A THEORETICAL PREDICTION OF THE NORMAL CARDIAC OXYGEN CONSUMPTION

THEODORE A. WILSON

From the Department of Aeronautics and Engineering Mechanics, University of Minnesota, Minneapolis, Minnesota 55455

ABSTRACT A model is described from which the entropy production associated with the process of transporting oxygen and carbon dioxide between the lungs and the muscles of the body can be calculated. The two entropy sources which are assumed to be the dominant ones for this process are the entropy production associated with the metabolism of the heart and the entropy production associated with the diffusion of oxygen and carbon dioxide into and out of the blood. The hypothesis that the observed blood flow is the one for which a given amount of oxygen and carbon dioxide is transported between the lungs and the muscles with minimum total entropy production is used to predict the value of the slope of the cardiac oxygen consumption vs. blood flow curve. At a blood flow of 15 liters/min, the predicted value of the slope of this curve is 1.2 ml/liter.

INTRODUCTION

There are many biologists who feel that the evolutionary process has resulted in an arrangement of biological systems and a method of operation of biological systems that could be described as a design. One hypothesis for describing the design is this: The parameters of the system have values for which the system can accomplish a given function with minimum entropy production. This hypothesis is motivated by the idea expressed by several physicists over the past century [Boltzmann (1886) and Schrodinger (1945), for example] that entropy is the critical thermodynamic quantity in maintaining both the function and the structure of the organism. This hypothesis has been tested as a description of the observed values of the following three parameters: the total ventilation as a function of the total oxygen consumption (Wilson, 1964), the capillary spacing in muscle tissue as a function of oxygen consumption in the muscle (Wilson, 1966), and the diameter of the tubes of the bronchial tree as a function of the location of the tube (Wilson, 1967). In each of these cases a model is postulated from which the total entropy production can be calculated as a function of the value of the parameter being investigated. The value of the parameter for which the total entropy production is minimum is calculated and this value is found to agree with the observed values. The success of the hypothesis in describing the values of physiological parameters in these cases perhaps justifies the use of the hypothesis to predict the value of a physiological parameter that has not been established experimentally.

In the following analysis, the principle is applied to the problem of describing the blood flow to the skeletal musculature. It is assumed that the circulating blood must supply oxygen to the muscles at a given rate and that the magnitude of the blood flow is chosen so that this function is accomplished with minimum entropy production. There are two entropy sources which depend on the magnitude of the blood flow and which are assumed to be the dominant entropy sources for this problem: the metabolism of the heart and the diffusion of oxygen and carbon dioxide into and out of the blood. The entropy production due to the metabolism of the heart increases with increasing cardiac output while the entropy production in the diffusion process decreases with increasing blood flow. There is a particular blood flow for which the total entropy production is a minimum. In order to carry out this analysis and obtain a hypothetical optimum blood flow which can be compared with the observed flow, the experimentally determined value of the heart metabolism must be known as a function of cardiac output. These data are not available and the principle will be used to predict the slope of the heart metabolism vs. cardiac output curves for a normal adult. The predicted cardiac metabolism is the one required in order that the hypothetical and the observed blood flow agree.

ANALYSIS

A schematic diagram of the process is shown in Fig. 1. In the steady state, the entropy content of the material inside the dashed lines is constant, and the total entropy production inside the box must equal the net entropy flux out of the box. The entropy production due to the metabolism of the heart is balanced by the entropy flux associated with the flux of heat out of the system. The entropy flux associated with the metabolites supplying the heart is neglected. The entropy production due to diffusion is balanced by a net entropy flux out of the box associated with the oxygen and carbon dioxide fluxes. The entropy of the oxygen entering the muscle is greater than the entropy of the oxygen being supplied by the lung and the entropy of the carbon dioxide entering the lung is greater than the entropy of the carbon dioxide being removed from the muscle.

The total entropy production or the net entropy flux from the system $\dot{S}$ is a function of the blood flow Q and the observed blood flow is assumed to be the one for which $d\dot{S}/dQ = 0$. The entropy production due to the metabolism of the heart is approximately equal to the energy released divided by the absolute temperature since all of the energy is eventually degraded into heat within the body. The entropy production in the gas transport can be evaluated as a function of Q by calculating the concentration of the oxygen and carbon dioxide in the muscle tissue as a function of Q since the entropy of the gases in the lung is fixed, independent of Q. Assuming that the dissolved gases have the properties of an ideal solution, the specific entropy s of the dissolved gases is a function of the temperature T which is independent of Q and of the logarithm of the concentration in the tissues which depends on Q

$$s = K(T) - R \ln c. \tag{1}$$

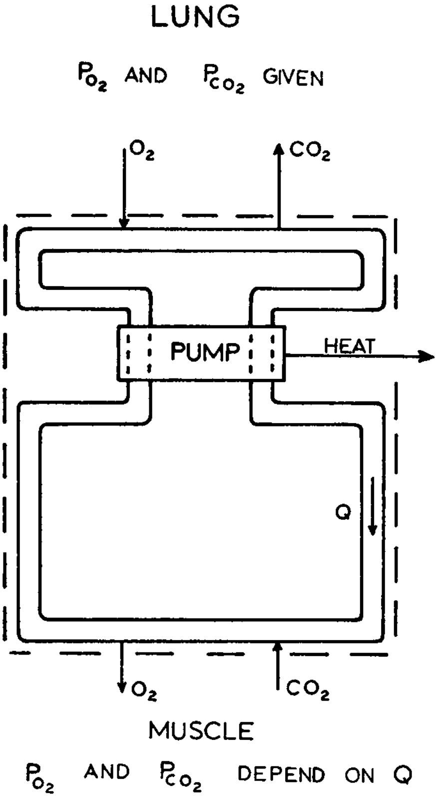

FIGURE 1 A schematic diagram showing the system for which an entropy balance is made. The part of the system inside the dashed line is assumed to be in a steady state so that the entropy production in this part of the system is balanced by a net entropy flux across the dashed-line boundary.

Then $d\dot{S}/dQ$ is given by equation (2)

$$\frac{d\dot{S}}{dQ} = \frac{H}{T}\frac{d\dot{V}_{\mathrm{H,O_2}}}{dQ} - \dot{V}_{\mathrm{M,O_2}}\frac{R}{C_{0_2}}\frac{dC_{\mathrm{C_2}}}{dQ} + \dot{V}_{\mathrm{M,CO_2}}\frac{R}{C_{\mathrm{CO_2}}}\frac{dC_{\mathrm{CO_2}}}{dQ} \tag{2}$$

where the symbols are as follows:

$\dot{S}$	total entropy production in cal/degree min,
Q	blood flow rate in liters/min,
$\dot{V}_{\mathrm{H,O_2}}$	cardiac oxygen consumption in ml/min,
$\dot{V}_{\mathrm{M,O_2}}$	oxygen consumption of the muscles in liters/min,

$\dot{V}_{M,CO_2}$	carbon dioxide production of the muscles in liters/min,
C_{O_2}	oxygen concentration in the muscle tissue
C_{CO_2}	carbon dioxide concentration in the muscle tissue.
$H =$	5 cal/ml, the energy released per milliliter of oxygen consumed by the heart,
$T =$	300°K
$R =$	0.09 cal/degree liter STP, the universal gas constant

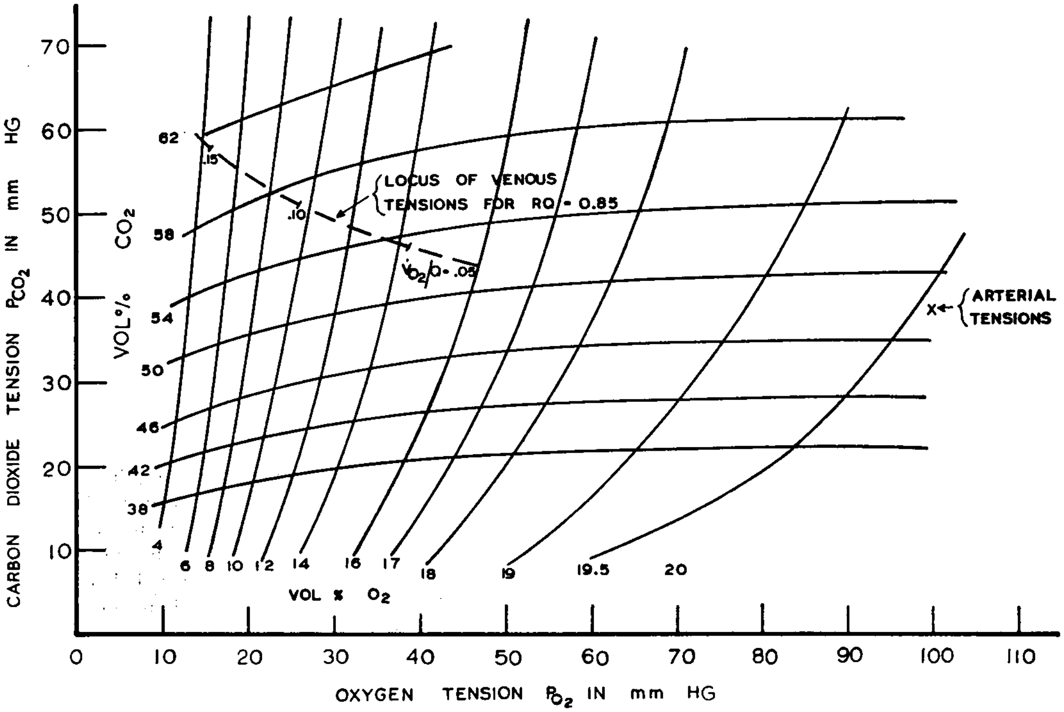

FIGURE 2 A diagram showing the oxygen and carbon dioxide content in liters STP per liter of blood for blood in equilibrium with the oxygen and carbon dioxide tension shown on the abscissa and ordinate. The assumed arterial tensions are marked by a cross. The locus of possible venous tension for an (RQ) of 0.85 is marked by a dashed line.

The last two terms in equation (2) have different signs because the fluxes of oxygen and carbon dioxide are in opposite directions.

In order for $\dot{S}$ to be a minimum at the observed value of Q, $d\dot{S}/dQ$ must be zero at the observed value of Q. The predicted value of $d\dot{V}_{H,O_2}/dQ$ is obtained by setting the right-hand side of equation (2) equal to zero and evaluating the last two terms at the observed value of Q corresponding to any given $\dot{V}_{M,O_2}$

$$\frac{d\dot{V}_{H,O_2}}{dQ} = 5.4\left[\frac{\dot{V}_{M,O_2}}{C_{O_2}}\frac{dC_{O_2}}{dQ} - \frac{\dot{V}_{M,CO_2}}{C_{CO_2}}\frac{dC_{CO_2}}{dQ}\right]\Bigg|_{Q_{OBS}}. \tag{3}$$

The rest of the analysis consists of graphical evaluation of the right-hand side of equation (3) using the blood chemistry characteristics and a model for the distribution of the circulating blood.

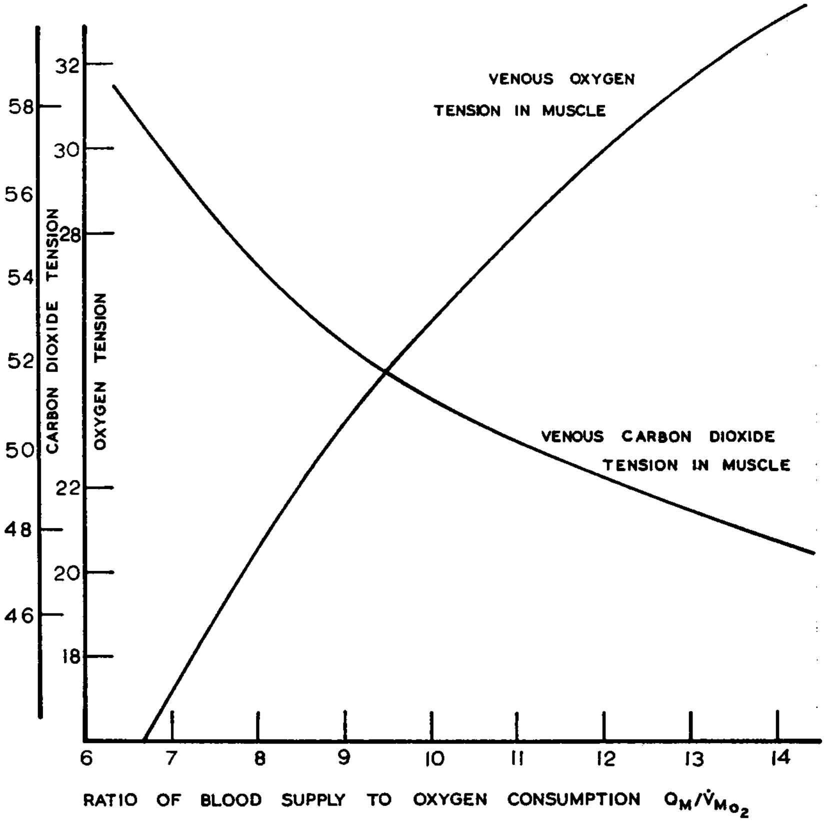

FIGURE 3 The venous oxygen tension and venous carbon dioxide tension is plotted against the parameter, blood flow to the muscles divided by oxygen consumption of the muscles. Points on these curves correspond to points along the locus shown in Fig. 2.

The respiratory quotient (RQ) is assumed to be 0.85

$$\dot{V}_{M,CO_2} = 0.85\ \dot{V}_{M,O_2}. \tag{4}$$

The partial pressure of oxygen and carbon dioxide in the lung and the corresponding tensions in the arterial blood are assumed to be 100 and 40 mm Hg, respectively. The locus of possible venous gas tensions for (RQ) = 0.85 is shown in Fig. 2. The particular venous tension on this locus is determined by the value of $Q_M/\dot{V}_{M,O_2}$ where Q_M is the blood flow to the muscles. The venous oxygen and carbon dioxide tensions P_{V,O_2} and P_{V,CO_2} are plotted as a function of $Q_M/\dot{V}_{M,O_2}$ in Fig. 3.

The concentration of oxygen and carbon dioxide in the muscle is assumed to be in equilibrium with the venous oxygen and carbon dioxide tensions. This is a very good approximation in the case of carbon dioxide which has a large diffusion coefficient. The diffusion of oxygen through the tissues outside of the capillaries is slow enough that the oxygen concentration varies from point to point. The average oxygen concentration is nearly equal to the one assumed here (Wilson, 1966). If it is further assumed that the concentration of the dissolved gas is linearly proportional to the tension with which it is in equilibrium, then the concentration appearing in equation (3) can be replaced by the venous tensions

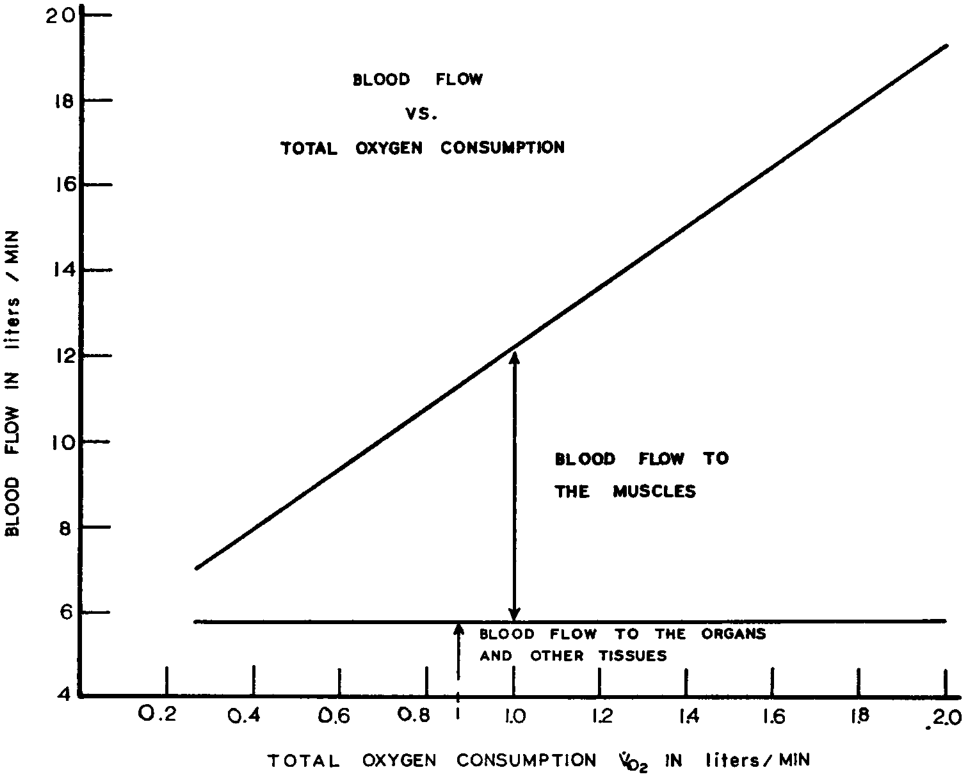

FIGURE 4 The assumed distribution of the total blood flow between the muscles and the organs and other tissues as a function of the total oxygen consumption.

$$\frac{1}{C_{O_2}}\frac{dC_{O_2}}{dq} = \frac{1}{P_{V,O_2}}\frac{dP_{V,O_2}}{dQ}$$

$$\frac{1}{C_{CO_2}}\frac{dC_{CO_2}}{dQ} = \frac{1}{P_{V,CO_2}}\frac{dP_{V,CO_2}}{dQ}. \tag{5}$$

It can be seen from Fig. 3 that for a fixed value of $\dot{V}_{M,O_2}$, the value of $dP_{V,O_2}/dQ$

is positive and $dP_{V,CO_2}/dQ$ is negative. The entropy production due to diffusion therefore decreases with increasing blood flow. This result is consistent with the idea that the diffusion of oxygen takes place across a drop in the chemical potential between the lung and the venous blood, for example, and that the magnitude of the chemical potential difference decreases with increasing blood flow.

An assumption concerning the distribution of the total blood flow between the muscles and the organs and other tissues is needed to complete the model. In Fig. 4, the total blood flow is shown as a function of the total oxygen consumption. This curve is a composite of the experimentally determined curves for four normal adults (Bock, Van Caulert, Dill, Fölling, and Hurxthal, 1928). At rest, the total blood flow is 7 liters/min. At rest, 17% of the total blood flow is used to supply the muscles and 83% of the total blood flow is used to supply the organs and other tissues. It is assumed that the oxygen consumption of the organs and other tissues and the blood supply to the organs and other tissues is constant, independent of total oxygen consumption, at 0.22 liters/min oxygen consumption and 5.8 liters/min blood flow. The blood supply to certain organs decreases with increasing load of exercise while the supply to other organs increases. Certainly, the most important contribution to the increase in the total blood flow with increasing oxygen consumption during exercise is the increase in the blood supply to the muscles. The blood supply to the

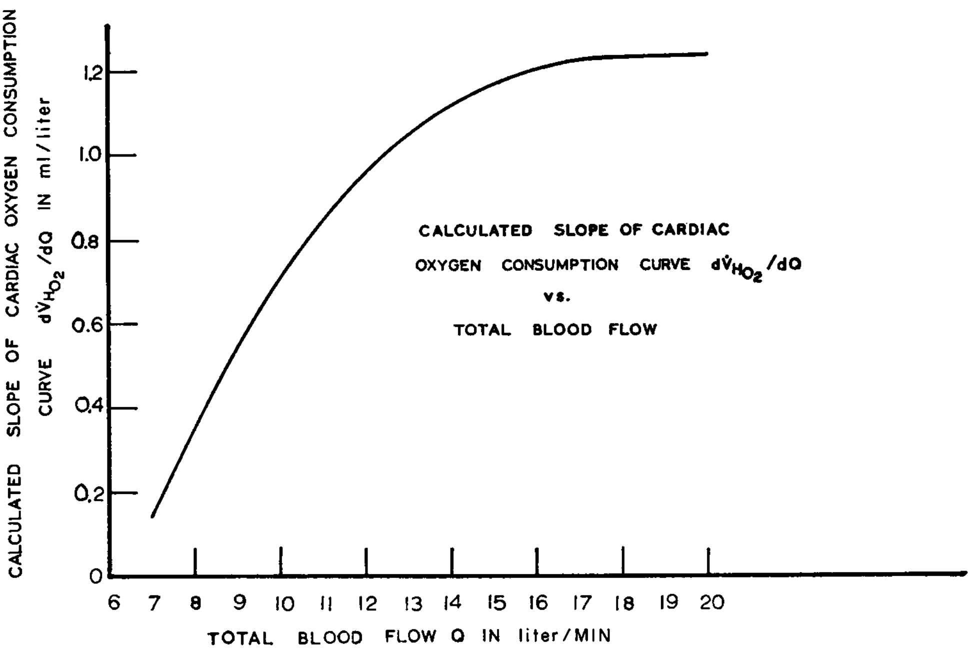

FIGURE 5 The calculated value of $d\dot{V}_{H,O_2}/dQ$ in milliliters per liter as a function of total blood flow.

muscles is assumed to increase from 1.2 liters/min at rest to 13.5 liters/min at a total oxygen-consumption level of 2.0 liters/min.

Now the right-hand side of equation (3) can be evaluated graphically using Figs. 2, 3, and 4. For example, at a total oxygen consumption of 1.0 liters/min, the oxygen consumption of the muscle is 0.78 liters/min, the total blood flow is 12.2 liters/min, the blood flow to the muscles is 6.4 liters/min, and $Q_M/\dot{V}_{M,O_2} = 8.2$. From Fig. 2, it can be seen that $P_{V,O_2} = 21.5$ mm Hg. Now the same figure can be used to evaluate $\dot{V}_{M,O_2}(dP_{V,O_2}/dQ)$ by taking $\dot{V}_{M,O_2}$ as fixed and measuring the slope of the curve for an imagined variation of Q about its observed value. The value at this point is

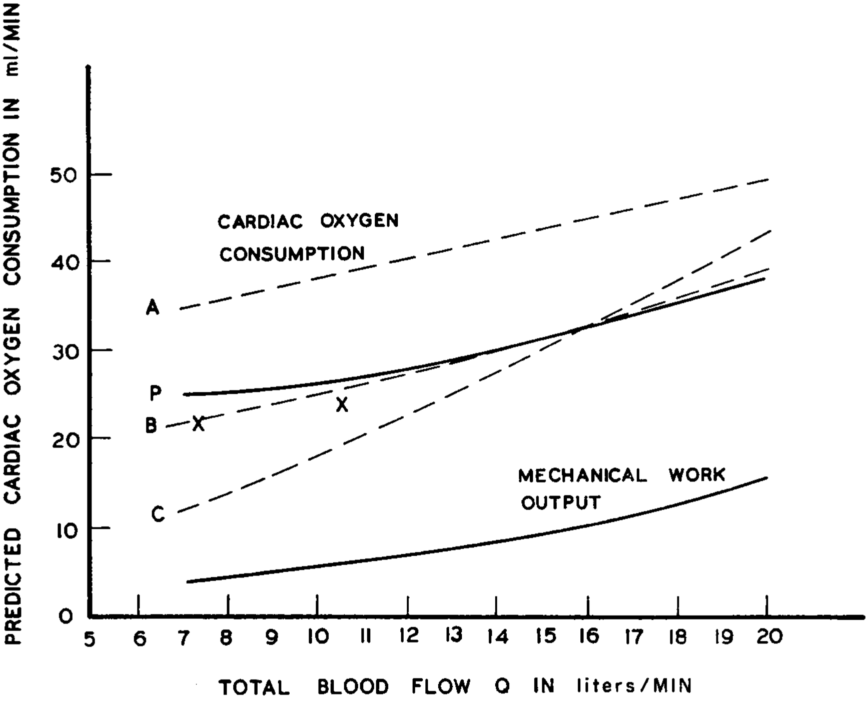

FIGURE 6 Curves showing cardiac oxygen consumption as a function of total blood flow. P, the value predicted from the hypothesis. A, B, and C, values inferred from various experimental data. X, two points for the human heart in vivo. The oxygen consumption equivalent of the mechanical work output of the heart is also shown for comparison.

$$\frac{\dot{V}_{M,O_2}}{P_{V,O_2}} \frac{dP_{V,O_2}}{dQ} = 0.15$$

Similarly,

$$\frac{\dot{V}_{M,CO_2}}{P_{V,CO_2}} \frac{dP_{V,CO_2}}{dQ} = 0.03$$

The predicted value of $(d\dot{V}_{H,O_2}/dQ)$ at $Q = 12.2$ is $(d\dot{V}_{H,O_2}/dQ) = 0.97$ ml/liter The value of $d\dot{V}_{H,O_2}/dQ$ calculated in this way for the range of Q is shown in Fig. 5. This curve can be integrated to give $\dot{V}_{H,O_2}$ except for the constant of integration, the value of $\dot{V}_{H,O_2}$ at rest. This value is taken to be 25 ml/min and the resulting curve of cardiac oxygen consumption vs. cardiac output is given in Fig. 6. The oxygen equivalent of the mechanical work done by the heart is also shown in Fig. 6. The predicted efficiency varies from 16% at rest to 45% at $\dot{V}_{O_2} = 2.0$ liters/min.

AVAILABLE EXPERIMENTAL EVIDENCE

Some indications of the value of the normal cardiac oxygen consumption which can be inferred from the available data on cardiac oxygen consumption are also shown in Fig. 6. Katz and Feinberg (1958) have reviewed the data from experiments on isolated hearts. The best relation between the observed value of cardiac oxygen consumption per 100 g of heart weight and the parameters of heart rate, blood pressure, and cardiac output for three sets of experiments are given below:

$$\dot{V}_{H,O_2} = 6.38\ (\pm 4.33) + 0.12\ (\pm 0.03)\ (BP) + 0.001\ (\pm 0.01) Q \qquad (A)$$

$$\dot{V}_{H,O_2} = -1.88\ (\pm 3.33) + 1.11\ (\pm 0.74)\ (HR) \times (BP) \times 10^{-3} - 0.005\ (\pm 0.005) Q \qquad (B)$$

$$\dot{V}_{H,O_2} = 6.58\ (\pm 2.88) + 0.60\ (\pm 0.34)\ (HR) \times (BP) \times 10^{-3} + 0.00\ (\pm 0.02) Q \qquad (C)$$

In these relations, BP is mean arterial blood pressure in millimeters of Hg and HR is heart rate in beats per minute. The curves labeled A, B, and C in Fig. 6 are obtained from these relations by using the representation of the physiological values of blood pressure and heart rate given below. These relations represent the data reported by Bock et al. (1928)

$$(BP) = 65 + 3.8Q$$

$$(HR) = 38 + 5.6Q.$$

The heart weight was taken as 200 g in calculating the curves shown on the figure. This is a small heart weight but the experiments were done with smaller hearts and the scaling would not be expected to be linear in heart weight. The uncertainty in the coefficients of relations A, B, and C and the differences between the curves obtained from these relations are at least in part due to the fact that each of the independent variables in these relations were varied independently over wide ranges in the experiments and many of the data are for the heart operating under conditions much different from the normal physiological conditions.

Lombardo, Rose, Taeschler, Tuluy, and Bing (1953) have reported measurements of the oxygen consumption of the left ventrical of the human heart in vivo. Only two points for a single normal subject are given. These are shown by the two crosses in Fig. 6.

The only feature of this experimental information that is significant for comparison with the results of the analysis in this paper is the slope of the curve of Fig. 6 since the placement of the predicted curve is not obtained from the analysis. The available experimental data do not seem to allow a conclusive comparison. Perhaps it indicates a slightly higher slope than the predicted one.

DISCUSSION

It is probably worth mentioning again that the application of the minimum-entropy-production design hypothesis has been reversed in this analysis. The point of view normally assumed in applying the hypothesis would be to take the cardiac-oxygen-consumption characteristics and the blood chemistry characteristics as given and to assume the blood flow to be free to take any value. The hypothesis states that the observed flow is the one for which the total entropy production is minimum. However, since the cardiac oxygen consumption has not been measured over the whole range of cardiac output under normal conditions, the calculation was inverted in order to find the cardiac oxygen consumption characteristics which must exist in order for the hypothetical blood flow to agree with the observed flow. The quantity directly calculated is the slope of the cardiac oxygen consumption curve $dV_{\mathrm{H},\mathrm{O}_2}/dQ$. This slope is found as a function of only one variable, the blood flow rate. The assumptions used in the model have a smaller effect on the calculation at higher blood flow. The critical test of the hypothesis is that the value of $dV_{\mathrm{H},\mathrm{O}_2}/dQ$ should be approximately equal to 1.2 ml/liter for a value of Q near 15 liters/min.

This work was supported by NIH grant HE-09724.

Received for publication 24 March 1967.

REFERENCES

Bock, A. V., C. Van Caulert, D. B. Dill, A. Fölling, and L. M. Hurxthal. 1928. *J. Physiol.* **66**:136.

Boltzmann, L. 1886. Address to the Kaiserliche Academie Der Wissenschaften.

Katz, L. N., and H. Feinberg. 1958. *Circulation Res.* **6**:656.

Lombardo, T. A., L. Rose, M. Taeschler, S. Tuluy, and R. J. Bing. 1953. *Circulation* **7**:71.

Schrodinger, E. 1945. What Is Life? The MacMillan Company, New York.

Wilson, T. A. 1964. *Experientia* **20**:333.

Wilson, T. A. 1966. *J. Theoret. Biol.* **11**:436.

Wilson, T. A. 1967. *Nature* **213**:668.