HEMODYNAMIC DETERMINANTS OF OXYGEN CONSUMPTION OF THE HEART
WITH SPECIAL REFERENCE TO THE TENSION-TIME INDEX

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ABSTRACT

SARNOFF, S. J., E. BRAUNWALD, G. H. WELCH, JR., R. B. CASE, W. N. STAINSBY AND R. MACRUZ. Hemodynamic determinants of oxygen consumption of the heart with special reference to tension-time index. Am. J. Physiol. 192(1): 148-156. 1958. —The hemodynamic determinants of myocardial oxygen utilization were ascertained in the isolated, metabolically supported, nonfailing canine heart. The primary determinant was found to be the total tension developed by the myocardium as indicated by the area beneath the systolic pressure curve (Tension-Time Index). The significance of these findings for the understanding of the low efficiency of the failing heart and the consequently increased importance of Laplace’s law are discussed.

THE PURPOSE of this investigation was to acquire a detailed and precise appreciation of the influence of each of the various hemodynamic phenomena, including the tension-time index, on the nonfailing heart’s utilization of oxygen. This required a preparation permitting a) independent control of these phenomena, b) essentially stable and nonfailing performance characteristics of the heart, and c) the ability to make determinations of total myocardial oxygen consumption with a high degree of precision. This experimental study was made possible by the isolated, metabolically supported, dog heart preparation (1).

METHODS

The isolated supported heart (ISH) preparation used in these experiments, its stability, and evidence concerning its nonfailing performance characteristics, and the techniques of measurement employed have been described in detail elsewhere (1). Briefly, it consists of an isolated dog heart, the left ventricle of which ejects blood through a Starling resistance and turbine flowmeter (2) into a reservoir from which blood returns to the left atrium through a second adjustable resistance. This constitutes a closed circuit except for the escape of coronary blood flow into the right heart which receives no other blood. This completely mixed coronary venous blood is ejected through the pulmonary artery, its flow is metered (3) and delivered to the jugular veins of a second dog. Biochemically normal arterial blood from this support dog is simultaneously returned to the reservoir system at the same rate at which it leaves. Aortic pressures, cardiac output and heart rate are independently controlled by appropriate adjustments of the outflow resistance, the inflow resistance and an electrical pacemaker.

The O₂ and CO₂ contents of arterial and mixed coronary venous blood were determined gasometrically (4). Coronary venous, and, in some experiments, arterial blood saturations were also continuously recorded with densitometers (5, 6). In conjunction with continuous coronary flow measurement, it was possible to be certain of the presence of the steady state (1) at the time of sampling, and thus to permit the application of the Fick principle. The heart’s myocardial O₂ consumption in cubic centimeters per minute (qO₂) was calculated as the product of coronary flow in cubic centimeters per minute and the coronary arterio-
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 RESULTS

The results of 27 attempted experiments, of which 20 yielded fruitful data, will be presented in two sections.

Section I. The first group of experiments was devoted to examining the effects on myocardial \( qO_2 \) of the independent variation of cardiac output, mean aortic pressure and heart rate. Figure 1 shows the results of a representative experiment of the type in which a) left ventricular work was increased by elevating aortic pressure while cardiac output and the heart rate were held constant (pressure run) and b) left ventricular work was increased by augmenting cardiac output while mean aortic pressure and heart rate were held constant (flow run). In the pressure run, the increase in myocardial \( qO_2 \) paralleled the elevation of aortic pressure and external efficiency therefore remained unchanged. Contrariwise, in the flow run, the increase in work was accompanied by a relatively slight increase in \( qO_2 \) and a striking increase in external myocardial efficiency therefore occurred. In the pressure run, a 175% work increase was accompanied by a 178% increase in \( qO_2 \). In the flow run a 66% work increase was accompanied by only a 53% increase in \( qO_2 \). It should be further noted that during the flow run, in which mean aortic pressure was held constant while increasing stroke volume, an elevation of systolic aortic pressure did occur. This difference in the effects of pressure and flow on myocardial
qO2 was consistently observed in the 12 dogs in which these relationships were examined. Further data were then obtained to ascertain whether the results shown in figure 1 are limited to a narrow hemodynamic range or apply generally to wide ranges of pressures and flows. These results are shown in figures 2A, B and C. Figure 2A shows representative results from that type of experiment in which data at three different aortic pressures were obtained at each of three different cardiac output levels. It will be observed that, when aortic pressure alone is elevated, the above-described parallel relationship between ventricular work and myocardial qO2 obtained over the entire range of cardiac outputs examined.

Representative results from that type of experiment in which data at three different cardiac outputs were obtained at each of three different mean aortic pressure levels are shown in figure 2B. It will be noted that the above-described nonparallel relationship between ventricular work and myocardial qO2, when cardiac output alone is augmented, obtained over the entire range of mean aortic pressures examined. That is, the increase in qO2 was small relative to the large increments in ventricular work which occurred.

The influence of heart rate is seen in figure 2C. With mean aortic pressure held constant at 120 mm Hg and the heart rate at 120/min., cardiac output was progressively augmented from 1.2 to 4.0 l/min. This was then repeated at heart rates of 160/min. and again at
It will be observed that a higher heart rate at any given work level is accompanied by an increased myocardial \( qO_2 \) and external myocardial efficiency is thereby decreased.

The above experiments strongly suggested that myocardial \( qO_2 \) bears little relation to the heart's external work per se. The absence of such an interrelationship could be even more convincingly demonstrated by the type of experiment shown in Figure 3. At a constant heart rate left ventricular minute work was progressively increased by augmenting cardiac output while lowering aortic pressure to a lesser extent. The 128% increase in work was accompanied by a 20% decrease in \( qO_2 \).

Section II. When it became clear that the aortic pressure, or the development of tension by the heart, was the dominant influence in determining its \( O_2 \) utilization, further analysis and experimentation were designed for the purpose of exposing more precisely that particular pressure parameter which most closely relates to \( qO_2 \).

It was noted above (fig. 1) that, as might be anticipated, aortic systolic pressure rises when stroke volume is increased at any given mean aortic pressure and heart rate (flow run). Of further interest was the observation that the increment of \( qO_2 \) which did occur in the course of any given flow run was consistently a function of the associated increment in aortic systolic pressure. This gave rise to the question of whether all or any portion of that increment in \( qO_2 \) which does occur during a flow run is attributable to the increased systolic tension rather than to the increased fiber shortening (stroke volume) that takes place.

It can be seen from figures 1, 2B and C, and 4A that the \( qO_2 \) varied within the course of any given flow run in which mean aortic pressure was held constant. Also, while the mean systolic pressure did rise slightly during the course of a flow run (fig. 4B), it likewise did not correlate well with the \( qO_2 \) per beat; the \( qO_2 \) per beat changed substantially with only slight changes in mean systolic pressure. It will be further observed in figure 4C that the duration of the tension state increased within the course of any given flow run. The product of the mean systolic pressure (4B) and the duration of systole (4C) yields the tension-time index in mm Hg seconds, (T.T.I.), which is an index of the total tension developed by the myocardium per beat. Figure 4D shows a good correlation between the T.T.I. and the \( qO_2 \) per beat.

However, an equally good correlation between \( qO_2 \) per beat and peak systolic aortic pressure (fig. 4E) was also consistently observed in the experiments described thus far, since, during the course of a flow run, the magnitude of the rise in peak aortic systolic pressure was similar to the rise of the T.T.I. Thus, to ascertain whether the peak pressure developed or the T.T.I. is the responsible determinant of the heart's \( qO_2 \), two additional differentiating types of experiments were performed.

The first type consisted of placing a resonance chamber into the aortic line. This made it possible to change peak systolic pressure without changing stroke volume, mean
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Figs. 4A, B, C, D and E. Relationships between certain hemodynamic parameters and myocardial \( q_{O_2} \) per beat (same experiment as in fig. 2B). Heart rate constant at 150/min. throughout. Data from each of 3 flow runs are shown by the solid dots (at a low mean aortic pressure), open circles (at a medium mean aortic pressure) and triangles (at a high mean aortic pressure).

Aortic pressure or heart rate. A flow run without the resonance chamber is shown under A through H of figure 5. With mean aortic pressure and heart rate held constant, cardiac output was progressively augmented and an increase in peak systolic pressure occurred in each of three experiments. A similar increase in peak systolic pressure was then brought about in each instance by the resonance chamber without altering stroke volume and therefore without the concomitant increase in the duration of systole (OBC to OBO in fig. 5). In the latter instance a substantially smaller \( q_{O_2} \) increment was observed than during the prior flow run indicating that the peak systolic pressure, per se, cannot be considered the fundamental determinant of \( q_{O_2} \).

In the second type of differentiating experiment, the peak systolic pressure was held constant, or allowed to fall slightly, while stroke volume was augmented, in order to increase the duration of systole (manuscript in preparation by Braunwald, Sarnoff and Stainsby) and thereby increase the T.T.I. The data from two such experiments are shown in figure 6, and are representative of 10 of the 11 such experiments in seven hearts. It will be observed that whereas peak systolic pressure was held constant, the T.T.I. rose as a result of an increasing stroke volume. A rise in \( q_{O_2} \) accompanied this observed rise of the T.T.I.

The relationship between myocardial \( q_{O_2} \) and the T.T.I. showed a convincing correlation in 35 of the 37 experiments in the 12 hearts in which the T.T.I. was determined.

DISCUSSION

Previous investigators who have studied the effect on myocardial \( q_{O_2} \) of varying the hemodynamic parameters in isolated heart or heart-lung preparations of the dog, cat, tortoise and frog emphasized various hemodynamic determinants of myocardial \( q_{O_2} \). It has been observed that increasing the heart rate increases the \( q_{O_2} \) (8, 9), and the above data confirm this. It has also been held that the energy of contraction is directly related to end-diastolic ventricular fiber length without regard to the nature of the contraction (7, 10–14). A correlation between \( q_{O_2} \) and external work was found by some observers (15–17), but in these investigations there was little or no separation of the effects of pressure and flow on the \( q_{O_2} \). Many have observed that a given increase in the work of the heart produced by raising aortic pressure while maintaining cardiac output constant resulted in a higher \( q_{O_2} \) than when a similar increase in work was achieved by raising cardiac output at a constant aortic pressure (18–26). The data presented above in section I are also consonant with the observations of this latter group as well as with the early observations of Rhode, who concluded that the heart’s \( q_{O_2} \) is proportional to the product of ventricular pulse pressure and heart rate (27). It is generally agreed, however, that the isolated heart or heart-lung preparations studied in all of the above investigations were either in incipient or varying degrees of overt failure. Since the preparation used in these experiments can be considered essentially nonfailing (r), it is now clear that
these considerations apply to the nonfailing heart as well. Biochemical evidence supporting this position is present in the experiments of Nachmansohn (28) on skeletal muscle wherein phosphocreatine breakdown was observed to be greater during isometric than during isotonic contraction. Recently, preliminary observations by Wollenberger (29) suggest that the myocardium also expends phosphate bond energy chiefly in developing tension rather than in emptying.

The discrepancy between the relative $O_2$ costs of pressure and flow has frequently been observed in the isolated heart or heart-lung as noted above, as well as in the dog with a complete circulation (30). However, that increase of myocardial $O_2$ which does occur at any mean aortic pressure with an increased cardiac output may now reasonably be attributed to the increased total tension (T.T.I.) resulting from the increased mean systolic pressure and increased duration of the tension state. This latter view is supported by the data in section II. The right hand panels of figure 2, as well as figures 3, 4 and 6, demonstrate the variety of circumstances under which observations were made and indicate that, whichever hemodynamic parameter was varied, the relationship between T.T.I. and myocardial $O_2$ obtained. It appears, therefore, that in any given functional state of the beating heart, the T.T.I. (mean systolic pressure times duration of systole) is the principal, if not the sole, determinant of myocardial $O_2$ utilization. If the correlations observed above are causal rather than coincidental, then the above data may result in the derivation of a more meaningful relationship between the $O_2$ used by contracting heart muscle and the physiologic purpose for which it is used.

At any given filling pressure, the myocardial $O_2$ can vary over a substantial range and will be a function of the T.T.I. developed during the course of the contraction (30). It appears, therefore, that the heart's $O_2$ is determined not primarily by the filling pressure prior to contraction, but rather by the events occurring subsequent to the onset of contraction from any given filling pressure. If marked changes in ventricular distensibility do not occur, this
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view implies that similar considerations apply to the relationship between fiber length and myocardial \( qO_2 \). The validity of this latter position, however, still awaits satisfactory experimental demonstration.

A variable which it was not found possible to control in the above described experiments was the rate of the development of systolic tension while holding the other hemodynamic parameters constant. The possibility must be considered, therefore, that these experiments are incomplete in that it has not been determined whether the rate of development of tension modifies the relationship between \( qO_2 \) and the T.T.I.

The term external efficiency as used herein refers to the ratio of external work to \( qO_2 \) and conforms to the general usage of the term efficiency as applied to the heart. It is suggested herewith that the term internal efficiency refer to the ratio between the actual total tension developed by the myocardium and its \( qO_2 \). External efficiency is primarily meaningful in terms of the relationship between the heart and the total organism but is relatively uninformative about the energetics of contracting myocardium. In contrast, the term internal efficiency is designed to expose the meaningful relationship between that aspect of the heart’s contraction which requires \( O_2 \) (total developed tension) and the amount of \( O_2 \) consumed. In the absence of any ready means of measuring the actual total tension developed, the area beneath the systolic portion of the pressure curve (T.T.I. in mm Hg seconds) has been used as an index of the actual total myocardial fiber tension. The ratio of T.T.I. to \( qO_2 \) thus provides an internal efficiency index. Any discrepancy between internal efficiency and the internal efficiency index will revolve around the extent to which integrated ventricular radius changes occur and considerations involving Laplace’s law therefore apply, for it is clear from such considerations that the same intraventricular T.T.I. will require a greater myocardial fiber tension in a large heart than in a small one. If it is assumed that the basic relationship is between the total actual tension developed by the myocardium rather than the reflection thereof in the observed T.T.I., then both the low internal and external efficiency of the greatly dilated or failing heart can logically be attributed, at least in part, to the interrelationship between Laplace’s law and the dependence of the heart’s \( qO_2 \) on its actual total developed tension. For example, if the dilated heart is called upon to develop any given intraventricular pressure, the myocardial fiber tension will be greater and its \( qO_2 \) will thus also be greater than that of the small heart producing the same intraventricular pressure at the same stroke volume and heart rate. In this sense the dilating heart may be thought of as one with an \( O_2 \) requirement which approaches or finally could exceed the limit of the \( O_2 \) available to it, especially when \( O_2 \) availability is limited by disease. It should be emphasized that such considerations are valid only if the assumption of the basic relationship between \( qO_2 \) and actual total tension developed is a correct one. Further, the accuracy of any efficiency calculation will be influenced by the extent, if any, to which sources of energy other than \( O_2 \) contrib-

\[ T = P \times R \]

For a cylinder, \( T = P \times R \) where \( T \) = wall tension, \( P \) = intraluminal pressure, \( R \) = radius. For further discussion see Woods (31) and Rushmer (32).
ute to the total energy utilization of the myocardium.

An extension of these findings to the diseased state in man may provide a more precise appreciation of the interrelationship between the heart’s O2 requirement and the deviations from normal produced by various pathological conditions. Thus, the overt manifestations of myocardial hypoxia are in general precipitated by conditions such as hypertension, aortic stenosis, and tachycardia, in which the T.T.I. is substantially elevated, but are infrequently brought about by conditions such as mitral insufficiency, intra and extracardiac shunts and beri-beri heart disease in which cardiac work is increased because of an increased cardiac output and in which the elevation of T.T.I. is limited.

Finally, the above observations may be of interest from the point of view of natural selection. Physical stress or conflict is accompanied by large increases in cardiac output in accord with the organism’s increased requirements for O2. Under such circumstances, at any given aortic pressure, heart rate and humoral environment, the O2 consumption of that organ which delivers greatly increased amounts of O2 to the whole organism is increased only slightly as a result of increasing stroke volume. Thus, it might be that the heart demands a progressively smaller fraction of the total O2 utilized by the organism as physical activity increases, especially when the heart rate is maintained at low levels as in well trained athletes.

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REFERENCES