Development of Interarterial Coronary Anastomoses by Chronic Anemia. Disappearance Following Correction of Anemia

By RICHARD W. ECKSTEIN, M.D.

The effect of chronic severe anemia upon functional interarterial coronary anastomoses has been studied in dogs. Retrograde flow measurements at controlled aortic pressures and under conditions of normal viscosity and hemoglobin concentration indicate that severe chronic anemia stimulates growth of collaterals to a significant degree. On the other hand, removal of this stimulus by spontaneous recovery from anemia induces regression of collateral function to control levels.

ABUNDANT observations indicate the importance of interarterial coronary anastomoses. When functionally adequate, these channels occasionally allow the occurrence of complete coronary occlusion without the usual clinical symptoms or pathologic changes in the myocardium. It is probable that lesser degrees of collateral function are responsible for the far lower mortality in human beings following coronary occlusion and myocardial infarction than is found in dogs subsequent to coronary ligation. Nevertheless, even the first coronary occlusion, if it does not lead to death, usually exacts a toll of functioning cardiac muscle. Simple measures which induce collateral formation in relatively normal individuals would effect lower mortalities as well as smaller degrees of infarction secondary to a first coronary occlusion. Such a measure would undoubtedly prolong the life, add to the comfort and productive ability of those who are destined to develop severe widespread coronary disease.

It has been shown that anemia is a stimulus for the occasional production of interarterial coronary anastomoses in pigs. This suggests that myocardial anoxia rather than differences in pressure between arteries may initiate collateral formation. The present report is concerned with the effect of chronic anemia on collateral development in dogs in an effort to differentiate the role of myocardial anoxia from that of pressure differences between arteries.

METHODS

Mongrel dogs were given a diet of bread and milk and were made anemic by repeated bleeding from the femoral artery through an 18 gage needle. Arterial punctures were preceded by the infiltration of the peri-arterial tissue with 1 per cent procaine. Heparin (20 mg.) was injected through the intrarterial needle to delay coagulation. Each animal was bled once weekly for the first four to five weeks and then usually twice weekly until the hemoglobin was below 30 per cent of the normal of 15.0 Gm./100 cc. The hemoglobin content was determined prior to each bleeding and was maintained between 15 and 30 per cent of normal for one month. The animals were then divided into groups designated as “chronic anemia” and “recovered anemia.” The “chronic anemia” dogs were anesthetized with morphine and pentobarbital. The left chest was entered between the fourth and fifth ribs after the institution of intermittent positive pressure respiration through an intratracheal tube. The circumflex and left common carotid arteries were isolated. After the administration of 200 mg. of heparin, blood from the cannulated left common carotid artery was led through a recording rotameter into the circumflex artery via a cannula inserted at its origin for measurements of coronary inflow. Connections to optical and mercury manometers made possible both records of pulsatile as well as mean pressures in the central aorta and peripheral circumflex artery (peripheral coronary...
ANEMIA AND CORONARY ANASTOMOSES

307

pressure). Retrograde circumflex flows were measured against atmospheric pressure through a side tube to evaluate the degree of maximal collateral function as described previously. Mean aortic pressure was held at 100 mm. Hg during all measurements by bleeding the animal through the cannulated jugular vein or by constriction of the thoracic aorta. The effects of circumflex occlusion on the ecg. were recorded from lead aVr and the changes were graded as follows: 0, no change; +, T wave inversion only; ++, T wave inversion with S-T segment depression less than 2 mm.; ++++, T wave inversion with maximum S-T segment displacement. Relative blood viscosity was determined in vitro on blood drawn at the time of retrograde flow measurements. In some instances simultaneous blood samples from the aorta and great cardiac vein were drawn and analyzed for oxygen content by the method of Neil and Van Slyke. The collection of data on the anemic animals with low blood viscosities was followed by rapid bleeding and transfusion with cells from a donor dog to elevate both the viscosity and hemoglobin to the ranges found in normal dogs. These animals were then designated as "transfused anemia." Circumflex inflow, retrograde flows and pressures, as well as the ecg. effects of circumflex clamping, were measured again on the transfused dogs.

The "recovered anemia" group was placed on a full diet. After five to eight weeks when the hemoglobin concentration had reached its maximum, these animals were treated as above with the exception that no transfusion was given. Flow, pressure and ecg. measurements were thus obtained for comparison with the data in the "transfused anemia" group.

The measurements on these transfused and recovered groups were compared with measurements on 41 control animals and the differences were statistically evaluated. The effect of an acute reduction in viscosity on collateral function was tested in nine dogs designated as "normal," which were bled and infused with normal saline to produce "acute anemia." Flows and pressures were measured and compared with the values in the same nine dogs prior to bleeding and infusion with saline.

At the end of each experiment the heart was removed and the circumflex artery injected with dilute India ink to stain the muscle normally perfused by this artery. This was followed by the injection of a barium and gelatin mixture at a

### Table 1. Showing Mean and Range of Values in all Groups

<table>
<thead>
<tr>
<th>No.</th>
<th>Dog Wt Kg</th>
<th>Retrograde Flow cc/min</th>
<th>Mean</th>
<th>Range</th>
<th>Mean Peripheral Coronary Pressure mm. Hg</th>
<th>Mean</th>
<th>Range</th>
<th>Relative Viscosity</th>
<th>Mean</th>
<th>Range</th>
<th>Hemoglobin %</th>
<th>Mean</th>
<th>Range</th>
<th>Coronary Flow Circumflex cc/min/100 gma.</th>
<th>Mean</th>
<th>Range</th>
<th>Effect* of Circumflex Occlusion</th>
<th>Oxyg. Content Vol. %</th>
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<tbody>
<tr>
<td>A. Chronic Anemia</td>
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<td>11</td>
<td>15.6</td>
<td>17</td>
<td>7.8-30</td>
<td>17</td>
<td>2.2</td>
<td>2.1-2.5</td>
<td>12-25</td>
<td>423</td>
<td>290-652</td>
<td>6</td>
<td>4</td>
<td>2.5</td>
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<td>B. Transfused Anemia</td>
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<td>11</td>
<td>15.6</td>
<td>9.6*</td>
<td>2.6-16.4</td>
<td>20.3</td>
<td>4.5</td>
<td>3.7-6.1</td>
<td>96-110</td>
<td>156</td>
<td>83-220</td>
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<td>C. Recovered Anemia</td>
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<td>85-91-98</td>
<td>82</td>
<td>70-107</td>
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<td>73</td>
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<td>3.1-7.4</td>
<td>94-128</td>
<td>63</td>
<td>45-87</td>
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<td>F. Acute Anemia</td>
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<td>209</td>
<td>72-302</td>
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* Differs from control at 5% level.
pressure of 100 mm. Hg for 30 seconds at 45 C. The heart was chilled, weighed, unrolled by the Schlesinger technique and x-rayed at standardized distances. The India ink-stained muscle was isolated and weighed. Sections were taken for microscopic examination.

Heart weight, dog weight ratios were calculated and are slightly high due to the weight of the injected barium. The diameters of the circumflex arteries were measured on the roentgenograms to permit calculation of the ratio of diameter to weight of muscle perfused by the circumflex artery.

RESULTS

Chronic Anemia. Eleven dogs were studied at the end of the four week period of severe anemia. The data are presented in table 1, A. When compared with the control dogs, significant differences are evident not only between the means of the retrograde flows (table 1, D) but also in their distribution (fig. 1, A and D). The incidence of protection against circumflex ligation as recorded by the electrocardiograph also suggests a favorable influence of anemia on the collateral function. However, two objections are evident. The retrograde flows are elevated by the decrease in vascular resistance resulting from the low viscosity, and possibly by the low arterial oxygen content (table 1, A) which induces coronary vascular expansion.

Transfused Anemia. From the foregoing considerations, it is believed that only the data following transfusion (table 1, B and fig. 1, B) are strictly comparable to those obtained from the control animals. Comparisons of the transfused and control dogs, in which mean viscosity and mean hemoglobin concentration are similar, show that statistically significant differences exist when either the mean retrograde flow values (table 1) or the qualitative distribution of individual flows (fig. 1) are considered. In addition, the ratio of protected to unprotected dogs is significantly higher in the transfused group.

Recovered Anemia. Thirteen dogs were allowed to regenerate blood spontaneously for from 5 to 8 weeks. Comparisons of these recovered dogs with the control animals (table 1, C and D) show that the mean blood viscosity and mean hemoglobin level are slightly lower in the recovered group. Consideration of the mean retrograde flows and of the distribution of the individual dogs (fig. 1, C and D) disclosed no statistical differences between these indices of collateral function in the two groups. Further support for this conclusion is found in the general agreement in the ratios of protected to unprotected dogs.

Normal Dogs with Acute Anemia. Nine normal dogs from the control group were bled and infused with saline to lower both blood viscosity and hemoglobin. Comparisons are shown in table 1, E and F and figure 1, E and F. It is obvious that an acute reduction in relative viscosity from 4.8 to 1.7 increases retrograde flow from 3.9 to 8.6 cc. per minute. This is substantially less than the retrograde flow of 17 cc. per minute in group A where there was an additional factor of time. The lower hemoglobin in the "chronic anemia" group is not responsible for this difference since it has been previously shown that severe ischemia increases retrograde circumflex flow only 1.3 cc. per minute above the control flow of 3.5 cc. per minute.

Pathologic Changes. The ratios of heart
weight to body weight were calculated for the "transfused anemia," "recovered anemia" and control dogs. These were .0090, .0088, and .0093 respectively. It is obvious that cardiac hypertrophy did not occur in the experimental period as a result of the severe anemia.

Comparisons of the microscopic appearance of the hearts after chronic anemia with that of normal hearts disclosed no changes in the amount of reticulum, collagen, or fat. The gross and microscopic pictures frequently described in human hearts following severe anemia were not present.

The inside diameters of the circumflex arteries were unaltered as a result of anemia since comparisons of the ratios of these diameters to the weight of the muscle perfused by the respective arteries showed no significant differences between normal and anemic dogs.

DISCUSSION

These studies indicate that severe anemia of four weeks duration results in the development of interarterial coronary anastomoses in otherwise normal dogs. This is in agreement with the experimental observations of Zoll and with the postmortem studies of Zoll and Scott in human hearts. That the increase in mean retrograde flow from 3.8 to 9.6 cc. per minute is sufficient to be of functional importance is shown by the ecg. changes subsequent to occlusion of the circumflex artery. The data indicate that ligation of this major artery produces severe ecg. changes in 70 per cent of normal dogs which is in significant contrast to the situation in transfused chronic anemia dogs where coronary occlusion results in serious ecg. changes in only 23 per cent of the animals.

The question as to whether collateral vessels resulting from chronic anemia persist after the dogs spontaneously recover normal hemoglobin levels must be answered in the negative. These findings do not support speculations based on the clinical observations of Amadeo. The mean retrograde flow of 4.2 cc. per minute in this group is not significantly different from that of 3.8 cc. per minute in the control dogs.

These experiments were originally designed to separate the effects of myocardial anoxia from the effects of pressure differences between arteries. Both have been suggested as stimuli for collateral growth. Our original supposition that chronic anemia results in myocardial anoxia without differences in pressure between coronary arteries is probably not well founded. The existence of severe myocardial anoxia in these animals is not certain. Pathological changes suggestive of tissue damage were not present and clinical signs of cardiac failure were not observed. On the other hand, the usual brief increases in coronary inflow which follow the release of temporary coronary clamping were slight or absent in these anemic dogs. This suggests that the coronary vascular bed was expanded maximally due to the chronic anoxic stimulus of anemia. This same stimulus probably also affects in a similar manner preexisting or newly formed collateral vessels.

The question as to whether chronic anemia disturbs the pressure relationships between coronary arteries is not clear. There is a strong possibility that a difference in pressure between coronary arteries is created by anemia. Indeed, it is difficult to conceive of equal pressures in the presence of high rates of flow through channels of various diameters with branches emerging at different angles. In addition, blood flow measurements in this laboratory (unpublished) indicate that pressure differences are sometimes created in normal dogs following the intravenous administration of epinephrine. It is therefore suggested that the stimulus of anoxia as well as differences in pressure probably operate in chronic anemia.

With these experiments as a basis, it is hazardous to make predictions regarding the effect of anemia on human hearts. However, it is probable that attempts to produce protective intercoronary collaterals in normal young human beings by the induction of anemia is unwise. These experiments suggest that a prolonged period of a severe degree of anemia is required for the production of collaterals in normal dogs. The increase in retrograde flow of 5.8 cc. per minute induced by anemia is about 17 per cent of the normal blood flow of 32 cc. per minute required by the muscle sup-
plied by the circumflex artery in normal dogs. This is indeed a meager accomplishment, especially when one considers the very severe anemia to which these animals were subjected as well as the fact that its attainment and maintenance required from three to four months of frequent bleeding and a diet of bread and milk. Furthermore, should collaterals develop in normal human beings with anemia, their disappearance following the correction of the anemia is likely.

The possibility exists that human coronary arteries lack the capacity for similar degrees of expansion which the large coronary flows indicate to have occurred in the dogs. Some coronary rigidity is likely in middle-aged human beings and is certain in those with coronary artery disease. Preliminary, unpublished observations from this laboratory show that collaterals are produced effectively by anemia in the presence of narrowing of the circumflex artery in dogs. There is no evidence at present to indicate whether these collaterals remain subsequent to the correction of the anemia. If, in the presence of coronary narrowing, anemia-induced collaterals persist following removal of the stimulus of anemia, it will be of clinical interest.

**SUMMARY**

The effect of chronic anemia on the development of interarterial coronary anastomoses has been studied in dogs. Collateral function was estimated by direct retrograde flow measurements from the peripheral circumflex artery. In addition, the physiologic adequacy of collateral function was measured by the electrocardiographic changes resulting from complete occlusion of the circumflex artery. Alterations in these indices which resulted from chronic anemia were established by comparisons with normal dogs.

Severe anemia of four weeks duration results in a significant increase in the functional capacity of interarterial coronary anastomoses. Spontaneous recovery from chronic anemia induces collateral regression to near normal function after five to eight weeks.

The inadvisability of the use of induced anemia to expand collateral function in normal human beings is discussed.

**Acknowledgments**

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**REFERENCES**

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