Influence of Coronary Flow upon Oxygen Consumption and Cardiac Performance

By Howard Weisberg, Ph.D., Louis N. Katz, M.D., and Eugene Boyd

Work of our department and of others has shown that the magnitude of coronary flow (CF) is determined primarily by the oxygen consumption of the heart (O2C) in such a manner that oxygen availability alters in a parallel fashion with O2C while oxygen extraction (O2E), within limits, remains constant. Two kinds of factors cause deviation of this relationship:

(A) Factors which independently change the caliber of the coronary vessels in the sense that they are specific coronary vasodilators. These include hypoxemia, hypercapnia, acidaemia, catecholamines, calcium, ouabain, as well as the spontaneous change occurring during periods of excessive stress.

(B) Changes in the mechanical factors controlling the perfusion pressure to the coronaries and in the duration of the phases of the cardiac cycle. All our work suggests that the metabolic factor determined by O2C is predominant. This has been illustrated by the influence of progressive hypoxemia where, until the hypoxemia becomes extreme, the CF rises to the extent, seemingly, of keeping oxygen availability commensurate with O2C.

The foregoing considerations are based on the presumption that it is O2C which determines CF, and not vice versa. Work by Gregg has suggested that the reverse may occur, i.e., augmentation of CF may also give rise to increase in O2C. The CF rises to the extent, seemingly, of keeping oxygen availability commensurate with O2C.

The possibility that it was mediated by an elevation of coronary pressure was not excluded. Since then we have had occasion to review some 11 experiments with this isovolumic preparation, some with and some without exhibition of ouabain. The results of our later findings are summarized in the present report.

Methods

Mongrel dogs (13 to 18 kg), anesthetized with 30 mg/kg sodium pentobarbital, were used in the eleven isovolumic preparations, a preparation in which the left ventricle ejects no blood. Each ventricle is bypassed by its own auxiliary pump. The azygos vein is tied off and the systemic venous return, through cannulae in the venae cavae, is pumped to a reservoir and then to the lungs of a donor-oxygenator dog (fig. 1) which receives a 95% O2 and 5% CO2 gas mixture from a demand valve positive pressure system. The oxygenated blood is returned to another reservoir, via a cannula in the left atrium of the donor dog, and then to the experimental animal by retrograde aortic perfusion, using a second pump of adjustable output. The volume of retrograde flow (cc/min) is adjusted to give a mean aortic pressure of 100 to 120 mm Hg at the start. This pressure range is sufficient to close the aortic valves, at the same time providing nourishment for the whole body including the myocardium. In this preparation CF is determined by the pressure, as influenced by the rate of input infusion, on the one hand, and by the vascular resistance existing...
in the systemic circuit and in the coronary bed, on the other; the latter depending upon changes in the durations of the phases of systole and upon direct actions on the smooth muscle tone (vasomotion) of the coronary vessels.

After complete heart bypass is established, a latex balloon attached to a polyethylene catheter is passed through the left atrium into the left ventricle. Bulging of the balloon into the atrium is prevented by passing ligatures behind the chordae tendineae of the mitral valve leaflets and closing the valve orifice around the neck of the balloon. The valve closure is slightly incomplete to permit exit of left ventricular Thebesian accumulation. The balloon is then filled with a measured volume of fluid while the pressures are monitored in the aorta and the balloon (left ventricle) circuit (fig. 1). The final volume in the balloon (7 to 20 cc), an amount which is below threshold for extrusion through the aortic valves, is kept constant during each experiment.

In this preparation the right atrium and ventricle are kept practically empty and therefore pump hypodynamically. They receive only coronary venous blood which is siphoned out through a cannula in the main pulmonary artery into the venous reservoir. The coronary venous flow is measured periodically (for 30 seconds) from the pulmonary artery outflow in a graduated cylinder.

The parameters observed in this series were: mean aortic blood pressure (BP), peak left ventricular pressure (PLVP), left ventricular pressure area (LVPA), coronary blood flow (CF), myocardial oxygen consumption (O2C), and oxygen extraction (O2E). Heart rate was used to calculate some of the above parameters per stroke. Hematocrits ranged from 39 to 46 (avg 43).

The average prevailing heart rate during these experiments was 125 beats/min (range 90 to 160).
Blood pressure and peak left ventricular pressure were measured simultaneously using Statham transducers and Sanborn recorders. Left ventricular pressure area was obtained by planimeter measurements of the left ventricular pressure curve; in one case the pressure area during systole (from the beginning to the peak of pressure) was also measured. Blood gas analyses were done according to the method of Van Slyke and Neill.24 Drugs were introduced through the aortic perfusion system and aortic input (A1) as well as aortic pressure changes were accomplished by adjusting the output of the aortic perfusion pump.

Results

In 9 of 11 experiments regression lines could be drawn relating O₂C and CF (fig. 2). In most of these (six out of nine), O₂C went up as CF was augmented. In two experiments, 11Y and 16I, it was found that increase of O₂C with augmentation of CF occurred only in the lower and not in the higher range of coronary flow. In one experiment, 19I, we found that O₂C did not change with CF during the first one-half hour but that when the experiment was repeated, after an interval of one-half hour, O₂C showed a rise with elevation of CF, even though the CF was in a higher range than in the previous experimental period. This unexpected result is attributed to deterioration of the preparation.6 It is our contention that when O₂C does not change with CF alteration then O₂C is CF independent. However, when O₂C varies with CF as the latter is changed, O₂C is CF dependent. The latter relationship is further revealed by the observation that O₂E remained constant, within narrow limits, in those instances where O₂C varied with CF change. On the other hand, O₂E declined as CF increased in those parts of the three experiments during which O₂C was CF independent.

Figure 2 shows a composite of experiments for which a reasonable single regression line, or pair of regression lines, could be constructed from the data. This figure shows that the curves of individual experiments are not superimposable even though adjusted for heart weight. This is understandable because, among other things, the ventricular end diastolic pressure and volume were not identical in the different experiments; because the part of the O₂C attributable to deterioration of the preparation6 was variable between preparations, and its rate of progress was also not the same; and because the velocity of heart muscle contraction13, 14 also differed from one preparation to another.

The next question we attempted to answer was whether or not this O₂C variation with CF change, when O₂C was CF dependent, was paralleled by a similar effect on the performance of the isovolumic left ventricle. This was first analyzed by determining the effect of CF/stroke upon the two indices of left ventricular pressure development (peak pressure and pressure area/stroke). By and large it was found that peak pressure gave as good results as pressure area.

In 5 of 11 experiments analyzed, no correlation between these two indices of performance of the heart and O₂C could be determined. These included the three experiments in which a pair of regression lines depicted the O₂C-CF relationship and one experiment, in which such a pair of regression lines depicted the relationship of CF/stroke to the performance parameter of peak left ventricular pressure (see below). However, when O₂C was CF dependent throughout an experiment, a good correlation was seen be-
CARDIAC OXYGEN CONSUMPTION

Relationship of peak left ventricular pressure to $O_2 C$ observed in six experiments, in each of which coronary flow was altered and heart size kept constant. In five of them $O_2 C$ was CF dependent throughout (fig. 2).

Between $O_2 C$ and a left ventricular performance parameter (figs. 2 and 3). This suggests that left ventricular performance exhibits a CF dependency when $O_2 C$ is similarly dependent, and further that good correlation between CF and $O_2 C$ is simply a measure of change in left ventricular performance caused by the induced variation in CF.

Because other factors besides the level of cardiac performance (as measured) affect $O_2 C$, we have compared CF/stroke vs. either peak left ventricular pressure or left ventricular pressure area. This is illustrated in figures 4 to 6. As expected, in a given experiment this correlation did not always coincide with that between $O_2 C$ and CF. In some experiments a regression line could be established between CF and $O_2 C$ but not between the parameters of left ventricular performance and CF, and vice versa. In others, the regression lines with CF could be identified both for $O_2 C$ and for the parameter of left ventricular performance and yet the regression lines were different. Attention is drawn especially to experiments 11Y and 16I in which left ventricular performance was CF independent throughout while $O_2 C$ was CF dependent at lower coronary flows and independent at higher coronary flows.

In figure 6 not only is there a straight line relationship of CF/stroke with total pressure area but also with the pressure area during systole, the two curves being parallel with the latter lower than the former, as expected. Because of the result in this experiment we have not computed the systolic portion of the area of the ventricular pressure curves in the other experiments.

Finally, the fact that only in a few instances was there a difference between the relation of CF to left ventricular peak pressure as compared to its relation to pressure area shows that the contour of the left ventricular pressure curve was not strikingly altered as CF was changed and that the duration of pressure development paralleled the change in peak pressure.

Discussion

It must be borne in mind that in these experiments with this isovolumic left ventricular preparation CF was the only planned variable introduced, and that the end diastolic volume and pressure of the isovolumic left ventricle were kept constant during any single experiment. Under these circumstances, and depending upon the conditions of the experiment and the levels of CF induced, $O_2 C$ was found to be either CF dependent or CF independent. In a few instances both phases, i.e., a CF dependent and a CF independent phase, could be demonstrated in a single preparation. The level of $O_2 C$/100 g heart wt and the rate of change with CF was variable from experiment to experiment, as was
also the turning point at which a change from CF dependency to CF independence occurred. When O₂C is CF dependent, the O₂C change is associated with a like change in the development of pressure and therefore with a change in the performance of the heart. This occurred despite the constancy of the end diastolic pressure and volume of the ventricle. That such parallelism between cardiac performance and O₂C did not occur in every experiment is not surprising because O₂C is determined not only by the level of cardiac performance as measured, but by other factors also: a) The heart may obtain some of the energy for its performance from substrates passing to it from the blood and this may modify O₂C independently of its performance, to varying degrees. b) The need for O₂C to maintain the architecture of the heart is variable. c) It is possible that a degree of O₂ debt, having developed in a deteriorating preparation, can be dissipated to varying extent by improvement of the coronary flow. d) There is an O₂C difference with disparities in the rate of pressure development during systole. Despite these variables, one can conclude that when O₂C is CF dependent it is primarily, but not exclusively, determined by the alterations induced in cardiac performance.

In previous work we have found that O₂E remains constant, within limits, when the metabolic factor controlling CF is predominant. However, whenever coronary resistance is changed by a direct alteration of the caliber of the coronary vessels or by changes in the duration of the phases of systole, O₂E deviates from its usual level. In this preparation we found that O₂E remained constant within narrow limits as CF was altered only in the CF dependent stage. Contrariwise in the CF independent phase, in which O₂C remained constant as CF changed, O₂E changed in the direction opposite to CF.

Extrapolating our results to the intact animal (and man), it is our tentative conclusion that under ordinary circumstances in the intact animal the presence of a fixed relationship between CF and O₂C is due to the fact that CF is predominantly controlled by the metabolic activity of the heart, as indicated by its O₂C. Only when CF becomes sufficiently inadequate for the energy needs of the heart, as determined by the level of performance or by factors which independently restrict CF, does one obtain the reverse situation in which it is CF which determines O₂C and not vice versa.

Several obvious conditions in abnormal
CARDIAC OXYGEN CONSUMPTION

527

physiology which can be encountered at the bedside come to mind, in which $O_2C$ and cardiac performance would become CF dependent. One is excessive hypoxemia in which $O_2$ availability becomes very limited. Another is anatomical narrowing or obstruction of the coronary channels, as is found in ischemic heart disease. Here the ischemia to local regions of the heart, or to the entire heart, may make $O_2C$ and performance of the heart CF dependent. The corollary to this is that any procedure which improves coronary flow, whether mechanical or pharmacological, and hopefully in the future corrective coronary vascular surgery, obviously will permit, per se, the heart to increase its performance and its $O_2C$. When the performance of the heart is not CF dependent, these procedures would seemingly have no utility unless considered as prophylactic measures to prevent the heart from getting into that range of CF where its performance would become CF dependent. Our recent experience reported here shows that the physiological facts and the relation between $O_2C$ and CF are more complex than our previous work had indicated. In conclusion, it appears that CF under certain circumstances can affect the performance of the heart and its $O_2C$.

Summary

The influence of induced changes in coronary flow upon oxygen consumption and cardiac performance were observed in the in situ isovolumic left ventricle. This preparation was established with auxiliary pumps which bypass the dog’s right and left heart and by inserting a balloon into the left ventricle so that the latter ejected no blood. Coronary flow was set or varied by a retrograde aortic perfusion pump. Oxygen consumption of the heart was found to be coronary flow dependent or independent, according to the conditions of the experiment. When it is coronary flow dependent there is usually a similar relationship between coronary flow and cardiac performance. In a single preparation, it was sometimes found that cardiac oxygen consumption was coronary flow dependent at lower rates of coronary flow and independent at higher flow rates. Possible explanations and clinical applications are given.

Acknowledgment

We appreciate the technical assistance Mrs. Alice Bremley has rendered.

References

13. **Feinberg, H., Boyd, E., and Katz, L. N.:**
Calcium effect on performance of the heart.

14. **Göksel, F., Katz, L. N., and Feinberg, H.:**
Effect of ouabain on coronary flow, performance of heart and its oxidative metabolism.

15. **Katz, A. M., Katz, L. N., and Williams, F. L.:**

16. **Katz, L. N., Göksel, F. M., Feinberg, H., and Boyd, E.:**

17. **Laurent, D., Bolken-Williams, C., Williams, F. L., and Katz, L. N.:**

18. **Anrep, C. V., and King, B.:**

19. **Cross, C. E., Rieben, P. A., and Salisburey, P. F.:**

20. **Katz, L. N.:**
Analysis of the several factors regulating the performance of the heart. *Physiol. Rev.* 35: 90, 1955.

21. **Katz, L. N., and Feinberg, H.:**

22. **Sarnoff, S. J., Braunwald, E., Welch, G. H., Jr., Cash, R. B., Steinsby, W. N., and Marcus, R.:**

23. **Gregg, D. E.:**

24. **Van Slyke, D. D., and Neill, J. M.:**

25. **Lendrum, B., Feinberg, H., and Katz, L. N.:**
The oxygen consumed and pressure developed by the dog's left ventricle at different end-diastolic volumes. *Acta Cardiol.* 16: 487, 1961.

26. **Coffman, J. D., and Gregg, D. E.:**

27. **Katz, L. N., Katz, A. M., and Williams, F. L.:**
Influence of Coronary Flow upon Oxygen Consumption and Cardiac Performance
Howard Weisberg, Louis N. Katz and Eugene Boyd

Circ Res. 1963;13:522-528
doi: 10.1161/01.RES.13.6.522

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1963 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/13/6/522

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/