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, 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...
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 technic,† 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 flow through the bypass flowed through the constricted segment than is a direct measurement with a probe.†

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 vascular bed was measured by a recording rotameter connected between the two circumflex cannulae. In addition, the narrowed segment could be bypassed through a direct connection between the left common carotid artery and the rotameter, so that unrestricted circumflex inflow could be measured. The pressure loss due to the rotameter was calculated by subtracting the pressure indicated on the distal manometer from that shown on the central manometer during metering of flow through the bypass. 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.

† 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.

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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 Nonexperimental Variables in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Rested</th>
<th>Exercised</th>
</tr>
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<tbody>
<tr>
<td>Final dog weight (Kg.)</td>
<td>15.3</td>
<td>15.0</td>
</tr>
<tr>
<td>Heart weight (Gm.)</td>
<td>124</td>
<td>125</td>
</tr>
<tr>
<td>Heart weight/Dog weight</td>
<td>.81</td>
<td>.84</td>
</tr>
<tr>
<td>Injected circumflex area (art./Gm.)</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Circumflex weight/Heart weight</td>
<td>.37</td>
<td>.36</td>
</tr>
<tr>
<td>Relative blood viscosity</td>
<td>5.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Hemoglobin (g%)</td>
<td>107</td>
<td>103</td>
</tr>
<tr>
<td>Mean aortic pressure (mm./Hg)</td>
<td>116.5</td>
<td>119.5</td>
</tr>
</tbody>
</table>

Fig. 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 nonexperimental 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 6, but only slight in 1 heart from an exercised animal.

In 9 of the 50 hearts the ratio of wall thickness to lumen diameter appeared to be substantially increased in occasional intramuscular 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.

* Additional tabular data on specific points will be furnished by the author on request.
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...
血管床。这些测量结果仅表示心肌每100克的相对收缩程度，但对我们的目的来说是满意的。无疑，这些心脏中存在差异。这未知因素可能解释部分结果的差异。

在安静状态下，当考虑时，冠状动脉的直径需要显著减少以降低冠状动脉流量，从而形成显著的压力降，刺激侧支生长。这可以理解，因为左冠状动脉能以至少700到800毫升/分钟的速度传递血液，对抗0毫米汞柱的压力（图2），而在基于100克心肌的基础上，只有65到100毫升/分钟的流量方足以供给100克的左心室。

心电图变化表明，在休息的狗中，在轻度动脉狭窄的条件下，心肌对血管阻塞导致的缺血是敏感的，因为适当的侧枝血管是不存在的。血管狭窄的患者比正常个体更可能因血管阻塞或血管破裂导致的出血而发生完全血管阻塞。它发生在疾病早期，当侧枝血管没有发育时。心肌疾病的发生是不可临床识别的，这些血管在心肌无症状的个体中更可能没有发育，但它们可能有助于鼓励中老年人的发展。它也可能表明，患者没有血管阻塞的疼痛，或因为冠状动脉疾病的阻塞，而应该要进行一个适度的锻炼计划来促进侧枝生长。没有明显疼痛的患者，或因冠状动脉疾病而住院的患者，应该得到一个适度的锻炼计划。疼痛作为医学问题的锻炼促进侧枝血管生长的效果可能不完全回答这些问题。

不可能估计人类心电图信号的等效。这些结果是在40到56小时的锻炼期间，持续6到8周。在这些动物中，更轻微形式的锻炼在数月和数年中可能同样有效。

数据强烈表明，压力差和降低冠状动脉流量是所需侧枝生长的必要条件。在中度和严重狭窄的急性实验中发现的冠状动脉流量减少肯定会降低心肌氧张力。结果支持的观点是，中度和严重狭窄后侧枝血管和血液流量会发生增加，直到压力差大约为10毫米汞柱，心肌氧张力接近正常。它可能意味着，大约10毫米汞柱作为临界压力差的估计，与引起血液流量通过小血管的压力梯度相似。

侧枝血管的发展自然地发生在冠状动脉之间，通过它们的生长，可以改善一段心肌的营养。基于这个假设，心肌收缩期间发现的血管密度降低可以被解释。同时阻塞两条动脉可能无法形成足够的压力差，即使 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.

从人和动物中充分的证据表明，自然提供的侧枝血管的优越性，以及在冠状动脉阻塞手术中应考虑医疗措施。这些实验表明，在某些程度的myocardial hypoxia的背景下，自然提供的侧枝血管的优越性提供了一个有效的压力差。在这些观察的基础上，可以建议在人类身上真正有益的结果可能是通过在冠状动脉中添加一个额外的血液来源来解释的。
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

The author wishes to express his deep appreciation to Elaine Zahtilla and to John Dattilo who faithfully exercised the animals used in this experiment, to Dr. Alan Moritz who examined the microscopic sections of the hearts.

SUMMARIO IN INTERLINGUA

Studios experimental ha demonstrate que un grado moderate de constriction de arteria circumflexe es requirite pro inducer un crescentia vascular collateral in canes in stato de reposo e que le disveloppamento collateral es alora proportional ai 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 suggerite que le uso judiciose de un prompte e continue exercitio physic pote reducer le manifestationes clinic 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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