Effect of Alterations of Coronary Blood Flow on the Oxygen Consumption of the Nonworking Heart

By Richard L. Kahler, M.D., Eugene Braunwald, M.D., Leslie L. Kelminson, M.D., Laurence Kedes, M.D., Charles A. Chidsey, M.D., and Stanton Segal, M.D.

Elucidation of the determinants of myocardial oxygen consumption (MV\textsubscript{o}) has been the subject of intensive investigation since the beginning of this century.\textsuperscript{1,2} It has been appreciated for many years that changes in cardiac performance are capable of influencing the MV\textsubscript{o} profoundly, and a considerable number of experiments have been concerned with the elucidation of the manner in which the heart's mechanical activity modifies its MV\textsubscript{o}. Among the variables which have been considered to be intimately related to the heart's energy requirements have been the ventricular end diastolic fiber length,\textsuperscript{3-5} the heart's external work,\textsuperscript{1-6,7} the heart rate,\textsuperscript{8-12} the tension-time index, i.e., the area beneath the systolic portion of the ventricular pressure pulse,\textsuperscript{13} and the product of heart rate and mean aortic pressure.\textsuperscript{14} In many experiments a close correlation between MV\textsubscript{o} and coronary blood flow has been demonstrated and it has been concluded that the heart's metabolic rate plays a dominant role in the control of coronary blood flow.

A number of investigators, working with a variety of skeletal muscle preparations, have suggested the possibility that, within limits, the muscle's oxygen consumption may depend on its blood flow.\textsuperscript{16-21} Gregg and his co-workers have presented preliminary evidence that alterations of coronary blood flow (CBF), for periods lasting up to 60 seconds, are accompanied by directionally similar changes in MV\textsubscript{o}.\textsuperscript{22,23} The purpose of the experiments described in this report was to determine whether sustained changes in CBF affect the MV\textsubscript{o} of a nonworking heart in which the mechanical activity is maintained at a constant level.

Methods

Two experimental preparations were employed to carry out the total of 23 experiments in 21 animals. In the first preparation the animals were maintained on total cardiopulmonary bypass, while the heart was hemodynamically isolated from the remainder of the circulation and perfused separately. The second preparation, utilized in 14 experiments, was identical to the first except that only an isolated heart was perfused. All of the experimental animals were premedicated with morphine sulfate (2 mg/kg sc) and were anesthetized 30 minutes later with an intravenous injection of chloralose (45 mg/kg) and urethane (450 mg/kg). Respiration was maintained with a Harvard pump through an endotracheal tube prior to the establishment of the extracorporeal circuit. Through a midline sternum-splitting incision the mediastinum and both pleural cavities were opened and the aorta and arch vessels were freed. Both venae cavae were isolated, the azygous vein was ligated and the main pulmonary artery was dissected free.

In preparation no. 1 large bore cannulae placed into the venae cavae drained venous blood into a rotating disc oxygenator, which was supplied by a gas mixture consisting of 96% O\textsubscript{2} and 4% CO\textsubscript{2}. The oxygenated blood was pumped with a roller pump, at a rate of 100 ml/kg/min, through a recording rotameter,\textsuperscript{24} into the cannulated femoral and distal brachiocephalic arteries. A second perfusion cannula was then placed into the left subclavian artery and directed toward the aortic arch (fig. 1). A large bore cannula was placed into the right ventricle through the right atrium or the pulmonary artery, and the main pulmonary artery was ligated. The aorta was then clamped just distal to the left subclavian artery, the brachi-
FIGURE 1
Schematic diagram of the canine heart preparation utilized to study the effects of coronary blood flow on myocardial oxygen consumption. Arterial blood is pumped by the "coronary pump" through a rotameter into the left subclavian artery (L.S.A.). The aorta is clamped just below the L.S.A. Aortic pressure is measured by means of a catheter inserted via the brachiocephalic artery (B.C.A.). The left ventricle (L.V.) is drained. Temperature is monitored by means of a thermistor inserted into the right ventricle (R.V.) through the right atrium (R.A.) appendage. Temperature is held constant by means of the heat exchanger. The pulmonary artery (P.A.) is ligated around a catheter inserted into the right ventricle (R.V.) for the measurement of pressure. A large multi-holed cannula is inserted through the azygous vein, the right atrium (R.A.) into the right ventricle. The coronary venous return is drained through this cannula into a graduated cylinder. Hematocrits ranged from 33 to 41 (avg 38).

In general, two pairs of arterial and coronary venous blood samples were obtained at each level of CBF. Following each change of blood flow a ten- to twenty-minute-period elapsed prior to sampling to assure a steady state and valid application of the Fick principle. The direction of change of CBF was randomized; in some experiments the first level was lowest and it was subsequently increased, while in other experiments the first level was high and it was then lowered. The specific manner in which each experiment was performed is shown in tables 1 and 2. Blood oxygen content was determined in duplicate on each sample by the method of Van Slyke and Neill. MVO₂ was calculated as the product of CBF and coronary arteriovenous oxygen difference. For most experimental points the averages of two determinations of MVO₂ made one to two minutes apart are presented in tables 1 and 2. The standard deviation of the differences between the duplicate measurements of MVO₂ equaled ±0.27 ml O₂/min. In five experiments the catecholamine concentrations in the blood perfusing the heart were determined by a fluorometric technic described elsewhere. In order to reduce the circulating catecholamine levels, bilateral adrenalectomy was carried out in the experimental animals and the dogs used as blood donors in three experiments. The animals were maintained with parenteral cortisone for the several days between adrenalectomy and the experiment.
Results

OBSERVATIONS IN HEARTS OF DOGS WITH A COMPLETE CIRCULATION

MV₀₂ was measured at two levels of CBF in three experiments, it was measured at three levels of CBF in one experiment, at four levels of CBF in four experiments, and at five levels of CBF in one experiment. In the total of nine experiments the effect of a stepwise change of CBF on the MV₀₂ could be determined in 21 instances. A higher level of CBF was associated with a distinctly higher value for MV₀₂ in 16 of these 21 changes in CBF. In three instances (Expts. no. 9, 11, and 13) MV₀₂ showed no change with an increase in CBF. In two instances an increase in CBF was accompanied by a decline of MV₀₂ (fig. 2, table 1). The relationship between the O₂ delivered to the myocardium per minute (CBF × arterial O₂ content) and MV₀₂ is shown in figure 3, and is quite similar to the relationship between CBF and MV₀₂ (fig. 2).

In all of these experiments the coronary venous O₂ content exceeded 4 vol % and the

| TABLE 1 |
|---------------------|---------------------|---------------------|---------------------|---------------------|
| Heart in Dog with Complete Circulation |
| Expt. no. | Heart wt. g | Determination no. | Cor. perf. press. mm Hg | Art. O₂ content | Ven. O₂ content | A-V O₂ difference | Coronary blood flow ml/min | MV₀₂ | O₂ delivery | O₂ extraction % |
| 6* | 143 | 1 | 25 | 10.31 | 4.00 | 6.31 | 40.0 | 2.49 | 4.1 | 60 |
| 7* | 158 | 1 | 45 | 16.95 | 10.00 | 6.95 | 55.5 | 3.86 | 9.4 | 41 |
| 7† | 150 | 1 | 34 | 18.62 | 12.80 | 5.82 | 108.0 | 6.29 | 20.1 | 31 |
| 9* | 169 | 1 | 39 | 14.60 | 6.75 | 7.85 | 46.0 | 3.61 | 6.7 | 54 |
| 10* | 145 | 1 | 47 | 15.21 | 8.37 | 6.84 | 78.0 | 5.34 | 11.9 | 45 |
| 11† | 145 | 3 | 76 | 16.80 | 13.06 | 3.74 | 156.0 | 5.83 | 26.2 | 22 |
| 13* | 208 | 1 | 17 | 16.59 | 8.33 | 8.26 | 154.0 | 5.76 | 16.4 | 32 |
| 14† | 187 | 1 | 71 | 13.34 | 8.25 | 5.09 | 113.5 | 5.78 | 15.1 | 38 |

*= Paced.
†= Ventricular fibrillation.
†= Result of a single determination.
§= Average of three determinations.
All other determinations were done in duplicate.
Cor. perf. press. = Mean coronary perfusion pressure.

Circulation Research, Volume XIII, December 1958
myocardial O₂ extraction, expressed as a percentage, was less than 75% (fig. 4, table 1). In any given experiment the higher levels of CBF and of myocardial O₂ delivery were associated with lower values of coronary arteriovenous O₂ difference, of the percentage of O₂ extracted from the arterial blood and with elevations of the coronary venous O₂ content. In all instances in which the myo-

\[
\frac{A-V}{A} \cdot 100
\]
OXYGEN CONSUMPTION OF NONWORKING HEART

Relationship between coronary blood flow (CBF) and myocardial oxygen consumption ($M\text{V}_O_2$) in the hearts of dogs which were maintained on cardiopulmonary bypass. In this, as in the subsequent figures, the solid lines join the points obtained in experiments in which the ventricular rate was maintained constant with an electrical pacemaker, while the broken lines join the points obtained in experiments in which the ventricles were fibrillating.

Cardiac $O_2$ extraction, at the lower level of CBF, ranged between 53% and 75%, an increase of CBF was accompanied by an elevation of $M\text{V}_O_2$. In the two instances in which $M\text{V}_O_2$ fell as CBF was raised, the $O_2$ extractions at the higher levels of CBF were only 20% and 22%, the lowest values observed in these experiments. In the three instances in which $M\text{V}_O_2$ remained constant in spite of an elevation of CBF, the $O_2$ extractions, at the higher levels of CBF, were 23%, 30%, and 34% (fig. 4, table 1).

Ventricular fibrillation was present in four of these experiments, while the hearts were paced in the five other experiments. One animal (no. 7) was studied both during ventricular fibrillation and at a constant heart rate. No differences between the results in these two groups of experiments were apparent (figs. 2 to 4, table 1).

OBSERVATIONS IN ISOLATED HEARTS

$M\text{V}_O_2$ was measured at two levels of CBF in nine experiments, at three levels of CBF in three experiments and at four levels of CBF in two experiments. Thus, in the total of 14 experiments, the effects of a stepwise change in CBF on $M\text{V}_O_2$ could be determined in 21 instances. In 16 instances the higher levels of CBF and of $O_2$ delivery were associated with higher levels of $M\text{V}_O_2$. In two instances (Expts. no. 18 and 23), the higher values of CBF and $O_2$ delivery were associ-
ated with lower values of \( M_V^0 \) (figs. 5 and 6, table 2). In three instances (Expts. no. 18, 21, and 23) \( M_V^0 \) showed no change with an increase of CBF. In all of the experiments on the isolated hearts the coronary venous \( O_2 \) content exceeded 4 vol % and the myocardial \( O_2 \) extraction was below 78%. As was observed in the experiments in dogs with a complete circulation, a fall or no change in \( M_V^0 \) occurred as CBF was raised only when the levels of myocardial \( O_2 \) extraction were extremely low (table 2). In the two instances in which \( M_V^0 \) fell as CBF was raised, the \( O_2 \) extractions at the higher levels of CBF were only 17% and 20%. In the three instances in which \( M_V^0 \) remained constant in spite of an elevation of CBF, the \( O_2 \) extractions at the higher levels of CBF were only 12%, 14%, and 18%. In all instances in which the myocardial \( O_2 \) extraction at the lower level of CBF exceeded 40% an increase of CBF was accompanied by an elevation of \( M_V^0 \).

Ventricular fibrillation was present in four of these experiments, and the hearts were paced in the other 10 experiments. One animal (no. 22) was studied both during ventricular fibrillation and at a constant heart rate. No differences between the results in these two groups of experiments were apparent.

The concentrations of circulating catecholamines in the blood perfusing the isolated heart were measured in two of the seven experiments performed on the dogs which had not been adrenalectomized. The concentrations of both norepinephrine (1.52 \( \mu \)g/liter and 1.20 \( \mu \)g/liter) and of epinephrine (5.57 \( \mu \)g/liter and 8.43 \( \mu \)g/liter) were markedly elevated in both experiments. Measurements of blood catecholamines were also carried out in three of the seven experimental preparations (Expts. no. 17, 21, and 23) in which both the donor and experimental animals had undergone adrenalectomy. The norepinephrine levels in these preparations were 0.39, 0.60, and 0.62 \( \mu \)g/liter, while the epinephrine levels were 0.05, 0.00, and 0.07 \( \mu \)g/liter. The relationships between CBF and \( M_V^0 \) were not altered by previous adrenalectomy (table 2).

**Discussion**

In the majority of previous studies on the relationships between CBF and \( M_V^0 \), the mechanical activity of the heart has been altered and the effect on \( M_V^0 \) determined. In the present series of experiments this relationship was examined from a different...
OXYGEN CONSUMPTION OF NONWORKING HEART

Aspect. An attempt was made to maintain the mechanical activity of the nonworking heart at a constant level while changes in CBF and in the O₂ delivery to the myocardium were produced and the effects on MV₉₀ were determined. It was observed that, in any given heart, the higher levels of CBF were usually associated with higher levels of MV₉₀. The exceptions noted occurred in experiments in which the O₂ delivery was already so high in relation to the MV₀₉₀ that the myocardial O₂ extraction was at extremely low, unphysiological levels.

The extraction of O₂ by the myocardium is greater than by other organs and it is apparent that if the O₂ delivery is so low that its extraction is almost complete and myocardial anoxia is induced, an increase of O₂ delivery would certainly be expected to be accompanied by an increase of MV₀₉₀. In the present experiments care was taken to avoid such low levels of O₂ delivery and all of the observations were carried out at levels of myocardial O₂ extraction which are similar to, or lower than, those occurring spontaneously in the closed-chest, anesthetized dog breathing room air. Other investigators have found average values of the coronary sinus O₂ content in such preparations of 3.3 vol %, 27 2.9 vol %, 28 and 6.5 vol %, 29 with average myocardial O₂ extraction ratios of 83%, 27 82%, 28 and 62%. 29 In the experiments reported herein the coronary venous O₂ contents were not permitted to fall below 4 vol % and myocardial O₂ extraction to rise above 78%. Indeed, most of the observations were carried out with coronary venous O₂ levels which were substantially higher, and myocardial O₂ extraction ratios which were substantially lower than these values (tables 1 and 2, fig. 4). Nonetheless, the possibility of cellular hypoxia at the lower levels of CBF employed in these experiments cannot be completely excluded.

The relationship between MV₀₉₀ and CBF was noted under a variety of experimental conditions. The correlation was observed in isolated hearts as well as in the hearts of dogs maintained on total cardiopulmonary bypass. Since the blood utilized for these experiments was obtained by total exsanguination of donor dogs, the circulating catecholamine content of the blood was, as anticipated, markedly elevated. This experimental complication was obviated in seven experiments on the isolated heart preparation by subjecting both the experimental and donor animals to prior adrenalectomy, but this maneuver did not appear to alter the results. Hence, augmented delivery of catecholamines to the myocardium could be largely eliminated as a factor contributing to the increased MV₀₉₀ observed during elevation of CBF. However, it is conceivable that increasing the delivery to the heart of a substance, which stimulates MV₀₉₀ other than a catecholamine, could have been responsible for the observed relationship between CBF and MV₀₉₀. Since the O₂ content of the coronary arterial blood was held constant, the delivery of O₂ to the myocardium and the coronary arterial blood pressure varied directly with the CBF. From the data at hand, it cannot be determined whether, under the conditions of these experiments, MV₀₉₀ is dependent on CBF, on myocardial O₂ delivery, on coronary vascular pressure, or on some combination of these variables.

In the majority of experiments the heart was paced electrically at a constant rate. The drainage cannulae in both ventricles maintained the intracavitary pressure at or near 0 mm Hg, kept the ventricular cavities collapsed, and thus prevented the heart from performing any external work. The relationship between MV₀₉₀ and CBF was also observed in eight experiments, four utilizing each preparation, in which the ventricles were fibrillating rather than contracting rhythmically. Despite the absence of external work some contractile activity persisted in all of the experiments, and the possibility must be considered that changes in coronary perfusion pressure and coronary blood flow altered the length of the myocardial fibers and in this or some other manner modified their force of contraction, thereby altering their O₂
requirements. Similarly, variations in coronary perfusion pressure could have resulted in varying amounts of myocardial edema, which in turn could have altered the mechanical activities of the myocardial fibers.

Heisey studied the effects of changing Wood flow on the V\textsubscript{O\textsubscript{2}} of resting mammalian skeletal muscle, and observed a significant positive correlation between blood flow and V\textsubscript{O\textsubscript{2}} in 20 of 37 dogs. He considered the possibility that this relationship could be explained by the changes in the capillary surface through which in turn could have altered the mechanical activities of the myocardial fibers.

It is possible that in the myocardium as well, the perfusion of additional vascular channels and/or the alterations in distribution of O\textsubscript{2} pressure might account for the influence of CBF on MV\textsubscript{O\textsubscript{2}}. Finally, it is possible that small changes in the quantity of O\textsubscript{2} attached to myocardial myoglobin occurred as CBF was altered and thereby affected the heart’s uptake of O\textsubscript{2}.

Thus, while under the conditions of these experiments, the MV\textsubscript{O\textsubscript{2}} of the nonworking heart was altered as the CBF was changed, the fundamental mechanisms responsible for this finding still await clarification.

Summary

The effect of varying CBF and myocardial O\textsubscript{2} delivery on MV\textsubscript{O\textsubscript{2}} was studied in 23 experiments. In 14 of the experiments an isolated dog heart was perfused, while in the others the heart of a dog, whose systemic circulation was maintained on cardiopulmonary bypass, was studied. The ventricles were kept empty, developed no pressure and performed no external work, while their temperature was held constant. CBF and myocardial O\textsubscript{2} delivery were controlled by pumping blood into the coronary arteries, total coronary venous return was collected from the right side of the heart and MV\textsubscript{O\textsubscript{2}} was calculated during a steady state by the Fick principle. Myocardial anoxia was avoided by maintaining the coronary venous O\textsubscript{2} content above 4 vol % and myocardial O\textsubscript{2} extraction below 78%.

A comparison of MV\textsubscript{O\textsubscript{2}} at two levels of CBF (and O\textsubscript{2} delivery) was made in 42 instances, and in 32 of them MV\textsubscript{O\textsubscript{2}} increased substantially as CBF was elevated, or vice versa. The ten exceptions all occurred when O\textsubscript{2} delivery greatly exceeded MV\textsubscript{O\textsubscript{2}}, with O\textsubscript{2} extraction ratios below 35%. The fundamental mechanisms responsible for these findings are not clear, but a number of possible explanations are discussed.

References

5. DECKER, G., AND VISSCHER, M. B.: The relative importance of the performance of work and the initial fiber length in determining the magnitude of energy liberation in the heart. Am. J. Physiol. 103: 400, 1933.
OXYGEN CONSUMPTION OF NONWORKING HEART


Effect of Alterations of Coronary Blood Flow on the Oxygen Consumption of the Nonworking Heart
Richard L. Kahler, Eugene Braunwald, Leslie L. Kelminson, Laurence Kedes, Charles A. Chidsey and Stanton Segal

Circ Res. 1963;13:501-509
doi: 10.1161/01.RES.13.6.501

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/13/6/501

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/