The Ineffectiveness of Cortisone on Functional Coronary Interarterial Anastomoses

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Cortisone was given to dogs by daily intramuscular injections for two months. Studies of retrograde circumflex coronary flows, electrocardiograms, and then x-rays after barium sulfate injections, reveal no difference between treated and control dogs. The conclusion is reached that cortisone does not enhance functional or anatomic interarterial coronary anastomoses in normal dogs.

Even in the absence of gross myocardial infarction, coronary interarterial anastomoses can be developed by a variety of methods.1' 2 Since these collaterals have been shown to reduce mortality, prevent infarction, and prevent electrocardiographic changes following coronary occlusion,4' 5' 6 the search for additional stimuli for their production becomes of great importance.

Recently, Johnson and co-workers7 reported that cortisone led to reduction in mortality rate and size of infarcts following ligation of the ramus anterior descendens artery in dogs. With injection techniques as a basis, he attributed the beneficial effects of cortisone to increased vascularity of the heart. More recently, Opdyke and associates8 gave cortisone to dogs and were unable to substantiate the findings of Johnson in regard to mortality or infarct size. Consequently, this investigation was undertaken to test the thesis of Johnson that the administration of cortisone for two months increases coronary interarterial anastomoses.

Methods

Three groups of mongrel dogs were studied as follows:

Group 1. This group consisted of 12 dogs varying between 7.7 and 12.3 Kg. in weight for control purposes.

Group 2. Five dogs weighing between 9.8 and 14.7 Kg. were given cortisone* (2 mg. per kilogram per day) by intramuscular injection daily for 56 days.

Group 3. Thirteen dogs varying between 7.9 and 12.3 Kg. in weight were given cortisone (5 mg. per kilogram per day) by intramuscular injection for 56 days.

At the end of the two-month period all animals were anesthetized with morphine and pentobarbital, and under intermittent positive pressure respiration the left chest was opened between the fourth and fifth ribs. The circumflex artery was isolated, ligated centrally and cannulated peripherally. The peripheral artery was perfused with blood led from the cannulated left common carotid artery. Coagulation was prevented with heparin,† 10 mg. per kilogram. Aortic pressure was recorded optically from the carotid cannula and during measurements was maintained at a mean level of 100 mm. Hg either by bleeding or by aortic constriction. Coronary inflow was temporarily clamped while peripheral circumflex pressure was optically recorded. Mean peripheral pressure was also read from a mercury manometer. Interarterial anastomatic flow from the peripheral circumflex artery was measured at 0 pressure in a graduate. This was done by clamping the circumflex inflow tube and opening a side tube from the circumflex cannula, the open end of which was held at the level of the heart. Several measurements were taken during 30-second periods at intervals of 30 seconds until maximum values were obtained, and the results were averaged and expressed as cubic centimeters per minute. Consequently this was a measure of all blood entering the peripheral circumflex artery from the right, ramus descendens.

* The cortisone was generously supplied by Dr. Elmer Alpert of Merck and Co., Rahway, N. J. This was a saline suspension of Cortisone Acetate, 25 mg. /cc. with 0.9% Benzyl alcohol as preservative.

† Part of the heparin was generously supplied by the Upjohn Co., Kalamazoo, Mich.
anterior or septal arteries. Since this retrograde flow is arterial and is abolished by temporary clamping of the common left and right coronary arteries, it is presumed to be a true measure of interarterial anastomotic function.

Electrocardiograms were recorded, using lead aVlt. The changes induced by clamping the circumflex inflow were graded as follows: +, T-wave inversion without S-T segment depression; ++, T-wave inversion with S-T segment depression less than 2 mm.; +++, T-wave inversion with S-T segment depression more than 2 mm.; ++++, maximum S-T segment depression. If the animal survived 12 minutes after clamping the circumflex inflow, the peripheral circumflex was allowed to bleed to atmospheric pressure. This induced maximal electrocardiographic changes in every instance. The animals in each group displaying the minor changes (+ or ++) following circumflex ligation were regarded as having significant protection against coronary occlusion.

The oxygen content of arterial blood was determined in all animals by the method of Neill and Van Slyke. Blood viscosity and hemoglobin content were measured.

After the death of the animal, dilute India ink was injected into the circumflex artery at a pressure of 100 mm. Hg to stain the perfused muscle mass. This was followed by the injection of a mixture of barium sulfate and gelatin at 100 mm. Hg pressure for 30 seconds at 45 C. The hearts were chilled, opened by the Schlesinger method, x-rayed and examined for the presence of barium in the right, ramus anterior descendens and septal coronary arteries. The weight of the total heart as well as that of the India ink stained circumflex area was obtained. The latter weight was used to express retrograde flow in cubic centimeters per minute per 100 Gm. of muscle supplied by the circumflex artery. The pituitary was removed and analyzed for its corticotropin content. Likewise the adrenals were removed and weighed.

RESULTS

Quantitative comparisons between the control and treated groups are shown in table 1. The values of P shown with groups 2 and 3 indicate comparisons with group 1.

Effect of Cortisone (2 mg. per kilogram per day). The retrograde flows in group 2 are not significantly different from those shown for the controls either when expressed as cubic centimeters per minute or as cubic centimeters per minute per unit weight of injected circumflex area. The large decreases in adrenal weight/body weight ratios in the treated animals are apparent. This group lost an average of 0.6 Kg. per dog during treatment.

Effect of Cortisone (5 mg. per kilogram per day). Even though the dose of cortisone was increased in group 3 to the levels used by Johnson,7 the results were unaltered. The original dog weights were identical with those in the control group, and during treatment the dogs lost an average of 0.7 Kg. each. The heart

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weights were similar to those in the control group. The heart weight/body weight ratio increased significantly when calculated on the basis of final dog weight. However, since there is no increase when calculated on the basis of pretreatment dog weight, it is believed that the heart weight did not materially change during treatment.

The small average increase in retrograde flows is statistically not significant. The similar decrease in the adrenal weight/dog weight ratio in both groups 2 and 3 shows that the cortisone dosage was adequate and effectively administered.

Figure 1 shows retrograde flows in cubic centimeters per minute plotted against heart weight, using the data from groups 1 and 3. The horizontal line is drawn through the mean of retrograde flows and heart weights for the combined group. The ratio of the number of animals above the mean to the number below the mean is the same for the treated and control groups.

The dogs which showed + or ++ electrocardiographic changes following circumflex occlusion are designated with the letter P (protected). It is noteworthy that most of these "protected" animals have retrograde flows above the mean. Furthermore, in added confirmation of the evidence in table 1, it is obvious that cortisone does not result in an increase in electrocardiographic evidence of protection against circumflex occlusion since 5 of 13 treated dogs, compared with 4 of 12 control animals, were protected.

Results of Barium-gelatin Injection. Careful study of the x-rays of the injected hearts reveals a striking similarity in both the treated and control hearts. There is no evidence that increased amounts of injected material has passed through interarterial anastomoses in the treated group. Furthermore, no differences in the vascular pattern of the circumflex artery can be detected. Figure 2 is a reproduction of a typical x-ray from each group.

Results on Paired Dogs. After about one-half of the dogs had been studied, because of the wide range of values of retrograde flows it was deemed advisable to study paired animals. Therefore 14 dogs were chosen on the basis of age and body weight and paired according to breed when possible. One member of each pair was randomly chosen to receive cortisone (5 mg. per kilogram per day).
mg. per kilogram per day). The control dogs were kept during the 56-day period in separate cages but on the same diet. Both members of each pair were studied on the same day, and differences in retrograde flows between members of pairs were handled statistically. Since the differences were not significant and the variability was as great as before, these animals are included in table 1 and figure 1.

**Pituitary ACTH Content.** The adenohypophyses of control and cortisone-treated animals were analyzed for corticotropin content by the adrenal ascorbic acid depletion method. Preliminary data indicate that the corticotropin content of pituitaries from cortisone-treated animals was reduced at least 50 per cent. This confirms other unpublished observations by Farrell and Laqueur.

**DISCUSSION**

It is believed that these experiments offer conclusive proof that cortisone in the doses given for two months does not modify coronary interarterial anastomoses in dogs. That the dosage used was adequate to affect other systems is shown by the facts that it not only inhibited corticotropin release, as evidenced by adrenal atrophy, but also inhibited its synthesis.

The conclusions drawn are substantiated from several viewpoints. First, the retrograde flows in the treated animals are remarkably like those in the control group, not only when expressed as cubic centimeters per minute, but also when expressed as cubic centimeters per minute per 100 Gm. of ischemic muscle. Second, the electrocardiographic changes induced by clamping the circumflex inflow are equally severe in both groups. Finally, the standardized method of barium sulfate and gelatin injection reveals the same pattern in the two groups. Admittedly, the estimation of the amount of barium in vessels outside the India ink-stained area is purely subjective. However, in the presence of extensive interarterial anastomoses the injection method employed in these experiments gives unquestionable evidence of complete filling of many branches of the ramus descendens anterior, right and septal arteries.*

The validity of the use of retrograde flows has been questioned by Wiggers on the basis that these flows are modified by aortic pressure. This criticism of the method cannot be applied to these experiments since mean aortic pressure was maintained at 100 mm. Hg during all flow measurements. The fact that continued bleeding of an artery to atmospheric pressure rapidly leads to maximal electrocardiographic changes and usually results in fibrillation is regarded as evidence that all interarterial anastomatic flow is being removed. Furthermore, in hearts having large retrograde flows the severe electrocardiographic changes and cyanosis induced by bleeding the peripheral artery can be readily abolished by clamping the bleeding tube, thereby diverting at least part of the retrograde flow into the capillary bed. That collateral flow after coronary occlusion supplies capillaries is therefore clear.

However, the relationship between the volume of retrograde flow measured at atmospheric pressure to the volume which actually perfuses the capillary bed after a coronary occlusion requires clarification. During retrograde flow measurement conditions for flow are optimal, since aortic pressures in the non-occluded arteries operate against zero pressure in the cannulated artery. Retrograde flows, therefore, are a measure of the full capacity of the collateral bed. However, when the peripheral end of the cannulated artery is occluded, as in any coronary occlusion, and retrograde bleeding is prevented, peripheral coronary pressure is no longer zero but rises to an average of 14.5 mm. Hg (table 1). Under these conditions the pressure difference between the normal arteries and the occluded artery is 14.5 mm. Hg lower than during retrograde flow measurements.

Consequently, capillary flow of interarterial origin following coronary ligation may be approximately expressed by the formula:

\[
\text{capillary flow} = \text{retrograde flow} \times \frac{A.P. - P.C.P.}{A.P.}
\]

where \(A.P.\) = aortic pressure, and \(P.C.P.\) = peripheral coronary pressure. Although this calculation is approximate, it expresses semi-quantitative values. In a flow model, measurements indicated that with a perfusion pressure...
of 100 mm. Hg, a peripheral coronary pressure of 15 mm. Hg resulted in a capillary flow of 94 per cent of that registered when peripheral coronary pressure was zero, as compared with a calculated capillary flow of 85 per cent of that existing at zero peripheral coronary pressure. Therefore, retrograde flows may overestimate by about 10 per cent the function of interarterial collaterals in normal dogs, and the criticism of this method by Prinzmetal on the basis that it underestimates collateral function is entirely unjustified.

On the other hand, peripheral coronary pressures show only fair agreement with retrograde flows in the ranges found in normal dogs. These pressures are modified by changes in heart rate which are not controlled in these experiments. Consequently, they are probably not a reliable index of interarterial anastomotic function.

The discrepancy between our findings and those of Johnson in regard to increased vascularity cannot be satisfactorily explained. However, published data from this laboratory reveal a wide range of functional intercoronary anastomoses in normal dogs. Indeed, preliminary observations on 37 dogs reveal that at least 25 per cent of these animals have very high retrograde flows. This fact renders the assumption of experimental differences in vascularity between small groups extremely hazardous, particularly when based on the x-ray appearance following the injection of radio-opaque materials.

**SUMMARY**

Studies concerning effects of cortisone upon coronary interarterial anastomoses have been made in dogs.

Cortisone acetate was given for from 56 to 60 days in doses of 2 and 5 mg. per kilogram per day by intramuscular injection.

Measurements were made of retrograde circumflex flows, peripheral circumflex pressures, and electrocardiographic changes induced by circumflex occlusion.

The validity of the retrograde-flow method as a measure of collateral function is discussed.

* To be published.

When compared with control dogs, cortisone-treated dogs exhibited no change in these indexes of coronary anastomoses.

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