemic blood flow readings may be taken without interrupting the flow of gas. The gas then flows through the blood reservoir, A, to the oxygenator via tube V, through the spirometer, VI, and absorption tubes, VII and VIII (which are thermostated).

Direction of the gas flow through tube E and the reservoir, A, prevents pocketing of blood in the former, and the sequestering of carbon dioxide in both. The spirometer, VI, is refilled from the storage cylinder, X, which connects with a gas tank, IX. In this manner new gas admitted to the system is already at the proper temperature, and does not cause a disturbance in the oxygen uptake record as a result of expansion.

The type and placement of the absorption tubes depends on the requirements of the particular experiment. If it is desired simply to measure carbon dioxide production, tube VII is charged with anhydrous magnesium perchlorate and the battery of absorbers, VIII, contains ascarite. These are preweighed, and arranged in parallel, so that they may be cut into the system one at a time. With ordinary precautions the absorbers can be weighed with a precision of ±0.3 mg. Thus, if the collection periods
are chosen so that about 30 mg. of carbon dioxide are taken up, the error of this measurement is ±1 per cent, assuming that the only error is that introduced by the weighing. Most of the measurements in the present work have involved weight changes of this magnitude. Additional errors may be introduced by changes in pH, which may alter the amount of carbon dioxide held as bicarbonate by the blood and myocardium, and by changes of carbon dioxide level in the gas phase, resulting from an altered rate of carbon dioxide production by the heart. Errors of this type have been obviated by reducing the volume of the gas phase to a minimum, by using a high rate of gas flow (about 850 ml. per minute), and by allowing a period of 45 to 60 minutes for the preparation to stabilize before beginning to make measurements. Gas samples drawn just beyond the oxygenator and analyzed in the Haldane apparatus have been found to contain about 0.4 per cent carbon dioxide, while the gas sampled beyond the carbon dioxide absorbers is virtually carbon dioxide-free. Thus, if over a period of two hours, carbon dioxide output were to double, the carbon dioxide content in the approximately 300 ml. of available gas volume in the system would rise from 0.4 to 0.8 per cent, and represent an accumulation of 1.2 ml. of carbon dioxide. Carbon dioxide production as measured would appear to be smaller by this amount (and since oxygen utilization is registered volumetrically, an error of similar magnitude and sign would occur in this measurement). Over this period of time a small cat heart will put out about 48 ml. of carbon dioxide, so that the error would be 2.5 per cent. This represents an extreme case, however, since the changes in carbon dioxide output over time were rather small in most of the present experiments, and quite negligible in those done at constant volume. Accordingly, error from this source in the experiments to be reported may be considered as negligible. Error in the measurement of carbon dioxide production due to progressive pH change has also been minimized by maintaining a low carbon dioxide tension in the gas phase. At the pCO₂ of less than 10 mm. Hg (and the resultant high plasma pH's, around 7.5 to 7.6) that prevailed, the bicarbonate-carbonic acid buffer system operates at a range in
which the ratio NaHCO₃/H₂CO₃ is quite insensitive to pH change. Taking a total blood volume of 50 ml. and heart weight of 10 Gm. as typical, a fall in pH of 0.2 units will result in a liberation of about 1.5 ml. of carbon dioxide under the conditions of pCO₂ and pH prevailing. Assuming that this takes place over a two hour period, during which total carbon dioxide output of about 48 ml. occurs, an error of 3 per cent will be introduced. This again is an extreme case, since in most instances in which it was measured pH changed by no more than a few hundredths to 0.1 unit. A correction can be made for this error if the magnitude of the pH change is known. It is therefore likely that the maximum overall error in the carbon dioxide measurements in the present experiments does not exceed ±2-2.5 per cent.

In studies with isotopic carbon, in which it is desired to recover the respiratory carbon dioxide for isotope analysis, a battery of absorbers of the type shown in the inset XI, replaces the ascarite tubes, VIII. These contain 50 to 100 ml. of 2 N carbonate-free sodium hydroxide, and a fritted glass finger for gas dispersion. The uptake of carbon dioxide is determined in the manometric Van Slyke apparatus or by precipitation as barium carbonate. When the liquid traps are used, drying tube VII is shifted to a position between the traps and the flutter valves II to protect the latter from moisture.

Oxygen utilization is measured by the rate of fall of the spirometer, VI, which is recorded on a smoked drum. The diameter of the spirometer is chosen to give a large enough vertical fall over a convenient time interval (10 to 20 minutes) so that the distance may be measured with a trivial error. A drum of 2.525 cm. internal diameter has been used in many of the experiments with cat hearts, while one of 4.096 cm. internal diameter has been found suitable for use with dog hearts of 30 to 50 Gm. weight. The drums are lathe-turned from solid brass to the minimal wall thickness consistent with rigidity. The spirometer is carefully counterpoised, and after each measurement period is refilled to the distance may be measured with a trivial error. The usual determination involves a fall of about 20 mm. which can be measured using a draftsman’s rule and engraving glass to within ±0.1 mm., or with an error of ±0.5 per cent. This part of the oxygen uptake determination is, of course, the least source of error. The main difficulty arises from factors that may distort the tracing by altering the steepness of the slope or by producing irregularities in its form. Rigorous thermostasis, as described, is absolutely essential to eliminate error due to random changes in ambient temperature. Alterations less easily controlled are those introduced by spontaneous and rapid changes in cardiac volume. Study of the diagram in figure 1 will make it clear that loss of blood from the system will be compensated by a drop in the spirometer. Since cardiac dilatation shifts blood from parts of the system in which it is in contact with the gas phase, such a change will produce an apparent increase in oxygen utilization. This is corrected for from the diastolic volume record inscribed by the small Krogh spirometer O. In the system used with small hearts this instrument gives an excursion of 1.0 mm. per 0.042 ml. volume change. Since the usual oxygen determination involves a volume change of about 10 ml., it is possible to correct for changes in diastolic volume without the introduction of a significant error, providing such changes are sufficiently gradual so as not to distort seriously the linearity of the spirometer record. Abrupt, transient changes in volume, caused by adventitious beats and seen frequently toward the close of an experiment, may render a segment of record unsuitable for analysis. In general, with evenly performing preparations, the slope of the spirometer record is rectilinear and no judgment is involved in selecting a straight line. Under such circumstances the only error of any consequence is probably that involved in the measurement of the spirometer record (±0.5 per cent). This conclusion is reinforced by results such as those charted in figure 3. In this experiment during the hour from 70 to 130 minutes there was virtually no change in diastolic volume. The oxygen uptake figures for successive intervals during this period are given in table 1. This strict agreement is, of course, fortuitous since the third figure should be subject to an error of at least 4 or 5 parts.

Where a judgment is involved in selecting the best straight line on the spirometer record, a comparison of the results obtained from the two most divergent plots indicates the maximum error. This has rarely exceeded ±2 per cent. Thus the maximum error in the measurement of both oxygen utilization and carbon dioxide production is around ±2.5 per cent. Maximum error in respiratory quotient determinations is ±5 per cent. The actual error in a good preparation is probably less than half the maximum.

Independent methods for directly checking the accuracy of gas exchange measurements in closed system respirometry under working conditions are not available. Measurement of the “respiratory quotient” of an alcohol lamp will invariably yield theoretic values if the system is leak-proof, properly thermostated, has an adequate carbon dioxide absorbing capacity, and is sufficiently sensitive. This,
however, is a far cry from testing the apparatus under working conditions. Varying the substrate offers an indirect check. Thus, while the usual preparation exhibits a respiratory quotient below 1.0, a respiratory quotient of 1.0 has been found following the infusion of glucose. In addition, respiratory quotient values approaching 0.7 have been obtained in preparations from animals on a high fat diet.

Left ventricular work has been calculated from the product of volume output (coronary plus systemic flow) by aortic mean pressure. The manner by which the flow readings are made has already been indicated. Duplicate readings can be made within ±2-3 per cent. Since the pressure has usually remained constant throughout an experiment, any error involved in this measurement will influence all calculations similarly. The kinetic energy imparted to the blood at the narrowest point in the external system, the brachiocephalic cannula, is included in the calculation, since pressure is measured central to this point. In computing efficiencies, a calorie equivalent of oxygen of 4.86 cal. per milliliter has been used, except in experiments in which the respiratory quotient has been determined, in which instances the value corresponding to this particular respiratory quotient has been employed. Calories have been converted to their work equivalent using established physical constants.

The right heart output is not included in the work calculation because, as will be noted in figure 1, this ventricle does not pump against pressure and hence does no appreciable work. The oxygenator into which the right ventricle drains lies well below the heart, so that the blood is actually siphoned off, keeping the right ventricle collapsed against the left. The right heart therefore undergoes no appreciable change in volume. Accordingly, significant alterations in diastolic volume and oxygen utilization can be assigned with certainty to the left ventricle. This offers a decided advantage over preparations in which both ventricles are loaded and capable of undergoing changes in volume independently, since it is impossible under such circumstances to determine the relative contribution of the separate chambers to the change noted. This arrangement also allows for the maintenance of adequate coronary flows at relatively low aortic pressures (60 to 90 mm. of Hg). The values of 0.70 to 2.14 ml. per gram of ventricle per minute found in the present work lie in the range reported by others using higher aortic and pulmonary pressures. Light pressure loading, in turn, makes for a smoother and longer-lived preparation. It should be noted that although the right ventricle does no work, it uses oxygen, and for this reason the efficiency as calculated is fictitiously low.

Arterial oxygen content by the Van Slyke manometric technic has been determined on many occasions to check the efficiency of the oxygenator. Oxygen saturations of 95 to 100 per cent are maintained. Blood pH has been measured using a Leeds and Northrup potentiometer and glass electrode. In many experiments blood glucose and lactate have been measured at intervals.

Serial blood cultures kindly run by Dr. Joseph T. King in a number of experiments revealed only a small increase in bacterial count over a one and one-half to two hour period. Although sterile technic has not been observed in making the preparations, all parts coming in contact with the blood have been scrupulously cleaned. Total bacterial counts did not exceed a few thousand organisms per milliliter. The total metabolism of a microbial population of this size is infinitely small compared to that of the myocardium weighing many grams. Other details of procedure will be discussed in connection with the experiments to which they relate.

![Fig. 2. Energy metabolism and efficiency in spontaneous failure (summary of 29 experiments with the completely isolated cat heart).](image-url)

**RESULTS**

In figure 2 the oxygen utilization and efficiency figures for 29 experiments, expressed in per cent change from initial values, are summarized. Diastolic volumes remained constant, increased, or decreased, and oxygen utilization, in most cases, varied accordingly. It is clear that, in the main, values for oxygen uptake are clustered around the zero line, while efficiency values all lie well below it. (Experiments in which significant deviations in oxygen utilization have occurred will be taken up separately.)
In figure 3 the pertinent data are summarized from a typical experiment in which diastolic volume was maintained relatively constant over a period of two and one-half hours. Heart weight (cat) was 8.1 Gm., with a total blood volume of 54 ml. Aortic pressure (60 mm. of Hg) remained fixed throughout, while coronary flow declined from 11.5 to 7.0 ml. per minute, the major change occurring in the first 30 minutes, with little alteration thereafter. Changes in oxygen utilization were slight reduction in cardiac load (brought about by restricting inflow), and since efficiency is known to be a function of load level, among other things, the possibility exists that the declining efficiency of the constant volume preparation is an artefact of the method. To examine this possibility, three experiments were carried out in which cardiac dilatation was permitted to occur freely. Values for oxygen utilization and efficiency, plotted in per cent change from initial values, are presented for these experiments in figure 4. In experiments 1 and 2, cardiac work showed little change, while a decline of 21 per cent was noted in experiment 3. Though decrements in efficiency were not as marked as in experiments carried out at constant diastolic volume, they were significant in all cases (25 to 35 per cent). It can therefore be concluded that although the degree by which cardiac efficiency is reduced during failure in the isolated state is probably exaggerated by load reduction when observations are made at constant diastolic volume, lowered efficiency, per se, cannot be regarded as an artefact of this particular experimental maneuver. It should be noted that practically

The Role of Diastolic Volume and Load Level

Since the maintenance of a constant diastolic volume usually necessitates a deliberate reduction in cardiac load (brought about by restricting inflow), and since efficiency is known to be a function of load level, among other things, the possibility exists that the declining efficiency of the constant volume preparation is an artefact of the method. To examine this possibility, three experiments were carried out in which cardiac dilatation was permitted to occur freely. Values for oxygen utilization and efficiency, plotted in per cent change from initial values, are presented for these experiments in figure 4. In experiments 1 and 2, cardiac work showed little change, while a decline of 21 per cent was noted in experiment 3. Though decrements in efficiency were not as marked as in experiments carried out at constant diastolic volume, they were significant in all cases (25 to 35 per cent). It can therefore be concluded that although the degree by which cardiac efficiency is reduced during failure in the isolated state is probably exaggerated by load reduction when observations are made at constant diastolic volume, lowered efficiency, per se, cannot be regarded as an artefact of this particular experimental maneuver. It should be noted that practically

and followed in direction the minor fluctuations noted in diastolic volume. Total output, however, fell off markedly, and with it the efficiency, which dropped from 4.6 to 2.9 per cent. Similar results have been obtained repeatedly, as noted in the scattergram in figure 2, and as will be shown subsequently in other detailed figures. In other experiments in which higher aortic pressures have obtained, the decline in efficiency has simply been more rapid and more marked.

FIG. 3. Course of spontaneous failure in the completely isolated cat heart at relatively constant diastolic volume.
all of the points for oxygen utilization given in the scattergram of figure 2 that lie above +10 per cent are accounted for in the three experiments summarized in figure 4.

The Role of the Metabolic Substrate

There is some evidence that in man and animals the efficiency of doing muscular work is influenced by the diet, being elevated by carbohydrates and depressed by fats. Since the perfusion medium in the isolated heart preparation is limited in volume, and is not subject to the regulatory mechanisms of the intact animal, the possibility of a progressive change in substrate (presumably from carbohydrate to fat) being responsible for the declining efficiency was investigated. Respiratory quotient values approaching 0.7 have been reported in the heart-lung preparation as the blood sugar falls to hypoglycemic levels. Attempts to gain useful information on this point from measurements of blood glucose and lactate levels proved futile, as anticipated. As found by others carbohydrate disappearance from the blood accounted for a highly variable fraction of the total metabolism of the preparation (as measured by oxygen utilization), even in the presence of respiratory quotients approaching unity. It is clear that complete information on changes in myocardial as well as blood composition is needed in order to arrive at a meaningful balance, and since this is not readily feasible in any single experiment, estimation of the respiratory quotient was undertaken as a possible means of detecting a shift in metabolic substrate.

In figure 5 are presented the results of four experiments in which the respiratory quotient was determined, using cat hearts taken from animals maintained on a stock diet. (Experiment 1 of this figure is the same one for which more detailed information has already been presented in figure 3.) The experiments were carried out at relatively constant diastolic volume, the small alterations in oxygen utilization corresponding, in the main, to simultaneous fluctuations in diastolic volume. (Small variations in this function have frequently been tolerated since it is often technically quite difficult to maintain strict constancy.) Although oxygen utilization was well maintained for rather extended periods, efficiencies all declined (by 37 to 84 per cent). Glucose was not infused in these preparations and blood sugar fell to hypoglycemic levels. Nevertheless the respiratory quotients within the error of the measurement, remained constant. The actual values found in these experiments were as shown in table 2. This relative constancy of respiratory quotient for a given preparation has been found repeatedly in similar experiments. The interpretation of disappearance values is further complicated by the fact that even in a relatively simple system such as that employed, they cannot easily be translated into unequivocal biochemical terms. Thus in a recent experiment in which glucose labeled uniformly with C¹⁴ was infused into the blood at a constant rate, no agreement could be found between disappearance of carbohydrate from the blood and the appearance of C¹⁴ in the respiratory CO₂. During a 44 minute observation period, the specific activity of blood glucose and respiratory CO₂ having reached a plateau, an R.Q. of 0.99 was found, and a total O₂ utilization of 121 ml. (A dog heart weighing 40.2 Gm. was used.) Of this, 81 ml. could be accounted for by the total carbohydrate which had disappeared from the blood. However, the C¹⁴O₂ collected during this period corresponded to an amount of glucose having an O₂ equivalent of only 61 ml. Although glucose was infused in sufficient quantity to establish an R.Q. of unity, mechanical efficiency declined just as in any other preparation.
VICTOR LORBER

305

ments carried out in relation to other problems, but not reported here because of inadequate data on work output. The failure to confirm prior reports of declining respiratory quotient\textsuperscript{13,16} may be due to the relatively light work load imposed on the hearts in the present experiments. Thus the results would indicate that there is no characteristic change in metabolic substrate complicating the present observations, and that the altered efficiencies noted cannot be considered as an artefact resulting from such a change.

An effort was made to gain additional information by experimentally altering the metabolic substrate by prior diet. Four cats were placed on a high fat diet and the hearts isolated after 11, 21, 36, and 39 days on the diet. Hearts isolated after such a dietary regimen have been reported to exhibit respiratory quotients around 0.7.\textsuperscript{19} The results of the respiratory quotient measurements in the four preparations are summarized in figure 6. The experiments are numbered in the order of increasing periods on the fat diet. The respiratory quotient values in experiment 1 are subject to an element of uncertainty because of the absence of data on pH, and faulty control of bath temperature. In subsequent experiments, blood pH was determined, the maximum change being 0.1 pH unit. A change of this magnitude in experiment 1 would not have altered the results significantly. It will be noted that in experiments 2 through 4, respiratory quotients around 0.7 obtained initially, and that in every

![Diagram](image)  
**Fig. 5.** Energy metabolism, efficiency, and respiratory quotient during spontaneous failure at relatively constant diastolic volume (summary of four experiments with the completely isolated hearts of cats on a stock diet).

<table>
<thead>
<tr>
<th>Period</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiment 1</td>
<td>.96</td>
<td>.97</td>
<td>1.00</td>
<td>.97</td>
</tr>
<tr>
<td>2</td>
<td>.93</td>
<td>.97</td>
<td>.94</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>.94</td>
<td>.95</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>.86</td>
<td>.89</td>
<td>.89</td>
<td>.83</td>
</tr>
</tbody>
</table>

**Table 2.**—Respiratory Quotients in Isolated Cat Hearts during Spontaneous Failure
ease the respiratory quotient drifted upward with time, the changes noted lying well beyond the error of the method. The cause of this change has not been determined.

In figure 7 the results of experiment 4 of this series are presented in detail. A cat heart of 5.4 Gm. was used. It will be noted that oxygen uptake followed the diastolic volume in an approximate fashion. However, while a maximum increase in diastolic volume of +0.5 ml. at around 120 minutes was accompanied by a 9 per cent increase in oxygen utilization, a comparable decline in volume (−0.5 ml.) terminally was associated with a 35 per cent decline in oxygen consumption. A failure of energy liberation of this degree has never been encountered in comparable experiments in the present work, except terminally in the presence of a marked decline in coronary flow. Although in experiment 4 aortic pressure (65 mm. Hg) and coronary flow (around 5 ml. per minute) were well maintained, it should be noted that the decline in energy liberation occurred after the third hour of the experimental period, the heart at this time having been beating for four hours in the isolated state. Without additions to the blood, it seems likely that substrate may become a limiting factor after such a period, under which conditions the relationship between diastolic fiber length and oxygen uptake would be expected to break down. What relationship the pretreatment accorded the animal may have had to this energy failure is unclear, but it is interesting that it should have been noted in the animal maintained on the high fat diet for the longest period of time.

When attention is turned to the values for work and efficiency in figure 7, it will be noted that these fell off drastically long before there was a significant change in oxygen utilization. The other preparations of this group followed a strictly similar course, and differed in no respect from prior experiments save for the change in respiratory quotient already noted. Initial efficiencies in the four experiments ranged from 2.1 to 8.7 per cent, and were similar to values noted in preparations from animals on a stock diet.

From these and the prior experiments it may be concluded that the declining efficiency that characterizes failure in the present experiments is independent of the metabolic substrate, and, consequently, may not be regarded as an experimental artefact due to an altered substrate.
The Role of Acapnia

As already indicated in the description of the method, the pCO₂ in the gas phase in the foregoing experiments was extremely low. This, on the technical side, is advantageous for the reasons already pointed out, and for the additional reason that the completely isolated cat heart appears to be a much less labile preparation under conditions of acapnia. However, as recognized by prior workers, this represents an unevolved point of departure from in vivo conditions.

An attempt to evaluate this factor was made by studying the efficiency of the heart as it failed in the presence of maintained concentrations of carbon dioxide in the gas phase. The shaft of the mercury-sealed stirrer of the oxygenator was extended to within a few centimeters of the bottom of the oxygenator and equipped with a series of propellers, so disposed as to direct the gas in the oxygenator against the stream created by the pump, and thus facilitate mixing of the gas before it left this chamber. It is apparent that if a low ventilation rate is used carbon dioxide will accumulate in appreciable concentration in the oxygenator until an equilibrium mixture is attained, at which level the pCO₂ will remain constant, providing no change occurs in the rate of carbon dioxide output. It is further apparent that if the correct ventilation velocity is selected, physiologic levels of carbon dioxide can be achieved. On the basis of prior data a probable average figure for cardiac carbon dioxide production was calculated, and the ventilating pump adjusted accordingly.

The defects of such a method are readily apparent. Since it is impossible to know in advance what the rate of carbon dioxide production for any preparation will actually be, physiologic concentrations of carbon dioxide can only be roughly approximated. Furthermore, alterations in carbon dioxide output by the heart will lead to changes in the level of carbon dioxide in the gas phase, which in turn will produce errors of opposite sign in the measurement of oxygen utilization.

The results from seven experiments carried out by the procedure are summarized in figure 8. Diastolic volumes in all experiments were held fairly constant. A change in oxygen utilization of greater than 10 per cent of the initial values occurred in three experiments (numbers 5, 6 and 7), while efficiency fell drastically in all.

![Graph](https://via.placeholder.com/150)

**Fig. 8.** Energy metabolism and efficiency in spontaneous failure at relatively constant diastolic volume and in the presence of appreciable carbon dioxide concentrations in the respiratory gas (summary of seven experiments with the completely isolated cat heart).

The values for carbon dioxide in the gas phase ranged somewhat above or below physiologic concentrations, and remained quite constant in experiments 1 to 3. No carbon dioxide data are available for experiment 4, and only one value, 7.1 volume per cent, was obtained mid-way in experiment 6. It will be noted that in experiments 5 and 7, in which the largest decrements in oxygen utilization occurred, the largest increases in carbon dioxide were also recorded. In experiment 5, the accumulation of carbon dioxide accounted for an apparent decrease of oxygen utilization of about 17
per cent, leaving an 8 per cent decrease which may be regarded as real. In experiment 7 in which oxygen utilization fell off by 17 per cent, the accumulation of carbon dioxide in the gas phase accounted for an apparent decline of 10 per cent. It must therefore be concluded that any real decrements in energy liberation that occurred in these experiments were small and of questionable significance, since the error in the oxygen utilization measurements in these experiments is undoubtedly somewhat greater than in the acapnic preparation. On the other hand, drastic reductions in efficiency occurred in all the experiments in this group, and were certainly greater than indicated in some experiments, since the efficiencies were computed on the basis of apparent oxygen utilization.

It should be noted that in the scattergram of figure 2, practically all the oxygen consumption values below the —10 per cent level are derived from the experiments of this group, the uncorrected data having been plotted. In the plot of efficiencies in figure 2, the points below —50 per cent are virtually monopolized by this series of experiments.

It must be concluded that the diminished mechanical efficiency which characterizes cardiac failure in the present studies is not an artefact resulting from low carbon dioxide tensions. On the other hand, the data taken at face value suggest that hypercapnia may be a factor in the failure of energy liberation.

The Action of Digitalis

There is ample evidence that the cardiac glycosides induce an increased respiratory rate in the heart in various types of in vitro preparation.5 It was therefore of interest to examine the effect of a glycoside of digitalis on the respiratory metabolism of the isolated heart using the present technic. In one preliminary experiment 7 γ of lanatosid-C (Sandoz) was administered to an 8.7 Gm. cat heart. A definite volume and efficiency effect was produced. In the 110 minute control period preceding administration of the drug, a respiratory quotient of 0.92 prevailed. During the following 100 minutes, a respiratory quotient of 1.01 was obtained. An effort was made to confirm this finding and determine its significance using C14-labeled glucose as substrate. It soon became apparent that this would be a considerable task, demanding, among other things, maintenance of a constant blood sugar level. Plans to pursue the problem further in a simpler preparation were abandoned when Wollenberger20 published results of experiments similar to those contemplated. Using heart muscle slices and C14-glucose as substrate, Wollenberger reported both an increase in respiratory quotient and glucose oxidation in the presence of ouabain.

Discussion

Investigation of the energy metabolism of the experimentally isolated heart in failure is complicated by the conflicting desire to employ conditions that approach the "physiologic" and the necessity to reduce the system to a level of simplicity that will permit an unequivocal evaluation of the changes noted. The present method, like its predecessors, is a compromise, but one in which necessity has been favored. Only the left heart has been permitted to do work and undergo volume changes, thus obviating complications that may be introduced by right heart failure, as in preparations in which this chamber carries a work load. In such preparations, the ventricles can dilate independently but only the total change is recorded. Thus the right heart might dilate appreciably, but because of its smaller mass, a large change in oxygen utilization would not be expected. A small simultaneous decrease in left heart volume could cancel the change in oxygen uptake with only a slight effect on the apparent volume change. Such a combination of events could produce a picture of cardiac dilatation with no apparent change in oxygen consumption. In addition to eliminating this possible source of error introduced by the structure of the heart itself, the various measurements have been refined to the extent that the errors involved are small relative to the changes being measured. It can thus be said with certainty that under the conditions of the present study heart muscle failure is characterized by an inability to convert chemical energy to mechanical work and not by a
failure to liberate chemical energy. This is so whether failure occurs at constant volume and declining load, or with dilatation and constant load. In both cases, oxygen utilization parallels diastolic volume while efficiency declines. This finding is in complete agreement with the classic experiments of Starling and Visscher.1

The significance of the relationship between initial fiber length (diastolic volume) and energy liberation has been questioned at both the fundamental and applied levels. In isolated frog skeletal muscle, Fenn21 has found that energy liberation is a function of the work done, a finding which would appear to imply a fundamental difference between cardiac and skeletal muscle.5 While there is no a priori reason for thinking that fundamental differences should not exist between these tissues (and, indeed, there is some fragmentary evidence that some do exist22), it should be noted that cardiac tissue has not been studied under circumstances strictly comparable to those employed by Fenn. In brief, present knowledge of the molecular events involved in muscular contraction does not appear to be sufficiently advanced to justify the contention that the Fenn effect in skeletal muscle and the diastolic volume relationship in the heart are fundamentally at odds.

It may be argued that at the relatively light work loads employed in the present experiments, work-dependence of energy liberation would be obscured. In this connection it should be pointed out that in the author’s experience heavy loading has always led to a very rapid work failure without change in oxygen uptake (so long as diastolic volume was held constant) and was not employed in the present experiments because of the time restriction imposed thereby. This is simply in confirmation of Starling and Visscher1 who found oxygen utilization paralleled diastolic volume changes, regardless of work performance, and over a greater range of work output and at higher levels of efficiency than those reported in the present study.

If the relationship between energy liberation and diastolic volume reflects a fundamental property of cardiac muscle, it should apply to in vivo function, subject, of course to the various modifying influences at work in the intact organism. It seems pertinent, therefore, to mention briefly some recent clinical studies, some of the results of which have been considered to be in conflict with conclusions based on in vitro work. Bing and colleagues,25, 24 using cardiac catheterisation, have made estimates of the oxygen utilization of the heart during clinical failure and have obtained values within the normal range, or slightly above. Work output and efficiency were reduced, as in experimental failure. Bing has questioned the applicability of the Starling and Visscher observations to the in vivo experiment because of the finding of little or no increase in cardiac oxygen utilization in the presence of left ventricular dilatation. This would appear to place too narrow an interpretation on the volume-energy relationship which, as originally put forward, includes “chemical constancy” as a precondition. In this respect, the laboratory and clinical phenomena may differ since the time units employed are of completely different orders of magnitude. Thus the myocardium in clinical failure may deviate significantly from the “chemical constancy” obtaining during competence, while between the periods of control and failure (periods measured in minutes) in the isolated preparation, no comparable difference may exist. The finding in clinical failure of a ratio of initial fiber length to energy liberation which differs from the normal may only indicate, in this view, that the volume-energy relationship in sustained failure as seen clinically operates at a different level from the normal.

The drop in mechanical efficiency noted in clinical failure was found to be reversed by a cardiac glycoside24 as in the case of the isolated heart.25, 26 It is interesting to note that the increase in efficiency seen clinically resulted from an elevated work output with no change in cardiac oxygen consumption. Since it may be assumed that cardiac volume declined as a result of therapy, this again may be interpreted as a departure from the volume-energy relationship. However, it is known that the action of the cardiac glycosides is accompanied by an increased myocardial oxygen up-
take, and the two effects may have canceled one another.

The report of an elevated cardiac efficiency in clinical hypertension is also a matter of some interest. This might result from the action of a humoral agent directly on the myocardium. Such an effect has been noted for one substance considered as a possible pressor agent in renal hypertension.

Finally it seems well to point out that, although certain factors (acapnia, substrate) appear not to be incriminated in the production of efficiency failure seen in the isolated heart, the factor that is responsible for the defect in the conversion of chemical energy to work, as well as the point at which it operates, remains unknown.

Neither the intimate nature of the disturbance which leads to faulty conversion of chemical energy to work nor the manner in which it is reversed by digitalis are likely to be elucidated until a more detailed knowledge of muscular contraction is at hand. While the main links between the energy-liberating and work-performing systems seem apparent at present, the factors responsible for their integration and control remain obscure. It is inviting to speculate that the digitalis glycosides exert their effect because of a structural resemblance to some as yet unidentified chemical regulator naturally present in the myocardium. This possibility is being investigated.

**SUMMARY**

The problem of the mechanism of failure in the completely isolated mammalian heart has been reinvestigated in a simplified system in which uncertainties introduced by the procedure have been minimized. In confirmation of Starling and Visscher, and others, the process of failure was found to be characterized by a deterioration in mechanical efficiency. In general, total energy liberation, as measured by oxygen consumption, was well maintained during the failure process, while work fell off, sometimes drastically. Efficiency declined during failure at constant diastolic volume, as well as in preparations in which dilatation was permitted to occur.

Respiratory quotients were determined in a number of experiments, and it was found that efficiency failure occurred with or without a change in respiratory quotient. It has been concluded that a changing substrate, considered as a possible experimental artefact, probably did not contribute to the results in an important manner. The role of acapnia, a recognized experimental artefact, was also investigated, and was found to be noncontributory.

The present experiments support the relationship of initial fiber length and energy liberation as an important generalization in cardiac function. Some apparent conflicts between this concept and recent clinical investigations have been discussed.

**ACKNOWLEDGMENTS**

It is a pleasure to acknowledge the important technical assistance rendered by Mrs. Dorothy Erickson Barker, Miss Margaret Cook, and Dr. Robert Kallsen.

**REFERENCES**


8. ——: A thesis submitted to the graduate faculty of the University of Minnesota, 1940.

9. Lorber, V.: The action of angiotonin on the com-
VICTOR LORBER 311


21 Fenn, W. O.: A quantitative comparison between the energy liberated and the work performed by the isolated sartorius muscle of the frog. J. Physiol. 58: 175, 1923.


Energy Metabolism of the Completely Isolated Mammalian Heart in Failure

VICTOR LORBEK

Circ Res. 1953;1:298-311
doi: 10.1161/01.RES.1.4.298

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1953 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/1/4/298

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/