Effect of Exercise and Coronary Artery Narrowing on Coronary Collateral Circulation

By RICHARD W. ECKSTEIN, M.D.

The effect of chronic coronary arterial narrowing on the coronary collateral circulation has been studied in rested and exercised dogs. The data indicate that moderate and severe arterial narrowing results in extensive collateral development proportional to the degree of narrowing, further that exercise leads to even greater anastomoses. The results also show that while mild arterial narrowing fails to initiate collateral growth by itself, the addition of exercise promotes an effective collateral circulation. An attempt is made to define the gross factors in the development of collateral vessels and to correlate them with the concept that exercise may play a beneficial role in building collateral vessels in patients with coronary disease.

EXERCISE may favorably affect the course of coronary artery disease by one or more of several means. It may actually delay the progression of the disease, or it may stimulate the growth of coronary collateral vessels during the disease process, or both. This report is based on a study of the effect of exercise on the growth of coronary arterial anastomoses in hearts previously prepared so as to resemble the situations found in various stages of human coronary disease.

METHODS

Dogs were anesthetized with morphine and pentobarbital, venous blood samples were drawn for determination of hemoglobin concentration and relative viscosity in vitro, and intermittent positive pressure respiration was instituted through an intratracheal tube. The left chest was opened under aseptic conditions and the circumflex artery was isolated near its origin. A no. 1 braided silk ligature was passed beneath the artery and tied over a probe held parallel with and external to the vessel. Various degrees of narrowing were effected in different dogs with probes whose diameters ranged from 0.75 to 1.3 mm. After the ligature was tied and before the probe was removed an electrocardiogram was recorded from lead A VR. Only animals which developed T-wave inversion and S-T segment depression were accepted. After such assurance that pre-existing collateral vessels were absent,1 the probe was removed and a return of the T-wave and S-T segment to normal or near normal indicated patency of the narrowed vessel. If the electrocardiogram indicated marked ischemic changes the ligature was removed and reapplied more loosely. The chest was then closed, air was evacuated from the pleural cavity, and penicillin was given for the following 3 days.

The 117 operated dogs were divided into two groups, both being kept at rest for one week to allow healing to occur. One group was then exercised on a treadmill placed at a positive incline of 30°. During the first week the speed was gradually increased to a rate of from 3.2 to 4.7 m.p.h. The animals were exercised from 15 to 20 min., 4 times daily, 5 days weekly for 6 to 8 weeks. During this period the second group remained at rest in cages.

The extent of arterial anastomoses to the circumflex arteries of both groups was then determined as follows: Dogs were anesthetized with morphine and pentobarbital. A venous sample was drawn for hemoglobin and relative viscosity determinations. The left common carotid artery was isolated, punctured with a large bore needle, and mean arterial pressure was measured by a mercury manometer. Intermittent positive pressure respiration was instituted through an intratracheal tube. After the left chest had been entered between the fifth and sixth ribs, the circumflex artery was isolated beyond the constricting ligature. Heparin was given and a cannula was inserted through the left common carotid artery to the level of the aorta and connected to a mercury manometer to record mean arterial pressure. Arterial blood was directed from the carotid cannula into a cannula inserted into the peripheral circumflex artery. A second cannula was directed centrally toward the constricting ligature (fig. 1). Both cannulae were connected to clamped rubber tubing (F and G), the distal ends of which were held at the level of the heart.

The mean aortic pressure was set (by bleeding or aortic constriction) to the level existing after anesthesia but before the institution of artificial respiration. Tube (G) was unclamped and the volume of blood passing through the constricted segment was...
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FIG. 1. Diagram of Experimental design. A. Left anterior descending artery.  B. Narrowed left circumflex artery. C. Circumflex artery cannulated to measure flow through narrowed segment. D. Distal circumflex artery cannulated to measure retrograde circumflex flow and to perfuse myocardium from left common carotid artery. E. Rubber tubing connected to cannula in carotid artery. F. Tubing with outlet held at level of heart to measure retrograde flow. G. Tubing with outlet held at level of heart to measure flow through narrowed circumflex. H. and I. Graduated cylinders.

measured in a graduated cylinder. This is a more reliable estimate of the functional size of the constricted segment than is a direct measurement with a probe after death, since resistance to flow is a function of both the diameter and the length of the segment.* At best a probe can only measure the diameter.

The mean aortic pressure was then adjusted to 100 mm. Hg and tube E was clamped and tube F opened. The volume of retrograde circumflex flow was thus measured. In view of the excellent correlations between the volume of retrograde flow and anastomoses demonstrable by injection technics,* it is believed that these present flows are proportional to the extent of the anatomic development of the collateral vascular bed. The maximum flow attained after several measurements during 30 sec. periods was recorded. This insured maximum collateral expansion as a result of myocardial hypoxia. Tube F was then clamped. An electrocardiogram was taken during this period of complete circumflex occlusion to test the functional significance of the collateral circulation. A second mercury manometer was con-

* Actually the present measurements probably underestimate the lumen size. Experiments in which the flows were measured against a pressure of 90 mm. Hg distal to the constriction (A, P, 100 mm. Hg) showed a flow reduction of 66 to 75 per cent in contrast to the expected reduction of 90 per cent. Presumably high peripheral pressures increase the size of the constricted lumen or minimize the effects of eddies which may operate to reduce the flow into a vessel whose walls are less distended.

nected to a side arm on the peripheral circumflex cannula and the peripheral coronary pressure was measured for purposes of comparison with retrograde flow values and electrocardiographic findings.

In an effort to study the effects of chronic vascular narrowing on the coronary inflow and on the pressure relationships between arteries, additional flow measurements were made. Aortic pressure was returned to and maintained at the level which was measured immediately after anesthesia. Coronary flow through the constricted artery into the peripheral artery was measured by a recording rotameter connected between the two circumflex canulæ. In addition, the narrowed segment could be by-passed through a direct connection between the left common carotid artery and the rotameter, so that unrestricted circumflex inflow could be measured. The pressure drop due to the rotameter was calculated by subtracting the pressure indicated on the distal manom-eter from that shown on the central manometer during metering of flow through the by-pass. Subtraction of this instrumental pressure loss from that measured during metering of the flow through the narrowed segment indicated the pressure drop induced by the narrowing itself. This approximates the pressure difference between the constricted circumflex artery and both the right and left anterior descending arteries. In an effort to study the changes in these indices during exercise its augmentary effects on coronary flow were simulated by the effects of myocardial ischemia produced by bleeding the peripheral circumflex artery for a period of 1 min.

After death of the animal, dilute india ink was injected into the distal circumflex artery and the stained area of myocardium was cut out and weighed. The flow through the narrowed segment against 0 pressure, retrograde flow, coronary flow through the narrowed segment, and coronary flow through the by-pass were expressed as ml./min./100 Gm. of myocardium. Most of the hearts were sectioned and examined microscopically.

The immediate effects of vascular constriction on coronary flow and pressure differential were studied in 6 acute experiments. Thirty-four different degrees of constriction were produced and measurements of the effects of each were made on: (a) flow through the ligature against 0 pressure, (b) the per cent reduction in coronary flow, and (c) the pressure drop created by each of the ligatures.

Results

Of 117 operated dogs 12 died as a result of operation and 6 died of distemper. Three animals developed anemia with hemoglobin concentrations of less than 12.4 Gm. per cent (80 per cent of normal) and were discarded. Gross infarcts were found in 2 exercised dogs and these were not included because of the loss of
Table 1.—Mean Values of Noneexperimental Variables in Each Group

<table>
<thead>
<tr>
<th>Final dog weight (Kg.)</th>
<th>Heart weight (Gm.)</th>
<th>Heart weight/Dog weight</th>
<th>Injected circumflex area (wt./Gm.)</th>
<th>Circumflex weight/Heart weight</th>
<th>Relative blood viscosity</th>
<th>Hemoglobin (g)</th>
<th>Mean aortic pressure (mm/Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rested</td>
<td>15.3</td>
<td>.81</td>
<td>46</td>
<td>.37</td>
<td>5.4</td>
<td>107</td>
<td>116.5</td>
</tr>
<tr>
<td>Exercised</td>
<td>15.6</td>
<td>.84</td>
<td>45</td>
<td>.36</td>
<td>4.9</td>
<td>103</td>
<td>119.5</td>
</tr>
</tbody>
</table>

Figure 2. Shows magnitude of retrograde flow with different degrees of circumflex narrowing in rested and exercised dogs. Ordinate, retrograde flow; abscissa, flow through constricted coronary vessel. Both flows calculated as ml./min./100 Gm. heart muscle.

unknown amounts of muscle mass. Satisfactory measurements were not obtained in 3 animals due to technical difficulties. One death occurred on the treadmill and whether this was due to coronary insufficiency could not be ascertained. The rigid requirements of these experiments were met by 90 dogs (46 rested and 44 exercised). The exercised animals lost some weight (average 0.8 Kg.) while the rested dogs gained (average 0.2 Kg.) during the experimental period. Table 1 shows the mean values of the important noneperimental variables of the 2 groups. It is clear that the groups are similar.

Fifty-nine representative hearts were examined microscopically. Five hearts of the exercised animals and 2 of the rested animals revealed foci of myocardial atrophy and replacement fibrosis. The circumflex narrowing was moderate to severe in 3 animals due to technical difficulties. One death occurred on the treadmill and whether this was due to coronary insufficiency could not be ascertained. The rigid requirements of these experiments were met by 90 dogs (46 rested and 44 exercised). The exercised animals lost some weight (average 0.8 Kg.) while the rested dogs gained (average 0.2 Kg.) during the experimental period. Table 1 shows the mean values of the important noneperimental variables of the 2 groups. It is clear that the groups are similar.

In 9 of the 50 hearts the ratio of wall thickness to lumen diameter appeared to be substantially increased in occasional intramural arteries. In some the apparent increase was medial, in some intimal, and in some instances both layers participated. It could not be determined whether in specimens showing medial thickening alone the process represented a true hypertrophy or only an apparent increase due to vasoconstriction. Intimal thickening was unquestionably associated with an increase in cellular components.

Figure 2 is a plot showing the magnitude of retrograde flow resulting from different degrees of circumflex narrowing in rested and exercised dogs. The retrograde flows are measures of collateral function, and the flows through the ligatures are measures of the degree of circumflex constriction. Animals with severe constrictions are on the left while those with mild constrictions are on the right. In general the extent of collateral blood flow is proportional to the degree of constriction. It is clear that exercise increases the extent of collateral communications by a significant amount above that due to narrowing alone. The absence of electrocardiographic changes following complete circumflex occlusion at the end of the experiment in the animals with high retrograde flows supports the functional adequacy of these channels. The rested animals with slight circumflex narrowing did not develop significant collaterals; the retrograde flows were low and the electrocardiographic changes resembled those following complete circumflex occlusion in most normal dogs. Surgical manipulation of these hearts had not promoted collateral growth. It is significant that the flow rates in exercised dogs with slight narrowing are clearly different from those of the rested dogs. Hence, the inference that exercise augments the collateral flow in a significant number of these animals.
A plot (not shown) of the mean peripheral coronary pressures and retrograde circumflex flows reveals a linear relationship in the pressure range between 10 and 75 mm. Hg. Beyond a pressure of 75 mm. Hg the relationship is expressed by a curve which rises steeply and roughly parallel to the flow axis. In this range of high retrograde flow values the mean peripheral coronary pressures reach but do not exceed 90 to 95 mm. Hg (i.e., they are from 5 to 10 mm. Hg less than mean aortic pressure).

The mean loss of pressure over the constricted segment was 14.2 ± 8 mm. Hg in the rested animals and 12.2 ± 8.1 mm. Hg in the exercised animals. After a 1 min. period of myocardial ischemia the mean of pressure differential increased to 35 ± 13 and 31.7 ± 12 mm. Hg in the 2 groups respectively.

The mean decrease in flow induced by the constricted segment was 21.5 ± 25 ml./min./100 Gm. in the rested animals and 21.1 ± 17 ml./min./100 Gm. in the exercised animals. After a 1 min. period of myocardial ischemia the constriction decreased flow 115.1 ± 67 ml./min./100 Gm. and 105.4 ± 46 ml./min./100 Gm. below that metered through the by-pass in the 2 groups respectively.

Flow rates at the end of the experimental period are somewhat low. Flow through the by-pass competes with the abundant collateral circulation present in most of these hearts; flow through the constricted segment is reduced not only by the resistance of the constriction but also by competition with the collateral flow. Indeed, the effects of this contest are apparent when retrograde flows are plotted against the circumflex inflows as measured through the by-pass (plot not shown). The unmodified effects of arterial constriction and exercise on coronary flow and pressure differentials were studied under two conditions: (1) in rested dogs without collaterals and (2) in acute experiments where collaterals had not yet developed.

Mild constrictions, ineffective in augmenting collateral flow in 10 rested dogs reduced coronary flow 4.5 ± 5.1 ml./min./100 Gm. and created a mean pressure drop of about 8.8 ± 2.8 mm. Hg. However, after a 1 min. period of anoxia simulating exercise, the narrowed segment reduced the flow 78 ± 38 ml./min./100 Gm. and created a pressure differential of 25 ± 4.9 mm. Hg.

Studies of the acute effects of various degrees of narrowing in normal dogs reveal that degrees of constrictions which transmit above 360 ml. blood/min./100 Gm. against 0 pressure create an average pressure drop of 8 mm. Hg (range: 4 to 17 mm. Hg) and an average reduction in coronary flow of 9 per cent (range: 0 to 19 per cent). Figure 2 shows that these mild constrictions fail to induce collateral growth in resting dogs. More severe constrictions which are effective in increasing collateral flow in rested dogs, create a mean pressure drop of 30 mm. Hg (range: 9 to 70 mm. Hg) and an average flow reduction of 36 per cent (range: 3 to 98 per cent). Actually, plots (not shown) which relate either the pressure drop or the per cent reduction in circumflex inflow to the degree of circumflex narrowing are practically superimposable upon the data shown in figure 2 concerning the rested animals.

**DISCUSSION**

These preparations may be compared to the human being with coronary disease limited to one major artery or with severe narrowing of one artery and minimal narrowing of the remaining arteries. Since these results agree with the findings of Zoll who studied human hearts with various degrees of narrowing, identical mechanisms probably operate to develop collateral vessels in both man and dogs. Although sudden constrictions are produced by this method, it is our impression that the degree of constriction slowly increases with time. The dynamic effects of the ligatures during the life of the animals, therefore, were derived from acute experiments in which constrictions were produced of functional degrees similar to those measured at the end of the experimental period.

The estimation of functional lumen size from rates of blood flow measured against 0 pressure is admittedly artificial. Actually, the measured flows are too high since the flow through a constricted segment of an intact vessel is reduced not only by the constriction but also by the resistance of the peripheral...
vascular bed. The present measurements express only relative degrees of constriction per 100 Gm. of heart muscle, but are satisfactory for our purposes. Undoubtedly there are differences in the myocardial oxygen consumption/100 Gm. of these hearts. This unknown factor may explain part of the variability of the results.

Substantial reductions in lumen size are required to depress coronary flow, to create sizeable pressure drops and to stimulate collateral growth in dogs at rest. This is understandable when it is considered that the circumflex trunk is capable of transmitting at least 700 to 800 ml. blood/min. against 0 pressure when calculated on the basis of 100 Gm. of muscle (fig. 2), whereas only 65 to 100 ml./min. are required to nourish 100 Gm. of left ventricle.

Electrocardiographic changes indicate that in rested dogs under the conditions of mild arterial narrowing, the myocardium is susceptible to infarction subsequent to sudden vascular occlusion because adequate collateral vessels are absent. Patients with minimal vascular narrowing are more likely than are normal individuals to develop complete vascular occlusion due either to thrombosis or to hemorrhage into the vascular wall. It is during this early stage of the disease process when collateral channels have not yet developed that exercise may be particularly effective in promoting collateral growth which would not otherwise occur. Since the onset of coronary disease is not clinically recognizable, it would probably be advisable to encourage middle-aged human beings who are without symptoms to exercise. It is also probable that patients without recent infarcts who have exertional pain due to coronary disease should be placed on a positive program of mild exercise which just falls short of producing pain. The question as to the effects of exercise after complete coronary occlusion and myocardial infarction cannot be answered from these data.

It is impossible to estimate the human equivalent of the exercise given these animals. The present results were achieved with 40 to 56 hours of exercise over 6 to 8 weeks. It is likely that milder forms of exercise continued over months and years may be equally effective.

The data reported strongly suggest that a pressure differential and decreased coronary flow are both necessary for collateral growth. Reductions in coronary flow of the magnitude found after moderate and severe constriction in the acute experiments are certain to result in decreased myocardial oxygen tension.

Results presented favor the view that subsequent to moderate and severe arterial narrowing collateral growth and blood flow increase until the pressure differential is reduced approximately to 10 mm. Hg and myocardial oxygen tension approximates normal. It may be significant that the estimate of approximately 10 mm. Hg as a critical pressure differential is similar to that pressure (yield pressure) required to initiate blood flow through small vessels.

It is the thesis of this report that collateral vessels will develop naturally between coronary arteries when by their growth the nourishment of a segment of myocardium can be improved. On the basis of this hypothesis the reduced vascularity found in hearts with narrowing of several branches is readily explained. Simultaneous narrowing of two arteries may fail to create adequate pressure differences even though myocardial hypoxia is present. Indeed, in instances of generalized arterial narrowing collaterals, even if present, could serve no useful purpose because of the lack of a sufficient driving head of pressure.

In view of the abundant evidence in both man and animals which shows the excellent collateral vessels provided by nature, the philosophy of surgical therapeutic measures designed to produce interarterial coronary anastomoses in coronary disease requires critical evaluation. The present experiments show that in the presence of some degree of myocardial hypoxia the excellent facilities of nature provide a wide distribution of blood if an adequate source of arterial blood exists to create an effective pressure differential. On the basis of these observations it is suggested that the truly beneficial results of surgery in the human being are probably best explained by the addition of an extra coronary source of blood.
whether this be supplied from an adherent pericardium or from other tissue or vascular grafts.

Summary

Experimental studies have shown that a moderate degree of circumflex arterial constriction is required to induce collateral vascular growth in resting dogs and that collateral development is then proportional to the degree of constriction.

The addition of exercise to mild arterial narrowing results in significant collateral anastomoses. It also promotes collateral growth above that due to moderate and severe constriction. It is suggested that the judicious use of early and continued physical exercise may reduce the clinical manifestations of coronary disease.

Evidence is presented that a significant pressure differential and decreased myocardial oxygen tension are necessary for collateral growth following arterial narrowing.

Acknowledgments

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Summary in Interlingua

Studios experimental ha demonstrate que un grado moderate de constriction de arteria circumflexe es requisitae pro inducer un crescentia vascular collateral in canes in stato de reposo e que le desvelopamento collateral es alora proportional al grado de constriction effectuate.

Le addition de exercitio al lave constriction arterial resulta in significative anastomoses collateral. Illo etiam promove un crescentia collateral in ultra de illo causate per moderate e sever grados de constriction. Es sugerite que le uso judiciose de un prompte e continue exercitio physic pote reducer le manifestationes clinica de morbo coronari.

Es presentate observationes que indica que un significative differential de pression e un reduction del tension de oxygeno myocardial es necessari pro le crescentia collateral occurrante post un constriction arterial.

References

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RICHARD W. ECKSTEIN

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