The Relation of Cardiac Effort to Myocardial Oxygen Consumption and Coronary Flow

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The current views of the authors regarding the relationship of the cardiac performance and its myocardial oxygen consumption and the relationship of the latter to coronary blood flow are presented. Recent attempts, including our own, to devise an index of total cardiac effort that will relate to the myocardial oxygen consumption are discussed. It is concluded that the cardiac performance requiring oxygen determines coronary flow while the arteriovenous oxygen difference across the bed remains constant. However, the level of the arteriovenous oxygen difference is altered by local conditions of oxygen and carbon dioxide concentrations, and the presence of catecholamines. Hence, the level of coronary flow for a given amount of cardiac oxygen consumption is altered by these circumstances.

The occasion of Dr. C. J. Wiggers' birthday permits us to respectfully dedicate this presentation to him as a token of our esteem and indebtedness. We have attempted to make this more than a progress report since, we feel strongly that too much of present-day, scientific reporting is fragmentary. There is need to communicate our frame of reference even though the picture within the frame is somewhat bare. The deductive reasoning we learned from Wiggers is not to be discouraged in the same way as excessive a priori speculations. It is the reasoning which makes scientific documentation more palatable.

The realization that the heart functions as a pump predates the revolution in physiology precipitated by Harvey's discovery of the circulation of blood. Ever since, the mechanisms by which the flow of blood through the heart muscle adapts to changing cardiac effort has stimulated the interest and imagination of physiologists; as in all fields of science, our understanding has been extended as a function of such imaginative interest and of the availability of tools of increasing sensitivity.

Coronary Flow Measurement

The modern era of the investigation of coronary flow might be considered as beginning in 1914 with the insertion of a cannula into the coronary sinus of the living animal. The data obtained with this device were interpreted on the assumption that the total venous return of the coronary bed was collected into the coronary sinus. It has since been shown that there is a considerable drainage of coronary blood directly into the right atrium and ventricle by channels other than through the coronary sinus, as well as into the left atrium and ventricle. The sampling of coronary sinus blood by cardiac catheterization has the obvious advantage of being the only method applicable at present to the unanesthetized animal and to man. This procedure has been justified on the basis that a representative and predictable aliquot of coronary venous blood is collected without altering the dynamics of coronary venous outflow. This has been seriously questioned, and the constancy of the distribution of coronary drainage, as dynamic conditions alter, remains to be proved. Until these objections are overcome, the coronary sinus method ought not to be considered the sine qua non of coronary flow methods.

Much of the early work on coronary flow made use of the heart-lung (or isolated-heart) preparation, which permitted the study of coronary flow in the naturally perfused heart. The increasing emphasis on the importance of innervation and of the enhancement of the ability of tools of increasing sensitivity.

*Recently, we have summarized our work.* The present report affords us the opportunity to broaden our interpretations as new findings have appeared.

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humoral regulation in the study of organ metabolism has made it mandatory that the findings obtained in the isolated heart be extended in a more nearly intact preparation.

Our attempts toward this end led to the development of an acute, open-chested dog preparation that permits the measurement of the total coronary flow, with the exception of the small drainage into the left atrium and ventricle. The right side of the heart pumps only the coronary-flow drainage and operates under hypodynamic conditions. The left ventricular output (pulmonary input) is set by a perfusion pump that substitutes for right-heart function. Aortic pressure and heart rate are permitted to vary spontaneously, or they may be controlled. Nervous and humoral influences are maintained within the limits permitted by the surgical procedure and anesthetization. There are many problems in cardiovascular research, particularly regarding the regulation of coronary flow, that can be investigated with this preparation despite the disadvantage of an open chest and surgery upon the heart. As an essential, first step, an extensive recapitulation of earlier work on the less intact preparations was carried out, to see how far they apply. We have systematically studied the response of this preparation to the usually tested physiologic variables, cardiac output, blood pressure and heart rate, under ordinary, controlled conditions and with some set deviations therefrom. What follows is by no means a review of our findings, but rather a comment on some of the pressing problems in this field, as we view them.

The design of the experiments using this preparation was aimed at obtaining information concerning (1) the oxygen cost of cardiac effort and (2) the dynamic and metabolic determinants of coronary flow. Our frame of reference in these studies is based on the following suppositions:

1. The metabolism of the heart is ultimately aerobic, and the utilization of oxygen is a measure of the chemical energy production of the heart.

2. The cardiac effort can be measured in all of its ramifications, and the total effort can be related to the oxygen metabolism of the heart.

3. The determinants of coronary flow are related to the various aspects of cardiac effort via their metabolic requirement and therefore to the oxygen utilization. In practice, the oxygen consumption can be calculated as the product of the coronary flow and the arteriovenous oxygen difference across this bed. The actual flow will relate not only to the total oxygen requirement of the heart but also to the interrelationship between the flow and the cardiac oxygen extraction. We have paid particular attention to this latter interrelationship in our studies, in an attempt to derive some understanding of the flow regulation mechanism.

**THE OXYGEN COST OF CARDIAC EFFORT**

There are 3 lines of evidence concerning the association between cardiac oxygen utilization and the effort of the heart.

**Studies on Tissue Slices, Homogenates and Isolated Enzyme Systems.** These studies have given some insight into the enzymatic details determining the oxygen cost of cardiac effort. In this regard we need to know the expenditure of high-energy phosphate for a given amount of cardiac muscular effort. This would be, in a true sense, the chemical-mechanical efficiency. Further, studies of this type provide us with knowledge concerning the number of moles of high-energy phosphate that are produced simultaneously with the utilization of one mole of oxygen (the P/O ratio) which appears at present to be rather constant (about 3) in the *in vitro* heart system. The association of high-energy material and mechanical effort with oxygen utilization will provide the ultimate quantitation between effort and oxygen utilization. At present, our understanding of both the isolated and the intact cardiac systems is insufficient to permit extrapolation from one to the other. We do know, however, that the enzymes of the respiratory chain necessary for aerobic metabolism are present in cardiac muscle in great abundance as compared to other body tissues. Thus, the necessary levels of oxidized diphosphopyridinenucleotide (DPN) are maintained, and the energy release from the hydrogen transfer system may be coupled to the synthesis of adenosine diphosphate (ADP) and adenosine triphosphate (ATP), as well as other nucleotide triphosphate, with maximum effectiveness.

However, in neither skeletal nor cardiac tissue are oxidative steps in the production of high-energy phosphate obligatory, although rapid accumulation of reduced DPN may only be prevented by an adequate oxygen supply. There may be several metabolic routes whereby such bonds can be synthesized without local oxygen utilization. One appears to be the conversion of glucose to pyruvate, which
produces two high-energy bonds. In the absence of oxygen, pyruvate is converted to lactate, and the reduced DPN is thus oxidized. Rapid depletion of glycogen reserves and glycolysis to lactic acid would have only limited survival value in the absence of oxygen. A small, net increase in lactic acid production would, however, serve to alleviate some of the local oxygen requirements. In this regard, it is well known that lactic acid may powerfully increase blood flow. Thus there is suggestive evidence that blood flow may be increased simultaneously with a relative conservation of oxygen requirements, or, expressed differently, an "escape" mechanism for the oxygen cost of effort may have associated vasomotor effects.

An interesting aspect of our work with the coronary flow preparation is the observation that certain stressful circumstances may be associated with a sudden and sustained increase in coronary flow to rather high levels, while at the same time the oxygen consumption commensurate with the cardiac effort is reduced. This sudden shift may also suddenly revert back to the usual flow rates and oxygen consumption levels expected for a given cardiac effort. It has been suggested that the heart either is calling on stored material for energy production or is submitting partial products of metabolism for complete treatment elsewhere. Unfortunately, up to the present we have no adequate measurement of utilization of metabolites other than oxygen, so that we cannot further analyze what happens when this special situation arises.

The Heat Production of Skeletal Muscle Contraction. The work of Hill and other muscle physiologists gives some insight on energetics which may be extrapolated to heart muscle. It has been shown that the time course of delayed heat production in skeletal muscle, when oxygen is readmitted after an aerobic contraction, is identical with the time course of oxygen consumption. The delayed or recovery heat in skeletal muscle is considered to be the sum of the heat of 2 processes, exothermic oxidative catabolism and endothermic resynthesis, a reversal of the reactions which are the source of the initial heart and work of the contraction. It is reasonable to assume that delayed or recovery heat is the thermal accompaniment of resetting the contractile process, as well as of the supportive reactions permitting it to go on in the absence of oxygen.

On this basis, oxygen consumption should be directly proportional to the energy expenditure of contraction, and should represent the most useful, though a rather remote, index of the conversion of chemical energy into mechanical effort. There is no reason to assume a qualitatively different relationship between oxidative processes and recovery in cardiac and skeletal muscle, except that the interval between oxidative recovery heat and contraction may be prolonged in skeletal muscle but not in cardiac muscle. Some day it may be possible to express the cardiac effort in terms of heat production. It seems safe to predict that when such information is obtained and an estimate of the calorie expenditure can be made on a physical basis, oxidative reactions may be said to account for most of the energy production.

An Analysis of the Cardiac Effort. An analysis of the several ways in which the cardiac effort may be changed can give insight into the mechanisms relating cardiac oxygen consumption to the effort of the heart. In such an analysis the rate of resting metabolism must be evaluated. Changes in the cardiac effort may be made manifest by alterations in cardiac output, arterial blood pressure (diastolic, systolic, pulse and mean), heart rate, the duration of the several phases of the heart cycle (systolic and diastolic), etc. By evaluating the cardiac energy release under these different variations, we may approach an oxygen cost accounting of each aspect of cardiac effort and of their interactions.

*Accompanying these changes, there is a reduction of coronary arteriovenous oxygen difference, and an increase in coronary venous oxygen content and in oxygen availability.
Cardiac Oxygen Consumption and External Useful Work

There are several ways in which the effort of the heart may be measured. One of these is the relationship of external useful cardiac work to the oxygen consumed by the myocardium, the so-called external efficiency. This has been, and continues to be, a major consideration in experimental work and in the understanding of cardiac disease, since pumping blood to the various organs of the body in adequate amounts is the primary task of the heart. Despite the overwhelming emphasis put on the work output of the heart and its external efficiency, it was recognized that this work accounted for only a small fraction (10 to 15 per cent) of the total oxygen consumption of the heart. It is also evident that the calculation of external efficiency emphasizes a component of cardiac performance, the cardiac output, that has little correlation with myocardial oxygen consumption and does not include another component, the heart rate, that has a decided influence on myocardial oxygen consumption. Thus it appears that external work represents only part of the cardiac effort, its dynamic effort. Another aspect of cardiac effort, more costly in terms of energy expenditure, depends upon the build-up and maintenance of tension in the ventricles, its static effort.

Studies of skeletal muscle have established that the isometric tension and the heat production developed by the stimulated muscle varies with its initial length. These studies provide the basis for the interpretation of the data obtained on the isolated heart and heart-lung preparation by Frank, Wiggers, Lovatt Evans, Starling, Visscher and, most recently, by Lorber as well as by ourselves. It was found that the oxygen consumption is determined by end-diastolic volume and therefore by the initial length of the heart muscle. With deterioration in time of the preparation, or after excessive overloading, the oxygen consumption and stroke work deviated, the oxygen consumption followed the end-diastolic volume, while stroke work decreased as a function of a fall-off in pressure or output or both. Efforts to correlate the oxygen consumption with changes in aortic pressure at constant diastolic filling were successful, but when pressure and filling changes occurred the oxygen consumption followed the filling rather than the pressure change.

The most recent studies of this department, having a bearing on this problem, are those of Alella et al. and of Laurent et al. which used the coronary flow preparation described above. The observations of Alella et al. failed to provide support for the overriding influence of cardiac output on myocardial oxygen consumption. Three mean cardiac outputs (800, 1,200 and 1,600 ml./min.), with a narrow range of variation, were examined at 3 mean, aortic blood pressures (72, 92 and 122 mm. Hg), also with a narrow range of variation. Then each aortic pressure was examined at the 3 cardiac outputs. This was done in each animal. The heart rate was not controlled and did not vary by more than 40 beats from the mean in any given experiment.

Multiple regression analysis was carried out, relating the mean blood pressure and the cardiac output, as the independent variables, with myocardial oxygen consumption as the dependent variable.* The regression coefficient attributable to blood pressure indicated a significant association of blood pressure (BP) and cardiac oxygen consumption (card. O₂ cons.), while the regression coefficient associated with cardiac output (CO) was not significantly different from zero: \[ \text{card. } O_2 \text{ cons.} = 6.38 \pm 4.33 + 0.12 \pm 0.03 \text{ BP} + 0.001 \pm 0.01 \text{ CO}. \]

*The original data was treated by pooling all the observations at an average blood pressure and observing the regression of cardiac output on myocardial oxygen consumption; similarly, the regression coefficient attributable to blood pressure was obtained by pooling all observations at the same average cardiac output. Blood pressure and cardiac oxygen consumption were found to be highly correlated, while cardiac output changes did not correlate with changes in cardiac oxygen consumption. Although the analysis based on the data from individual animals is somewhat more rigorous, it does not change the interpretation of the original presentation.
KATZ AND FEINBERG

The explanation of these findings are perhaps better understood in the light of the experiments of Gollwitzer-Meier in which the innervated and denervated heart-lung preparation were compared. While the classical response to end-diastolic volume was still seen in the innervated heart-lung preparation, increases in blood pressure at constant venous return and heart rate were not associated with the cardiac dilation seen in the denervated preparation. Wiggers and associates and work in this department have emphasized that such factors as the rate and degree of ventricular filling, the variable effect of atrial systole, the time interval available for ventricular filling, coronary blood supply, humoral agents and neural impulses, etc. modify the interpretation of the Starling school, that end-diastolic volume is the primary factor affecting cardiac effort. Recently, an extensive discussion on the regulation of the cardiac performance delineated the role of a number of factors, other than end-diastolic volume, in the intact, open-chested animal and the completely intact animal—viz. the afterload against which the heart contracts, the neurogenic and humoral stimuli controlling the contractile power of the heart, the diastolic tone, the filling pressure, the filling time, the systolic residue, etc. These, as well as the previously mentioned factors, modify significantly the application of the Starling relationship.

**Cardiac Oxygen Consumption and Total Effort**

Stimulated by the recent report of Sarnoff and his co-workers that a correlative relationship exists between oxygen consumption per beat and the product of average systolic pressure and the duration of systole, we analyzed our earlier and more recent data with the preparation we developed. The best correlation of cardiac oxygen consumption we found was obtained with cardiac effort, when the effort was expressed as the product of mean aortic pressure (as integrated by the capacitance manometer) and the heart rate—the \( BP \times HR \) index. The experimental design of the earlier work of the department proved crucial in the interpretation of this relationship. The regression analysis of the product \( HR \times BP \) on myocardial oxygen consumption

\[
\text{card. } O_2 \text{ cons. } = -1.88 \pm 0.33 + 1.11 \pm 0.74 \text{ (card. } O_2 \text{ cons. )}
\]

showed a significant relationship of this product to myocardial oxygen consumption, while the simultaneous regression of cardiac output on its oxygen consumption was not significantly different from zero. The prediction value of the \( HR \times BP \) index for myocardial oxygen consumption was far better than that obtained with cardiac work (\( BP \times CO \)). This was also true of the experiments of Laurent et al., in which heart rate was altered by electric stimulation up to 300 beats/min. (fig. 1). The variations of cardiac output showed no apparent relationship to changes in cardiac oxygen consumption, and the regression of the product \( HR \times BP \) on myocardial oxygen consumption was much superior to that of cardiac work on oxygen consumption

\[
\text{card. } O_2 \text{ cons. } = 6.58 \pm 2.88 + 0.60 \pm 0.34
\]
Subsequent work on the preparation revealed that hypercapnia did not affect the relationship of cardiac oxygen consumption to the $BP \times HR$ index, while in hypoxia the relationship was affected only at extremely low arterial oxygen content. Thus far, only the administration of catecholamines has altered the nature of the correlative relationship.

In order that the $BP \times HR$ index bear a close correlative relationship to cardiac oxygen consumption it must bear some fixed relationship to the total tension developed by the ventricle. This also applies to the time-tension index put forth by Sarnoff et al.

Early in the development of skeletal muscle physiology, Hartree and Hill considered the case of isometric contraction that was sustained over a period of time. It was obvious that energy was utilized while no external work was done. While the expenditure of energy could be characterized by heat production which was ultimately related to recovery heat and oxygen consumption, they suggested the integral of tension over the time it was sustained (St.dt) as a useful approximation of the effort expended. With regard to the heart, Wiggers and Katz commented that the area under the left ventricular pressure curve, the tension-time value per stroke, may be a better index of mechanical activity than the total external useful work performed when the muscle shortens. Recently, Burton also stressed the importance of the static effort as compared to external work. Starr faced the problem of characterizing muscular work in units that could be correlated with subjective effort, and ultimately oxygen consumption, agreed with this formulation and devised a formula that essentially accounted for the area beneath the curve of the second derivative of the distance versus the time for a unit weight raised and lowered in a given sequence. The result was a term in dynes-seconds. The $BP \times HR$ index we have employed is convertible into similar units on the basis of the equivalence of 1 mm. Hg to 1.33 dynes. The logical inference of the use of this product is the concept that mean blood pressure relates to the total effort of the cardiac cycle and that this, multiplied by the heart rate, is an index to the minute effort of the heart and its minute oxygen consumption.

It must be pointed out that the significance of the correlation between cardiac oxygen consumption and the product heart rate and blood pressure does not negate the role of end-diastolic volume as a conditioning factor in the energy release of the subsequent contraction. The manner in which stroke output and end-diastolic volume might operate will be discussed further.

The plot of the intraventricular pressure and the ventricular volume of the average normal heart can be constructed into a pressure-volume loop (fig. 2). With the additional information concerning the change of shape of the ventricle, the time course of tension developed by the myocardial fibers may also be obtained from such a loop. Put in terms of an analogy with our understanding of skeletal muscle, the energy released by the heart in association with contraction will appear either as tension or work. The energy release that is manifest as tension, and does not appear as work, is degraded to heat; the energy release associated with the performance of work also has a counterpart in heat production, the shortening heat. Provided the relaxation of the ventricle is accomplished against a load, the relaxation heat corresponds in energy release with the work. It is more likely that relaxation in the heart is comparable to the non-after-loaded muscle. Therefore, the only heat production associated with work would be the shortening heat.

Proceeding further with this analogy, we may ask how the energy release manifest as tension can be approximated without measuring the heat production. The answer may be as follows:

Up to the point of opening of the semilunar valves, none of the cardiac muscle tension is manifest as external work. It could be measured either as the tension that acts to separate the muscle fibers tangential to the ventricular muscle (integrated for the entire ventricle on the basis of the mass of the ventricular volume.
Fig. 2. The pressure-volume interrelationship of a fully relaxed (lower right curve) and the fully contracted (upper left curve) left ventricle of man. Ordinate, pressure (scale in 30 min. Hg); abscissa, left ventricular volume in cm.$^3$ If a point on the abscissa is taken to represent end-diastolic volume, then the end-diastolic pressure can be found on the ordinate. The same procedure can be followed in determining systolic pressure for various systolic volumes. As end-diastolic volume increases, end-diastolic pressure rises more and more steeply. (This relationship has been worked out on skeletal muscle and found to apply to the hearts of frogs and turtles.) As the systolic volume rises, the systolic pressure rises steeply until a maximum value is reached, after which the systolic pressure falls off with further increases in systolic volume.

Between the 2 curves representing pressure-volume relationships, 3 compression cycles (work diagrams) are drawn, represented by the enclosed loops shaded with diagonal, horizontal and vertical lines. Diagonal lines, the control work diagram for the purpose of this presentation. Horizontal lines, conditions when the work of the ventricle is increased primarily by elevating the systemic arterial pressure. During systole a large change in pressure occurs, and the ventricle empties less completely than before. Vertical lines, conditions when the work is increased primarily by augmenting the cardiac output. During systole a small change in pressure occurs, although the ventricle empties itself almost completely. In each of these 3 instances the work done by the ventricle during its systole is shown by the upper curve bounding the shaded areas starting from the diastolic P/V curve on the right and ending on the systolic P/V curve on the left. Work done upon the heart during its diastole by passive filling is shown by the lower curve bounding the shaded areas starting at the systolic P/V curve on the left and ending on the diastolic P/V curve on the right. The shaded area in each case therefore represents the excess of work done by the heart as a compression-pump system over that done upon it. (Reprinted from Physiol. Rev. 35: 90, 1955.)
of the former. The ventricle can be considered as a cylinder which decreases in its base to apex axis during systole, so that the heart acts as a piston with cylindrical walls. In this case volume relates to the internal area directly as the height of the cylinder alters.

In the case of either a sphere or a cylinder, pressure \( P \) can be considered as force per unit area \( A \) and the product of pressure and area will be equal to the tension \( T \) exerted by the muscle tangential to the surface of the ventricular cavity. From this it follows that during the ejection phase of systole, as the heart internal surface area decreases, the ratio \( T/A \) will increase. Thus, aside from any absolute \( P \) value, \( T \) will be a function of \( A \). The larger the stroke output \( dA \) the less will pressure \( dP \) reflect tension \( dT \); however, the absolute tension will be partly determined by the end-diastolic volume, so that if the stroke output is increased with increasing rather than decreasing end-diastolic volume, the total tension will be greater.

After an inspection of the problem of the determinants of cardiac performance in the above manner, several factors which are obscured in the simple relationship between diastolic filling and cardiac oxygen consumption became apparent. It would appear that the onset of shortening in the left ventricle is as much a function of the aortic diastolic pressure as it is of end-diastolic volume. Also, the peak pressure attained is as much a function of aortic resistance and end-systolic volume as it is of end-diastolic volume. It must also be added that sudden change of the range of fiber length variation as found in cardiac dilatation, while not abrogating the relationship between mean blood pressure and total tension, will nevertheless alter it, as will changes in the magnitude of the stroke volume.

Thus far we have assumed that heart rate bears a relationship to oxygen consumption as a multiple of the total tension developed per cycle. This is supported by the work of Laurent et al., although extremely high rates at physiologic blood pressures and various cardiac outputs resulted in regression curves not very different from those derived from the data of Alella et al. Therefore it is nevertheless conceivable that heart rate may play several roles. Since heart rate is in effect a determinant of stroke volume and will affect both end-diastolic volume and end-systolic volume, it will significantly modify the tension per stroke. Gollwitzer-Meier noted, as we have, that increasing the mean blood pressure by means of a clamp on the aorta will decrease the heart rate, while increasing the cardiac input will increase the heart rate. Thus, the paired values of heart rate and blood pressure may bear a compensating relationship in terms of tension developed.

At constant cardiac output, a heart rate increase (stroke-volume decrease) will be associated with a lesser range of variation of \( T/A \) than at slower rates. \( dP \) is thus a better index of \( dT \) at fast heart rates than at slow rates. Heart rate thus has an effect on the relation of \( T/A \). The heart rate may act in other ways as well. It alters the ratio of the period over which the ventricle is under systolic tension to that in which it is not. It also alters the duration of the pressure-time curve of the ventricle. Finally it alters the shape of the pressure-time curve. With regard to the \( BP \times HR \) index, and as far as the systemic arteries are concerned, the integrating device used to get mean systemic pressure takes care of these latter effects. It might also do the same for left ventricular pressure curves. There is no reason to doubt that the relationship with cardiac oxygen consumption would hold equally well if the blood pressure used for calculation were the mean of the left ventricle pressure curve rather than that in the systemic arteries. The \( BP \times HR \) index would then represent the energy released by the ventricles which appears principally as the tension over a period of time. Calculation

\*In such an event, the pressure measured would include that present during isometric contraction and isometric relaxation. The former should be included, the latter probably not. Further, the mean pressure would be lower than in the case of the arterial pressure, but in a proportional degree at various arterial pressure levels.
to date of 49 experiments, under a wide variety of circumstances, reveal a relationship which can be expressed as follows: \( \text{card. O}_2 \text{Cons.} = 3.9 + 0.45 (BP \times HR) \times 10^{-3} \).

In order that the total effort of the heart be obtained, there must be added to the tension developed (computed either as heat evolution, shearing force in the ventricular muscle, or the manifestation of tension in terms of pressure and volume) the relatively smaller amount of energy release that appears as external useful work. This latter can be expressed as \( PV \), or as \( \int_{T_0}^{T_1} PdV \), or, most rigorously, as \( \int_{T_0}^{T_1} PdV + \int_{T_0}^{T_1} dmu^2/2g \), where \( T_0 \) and \( T_1 \) represent the beginning and the end of ejection, \( P \) the pressure in the aorta, \( V \) the volume of blood ejected, \( m \) the mass of blood ejected, \( v \) the linear velocity of the blood in the aorta and \( g \) the gravitational constant.

It was mentioned in the foregoing that only infusions of catecholamines altered the relationship between cardiac oxygen consumption and the \( BP \times HR \) index. This could be assumed to be a metabolic effect of the catecholamines. However, if we seek an explanation on a hemodynamic basis, several other possibilities emerge:

1. Blood pressure values during 1-epinephrine or 1-norepinephrine infusions were invariably coupled with higher heart rates than the comparable control values of blood pressure. Thus the product \( BP \times HR \) for the control and catecholamine-treated periods are not strictly the same, since, for the same value of the \( BP \times HR \) index, blood pressure is higher in the controls than in the catecholamine data, and heart rate is less. It may be that the repetitive development of less tension is more costly than the less frequent development of higher tension.

2. The "contractility" of the heart is affected by catecholamines and the shape of the pressure-time curve, and its duration is altered independently of heart rate.\(^{35}\) This may also be associated with a change in diastolic tone, with more complete emptying and with a change in heart size.\(^{36}\) These alterations might be expected to shift the relationship of mean aortic pressure (and the tension developed) to the cardiac oxygen consumed. Such hemodynamic alterations must be excluded before metabolic actions of catecholamines are assumed.

In view of this entire discussion, the claims that can be made for the indices proposed for cardiac tension must be modest. It is hoped that the recent technological innovations of Rushmer\(^{34}\) and of Perry and Hawthorne,\(^{37}\) when applied to a study of myocardial oxygen consumption, will provide a better basis for such indices. In the meantime the easily derived relationship (the \( HR \times BP \) index) appears to serve as an opening wedge for future advances.

**Cardiac Oxygen Consumption and Coronary Flow—A-V Oxygen Difference**

In the remainder of this discussion we would like to make some comments on the relationship between the cardiac oxygen consumption and coronary flow, or, more properly, the relationship between the coronary flow and the arteriovenous oxygen difference across the coronary bed. During the course of our studies it became evident that, under conditions of normal arterial oxygen content and arterial carbon dioxide content, and in the absence of undue stress, one attribute of our preparation is a relative constancy of the coronary arteriovenous oxygen difference, or the present oxygen extracted (arteriovenous oxygen difference per unit of arterial oxygen content).\(^{19}\) This has been found to be true for some, but not all other preparations. The logical consequence of this finding with regard to cardiac oxygen consumption and coronary blood flow is that these parameters are closely correlated, since cardiac oxygen consumption is calculated as the product of coronary flow and the arteriovenous oxygen difference across this bed. Thus, provided the percentage of oxygen extracted remains constant, any change in the activity of cardiac tissue.
that alters myocardial oxygen consumption will, of necessity, simultaneously determine the coronary flow.

Not all conditions under which the heart beats are associated with the same coronary arteriovenous difference or percentage of oxygen extracted by the heart. However, once a "steady state" is reached under the altered conditions, the new value of coronary arteriovenous oxygen difference, or of myocardial oxygen extraction, remains relatively constant when the heart's performance alters; further, when the blood pressure or heart rate are altered in this new steady state, there is once again a high degree of correlation between the varying cardiac oxygen consumption and the coronary flow.

Thus far the 3 variations from the normal (unmodified) condition that we have studied are hypoxia, hypercapnia, and catecholamine infusion at a constant rate. In these 3 modified experiments the design of the sequence of observations was identical. First, the animal was observed over a range of cardiac effort during the administration of 5 per cent carbon dioxide in oxygen and in the absence of drug administration. Subsequently, the experimental period was carried out (hypoxia, hypercapnia or catecholamine infusion), and again the animal was observed over a range of cardiac effort. Changes in cardiac effort were produced by constricting the aorta at constant cardiac output; the heart rate was not controlled. The changes in external work were those of pressure-work. Efforts were made to examine the animal over a comparable range of cardiac performance before and after the onset of the experimental period.

In hypoxia, a decrease in coronary venous oxygen content took place with the decline in arterial oxygen content. The decrease in the coronary arteriovenous oxygen difference was proportional to the decrease in the arterial oxygen content, and the percentage of oxygen extraction by the heart remained relatively constant. During a steady state of reduced arterial oxygen content, the coronary arteriovenous oxygen difference remained relatively constant, and the coronary flow followed the induced changes in cardiac oxygen consumption.

Thus, at any cardiac oxygen consumption level, the coronary flow is a function of the oxygen cost of the effort, but the flow response is increased in hypoxia above that when it is absent, in compensation for the decreased coronary arteriovenous oxygen difference accompanying the hypoxia. Coronary flow increases beyond this point were rarely seen in our experiments. The hypoxia experiments therefore confirm the interrelationship of cardiac oxygen consumption and coronary flow rate seen in the absence of hypoxia. Just as in the presence of normal arterial oxygen content, the coronary flow regulation is sufficient to maintain practically unchanged the oxygen extraction by the heart. In short, coronary flow adjustments in hypoxia tend to keep constant the correlation of the heart's oxygen availability (arterial oxygen content × coronary flow) with its oxygen consumption.

Hypercapnia is also associated with increased coronary flow rates and decreased coronary arteriovenous oxygen differences, just as is hypoxia. Further, as in hypoxia, the coronary flow is a function of the rate of myocardial oxygen consumption, even though at any given value of the latter it is higher than that found in the control before hypercapnia was induced. The increase in coronary flow and the accompanying decrease in coronary arteriovenous oxygen difference in hypercapnia, unlike hypoxia, is associated with normal arterial oxygen content and an increase in coronary venous oxygen content. Therefore, the percentage of oxygen extracted by the heart is decreased in hypercapnia. The decreases in myocardial oxygen extraction in hypercapnia were exactly related to the decrease in coronary arteriovenous oxygen differences.

A steady state of hypercapnia may be characterized by a decreased arteriovenous oxygen difference, and wide changes in cardiac oxygen consumption subsequent to alterations of the cardiac performance are met by changes...
in coronary blood flow. Thus hypercapnia increases the oxygen availability for the same level of cardiac oxygen consumption.

Catecholamines infused at a constant rate produce a steady state of increased coronary flow and decreased myocardial oxygen extraction exactly parallel to the rise in coronary venous oxygen and the decline in coronary arteriovenous oxygen difference. The comparison with hypoxia is not as clear as it was in the case of hypercapnia, since there are clearly discernible changes in the nature of the cardiac response; e.g., catecholamines produced an increase in blood pressure and heart rate. Nevertheless there is no doubt that catecholamine infusion brings about an increased oxygen availability for a given cardiac oxygen consumption.

A comparison of the effects of these modifications of blood flow during hypoxia, hypercapnia and catecholamine infusion provide clues to coronary flow regulation. First, there is the basic over-all influence of the cardiac effort as evidenced by the heart's oxygen requirement. Alteration of the effort and associated changes in the oxygen requirement produce comparable changes in blood flow in all 3 modifications of the experiment.

In hypoxia, the extra coronary flow response for a given effort of the heart occurs with no change in oxygen extraction. Apparently the reduction in arterial oxygen is interpreted by the cell in the same way as is increased oxygen demand following increased effort. The coronary venous oxygen may be taken as a function dependent on the flow rate, the arterial oxygen content and the oxygen requirement of the heart. The constancy of the coronary venous oxygen with wide variation of coronary flow in a steady state of reduced arterial oxygen content speaks for a closely guarded regulation of perfusion as governed by metabolism.

In hypercapnia and during catecholamine infusion the coronary flow continues to respond principally to the oxygen demand of the heart. The arterial oxygen content may be normal and constant, and yet the coronary venous oxygen rises and the oxygen extraction decreases. Of the factors that affect the coronary venous oxygen, the arterial oxygen and the oxygen requirement may be considered, in a given case, to be equal; thus the increased coronary venous oxygen is chiefly related to the extraneous response brought about by the experimental conditions.

On the basis of the present evidence, the initiating factor in the new equilibrium between coronary flow and oxygen extraction by the heart cannot be decided. What is more than likely is that hypercapnia and catecholamines have an effect on the basic vascular tone, probably at the level of the precapillary sphincter, that results in enhanced flow and reduced oxygen extraction. However, no matter what the effect may be of these maneuvers on the vascular tone, the basic vascular response to the oxygen requirement subsequent to changes in cardiac effort is not abrogated.

SUMMARY

It is hoped that this presentation has helped to define the problems related to the energetics of the heart. Apart from the ever present question of the justification of extrapolation to the completely intact animal, the following questions appear to us to be urgent and of the type that may be approached in such a system as we have described:

The use of oxygen metabolism as an index of energy production, without regard to the kind of substrate that is metabolized, is justified on the basis of a first approximation. Studies including other metabolites must be carried out on the in situ beating heart that is given a measurable task. The influence of the substrate on oxygen utilization, and the effect of cardiac effort on this relationship under conditions approaching those existing in the intact animal, may then be studied.

The vexing question of the so-called resting metabolism of the (nonbeating) heart has been side stepped in this presentation. It needs elucidation. Is it constant or is it a variable fraction of the total metabolism? The oxygen cost-accounting scheme that we have thus far employed permits only an extra-
polated estimation of the resting metabolism, and employment of the actual nonbeating heart for this purpose is, in a sense, use of an artefact. It seems to us that this problem will be approached more closely when the cost accounting of the cardiac effort can be done on the basis of high-energy phosphate requirements rather than of oxygen. This may be true as well for the study of cardiac effort in terms of tension and external useful work.

We seem to be in a somewhat better position with regard to experimental design for further breakdown of oxygen cost. For example, it is possible to compare the oxygen cost of cardiac effort of increasing isovolumetric character, in which the external useful work declines and the development of tension increases, even to the point of preventing external useful work entirely. This is currently being investigated.

Finally, we are far from a detailed understanding of the relative importance of mechanical, neural and humoral factors in the interrelationship of oxygen consumption and cardiac effort, and of oxygen consumption and coronary flow. For example, what is the significance, if any, of extravascular pressures and of intravascular distending forces on the coronary vessels? Are they regulatory factors of blood flow, or factors that require adaptation of the existing regulatory mechanisms? Where and how do extracardiac neural impulses act on heart muscle and coronary vessels? In what way do they interact with local metabolic factors? These same questions can be asked regarding hormonal actions.

It would appear that, as is usually the case, more questions have been raised in this presentation than have been answered.

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We wish to take this opportunity to thank Drs. A. Gerola and A. M. Katz for their critical comments which were invaluable in preparing this manuscript.

Summary in Interlingua

Le autor exprime su spero que le observations presentate per ille ha contribuite al definition del problemas inherente in le energetica del corde. A parte le semper presente question del justification de supponer que resultatos experimental es valide pro completely intacte animales, le sequente questiones pare esser urgent e pare esser del typo que pote esser attaccate in un systema del genere descripte.

Le uso del metabolismo de oxygeno como indice del production de energia, sin reguardo al typo de substrato que es metabolisate, as justificate si le objectivo es un prime approximation. Studios concernite con altere metabolitos debe esser effectuate in le corde pulsante in sito que executa un labor de magnitude mesurabile. Alora il es possibile studiar le influentia del substrato super le consumption de oxygeno e le effecto del effortio cardiac super iste relation sub conditiones simile a illos que existe in animales intacte.

In le presente articulo, le vexante question del si-appellate metabolismo de reposo del (non-pulsante) corde ha essite negligite. Illo require elucidation. On volerea saper si illo es constant e o un fraction variabile del metabolismo total. Le schema del "constabilitate" de oxygeno, le qual no ha empleate usque nunc, permite solmente un extrapolate estimation del metabolismo de reposo, e le empleo del non-pulsante corde pro iste objectivo es, in un certe senso, le empleo de un artefacto. Nos opina que iste problema pote esser attaccate plus directemente quando le "contabilitate" del effortio cardiac pote esser effectuate super le base del requirimentos de phosphatos a alte energia plus tosto que super le base del consumption de oxygeno. Isto vale possiblemente etiam pro le studio del effortio cardiac quanto a tension e labor de utilize extrinsec.

Il pare que nostre position es elique plus favorabile con respecto al techniques experimental pro le detailiation additional del costo de oxygeno. Per exemplo, il es possibile comparar le costos de oxygeno in effortios cardiac a crescente character isovolumetric in que le labor de utilize extrinsec es reducete e in que le disveloppamento de tension es augmentate—possiblemente usque al puncto ubi illo preveni labor de utilize extrinsec.
completely. Iste question se trova currentemente sub investigation. 

Finalmente, nos nos trova ancora a un grande distanza ab le comprension detaliate del importantia relative de factores mechanic, neural, e humoral in le interrelation de consumption de oxygeno con effortio cardiac e de consumption de oxygeno con fluxo coronari. Per example, que es le signification, si un tal existe del toto, de pression vascular e de fortias distensive intravascular in le vasos coronari? Es illos factores regulatori in le fluxo de sanguine o factores que require le adaptation del existente mechanismos regulatori? Ubi e como age extra-cardiac impulsos neural super le musculo del corde e super le vasos coronari? In qual manera interage illos con local factores metabolic? E iste mesma questions pote esser ponite con respecto al actiones hormonal.

Il pare—e isto non esserea un phenomeno exceptional—que le problemas sublevate per iste presentation es plus numerose que le problemas solvite.

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