THE INFLUENCE OF EPINEPHRIN UPON THE CORONARY CIRCULATION OF THE MONKEY.*

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PLATE 22.

Epinephrin (adrenalin) undoubtedly dilates the coronary arteries of the animals that are usually made the objects of laboratory investigation. That a better blood supply should thus be afforded the heart by a hormone which arouses a marked increase in activity seems a suitable provision of nature.

The most important ways in which epinephrin may influence the coronary circulation probably are: (1) directly, by acting upon the myoneural junctions of the vessels themselves; (2) indirectly, (a) by changes in the activity of the heart, which may affect the vessels by the production of metabolites (Markwalder and Starling[1]), or mechanically, (b) by changes in the general arterial pressure, (c) by possible actions on the central nervous system.

As has been shown by the classical studies of Langley and his coworkers, the direct action of epinephrin upon the coronary vessels depends presumably upon their innervation. In the laboratory animals thus far investigated these arteries appear to be innervated by dilators of true (thoracicolumbar) sympathetic origin, because epinephrin increases the coronary flow in perfused isolated hearts (whether active or at rest) and causes a relaxation in isolated coronary strips or rings.

Electrical stimulation of the accelerator nerve was found by Maass[2] to increase the coronary flow in the cat, thus indicating in a more direct manner the existence of coronary dilators of sympathetic

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[1] Markwalder, J., and Starling, E. H., *Jour. Physiol.*, 1913, xlvii, 275.

[2] Maass, P., *Arch. f. d. ges. Physiol.*, 1899, lxxiv, 281.

origin in this animal. This has recently been corroborated by Morawitz and Zahn.[3]

These authors were impressed by the fact that for the study of many questions relating to the coronary circulation the intact animal is best adapted. The indirect factors in the living animal, of course, modify the influence of the direct. This had been recognized previously by Bond,[4] who worked on the coronary circulation of intact animals in 1910.

Morawitz and Zahn inserted a catheter through the right auricle into the coronary sinus of the hirudinized cat or dog. After measuring with a suitable flow recorder the coronary blood thus collected, they returned it through a slow feeding burette into the jugular vein. Records were obtained of the increase in coronary flow resulting from raising the general arterial pressure in various ways.

The effect of epinephrin upon the coronary flow was then shown to be one of extreme augmentation, even out of proportion to the increase in general arterial pressure. This indicated again the influence of other factors such as increased metabolites or an actively stimulated vasodilator mechanism. Similar, although less marked, effects were obtained by subcutaneous injections of epinephrin.

Angina pectoris was then treated in this manner by Büdingen[5] at the instigation of Morawitz and Zahn. No positive results being obtained, these authors were led to remark that it is by no means clearly established that anginal attacks are due to coronary spasm.

On the other hand, one of us[6] obtained evidence three years ago that the action of epinephrin in man differs from its action in the usual laboratory animals as regards the coronary arteries. It was demonstrated that isolated rings of these arteries obtained from fresh cadavers respond to epinephrin by contraction only. These experiments were controlled by many upon coronary rings of the calf, sheep, and pig, in which was constantly seen the usual relaxation. The conclusion was drawn that epinephrin constricts the

[3] Morawitz, P., and Zahn, A., *Zentralbl. f. Physiol.*, 1912–13, xxvi, 465; *Deutsch. Arch. f. klin. Med.*, 1914, cxvi, 364.

[4] Bond, G. S., *Jour. Exper. Med.*, 1910, xii, 575.

[5] Büdingen's results are reported by Morawitz and Zahn, *Deutsch. Arch. f. klin. Med., loc. cit.*, p. 388.

[6] Barbour, H. G., *Jour. Exper. Med.*, 1912, xv, 404.

human coronary vessels and that they are therefore supplied, presumably, with vasoconstrictors of true sympathetic origin.

Morawitz and Zahn express themselves as willing to entertain this view as an alternative explanation of Büdingen's negative results with epinephrin in angina pectoris.

The constricting influence of epinephrin upon the human coronaries has, however, been doubted by some orthodox students of epinephrin; for example, Park.[7] With the hope of obtaining corroborative evidence from the monkey the following work was undertaken.

METHOD.

The experiments were made upon normal members of the species *Macacus rhesus,* the control animals being normal rabbits. In these two classes of animals we sought a variation in the action of epinephrin upon the coronary vessels themselves. We selected, therefore, a method which excluded some of the above mentioned indirect factors, employing isolated hearts. For this purpose the perfusion apparatus described by Locke and Rosenheim[8] was found well adapted.

The animals were decapitated and the blood was collected into a vessel containing 0.02 to 0.04 of a gram of hirudin dissolved in 50 cubic centimeters of Locke solution. The blood mixture was filtered and diluted further when necessary to make about 150 cubic centimeters. The blood constituted one-third to one-half of the total mixture.

The heart was immediately excised and connected with the aortic cannula of the perfusing system. After thorough irrigation of the coronary vessels with Locke solution, the blood mixture was transferred to the reservoir of the apparatus and the experiment begun.

In order to obtain a uniform record of the coronary flow it was found advisable to suspend the heart, apex upward, thus preventing the accumulation of blood in the right auricle and ventricle, which leads to an irregular outflow from the beating heart. The heart was held in this position, below, by means of a fixed, curved aortic cannula and above by a thread sutured to the apex of the ventricles.

The rate of coronary flow was measured with Condon's[9] tipper

[7] Park, E. A., *Jour. Exper. Med.,* 1912, xvi, 532.

[8] Locke, F. S., and Rosenheim, O., *Jour. Physiol.,* 1907–8, xxxvi, 205.

[9] Condon, N. E., *Jour. Physiol.,* 1913, xlvi, p. xlvi.

recorder. The perfusion fluid unit was constant during each experiment. It varied somewhat in the series, averaging about 2 cubic centimeters. The injections were made obliquely through the rubber tubing at a point a few centimeters above the aortic cannula. To avoid changes in arterial pressure this was done slowly and with the needle directed against the current of the perfusing fluid.

As shown in the tables, perfusion pressures of 50, 75, and 100 millimeters of mercury were employed. The perfusion fluid was maintained at a constant temperature of 38° C.

Commercial adrenalin chloride was used throughout the work.

RESULTS.

The experiments are summarized in tables I and II. In these it will be noted that no time has been allowed between the injection and the arrival of epinephrin at the coronary vessels. Thus the degree of response is in all cases underestimated. A further source of underestimation in the tables is the fact that the three minute interval chosen often expired before the full effect of the drug was seen. It suffices, however, for demonstrating the main fact, which is a qualitative one.

A better conception of the character of the individual results is obtained from the reproduced tracings. In these the upper line records the rate of coronary flow, the lower the time in five second intervals.

Rabbit Controls.—Seven experiments were made upon two rabbit hearts. The first table shows that all doses employed, varying from 0.025 to 0.25 of a milligram, gave constantly an increase in coronary flow.

TABLE I.

Isolated Rabbit Hearts.

Animal.	Experiment.	Perfusion pressure.	Epinephrin.	Units of perfusion fluid in 3 min.	
				Before epinephrin.	After epinephrin.
Rabbit 1 (3,300 gm.).....	1	50 mm. Hg.	0.00025 gm.	3.2	5.4
	2	50 mm. Hg.	0.0001 gm.	3.0	3.8
	3	50 mm. Hg.	0.00025 gm.	1.8	2.9
Rabbit 2 (1,600 gm.).....	4	100 mm. Hg.	0.0001 gm.	7.2	13.3
	5	100 mm. Hg.	0.000025 gm.	3.2	3.8
	6	100 mm. Hg.	0.0001 gm.	3.1	4.3
	7	50 mm. Hg.	0.0001 gm.	1.5	3.2

Figure 1 is a sample record from a rabbit's coronary flow (experiment 1). A pre-injection period is shown, followed by the increase produced by epinephrin and a partial return to normal.

Monkeys.—That constriction of the coronaries by epinephrin is as constant in the isolated monkey heart as dilatation of the coronaries in the rabbit heart is shown by table II.

TABLE II.

Isolated Monkey Hearts.

Animal.	Experiment.	Perfusion pressure.	Epinephrin.	Units of perfusion fluid in 3 min.	
				Before epinephrin.	After epinephrin.
Monkey 1, ♂ (1,400 gm.)..	8	50 mm. Hg.	0.00025 gm.	9.3	7.8
	9	50 mm. Hg.	0.00025 gm.	6.0	5.2
Monkey 2, ♀ (1,200 gm.)..	10	75 mm. Hg.	0.0005 gm.	13.4	13.1
	11	50 mm. Hg.	0.0005 gm.	5.8	5.4
	12	50 mm. Hg.	0.001 gm.	4.9	4.5
	13	50 mm. Hg.	0.002 gm.	4.2	3.5
	14	50 mm. Hg.	0.002 gm.	10.0	3.6
	15	75 mm. Hg.	0.002 gm.	3.0	1.8
Monkey 3, ♂ (1,800 gm.)..	16	100 mm. Hg.	0.000025 gm.	5.8	4.7
	17	100 mm. Hg.	0.0001 gm.	3.7	3.2
	18	100 mm. Hg.	0.0001 gm.	1.8	1.4
	19	100 mm. Hg.	0.001 gm.	4.2	3.8
	20	100 mm. Hg.	0.0001 gm.	8.2	6.3
	21	100 mm. Hg.	0.002 gm.	6.7	4.3

Fourteen experiments were made upon the hearts of three monkeys, the doses varying from 0.025 to 2 milligrams.

Figure 2 (experiment 8) is from the coronary flow of a male monkey, weighing 1,400 grams, a few minutes after removal of the heart from the body. The beat was active and regular; the heart rate per ten seconds is indicated by the numbers written on the tracing between the flow and time records. By comparison of the eight minute periods before and after the injection of 0.00025 of a gram of epinephrin, it will be seen that 26 perfusion units before were succeeded by 21 units after. The heart rate increased from 84 to 108 as a result of the injection. The tracing shows also the beginning of recovery from the coronary constriction.

Figure 3 illustrates the coronary flow of a female monkey, weighing 1,200 grams, several hours after removal of the heart, being the last of the series on the animal (experiment 14). Two milligrams of

epinephrin were given. The heart had ceased to beat for some time, but had been active during the earlier experiments tabulated from this animal.

The third monkey was a male weighing 1,800 grams. Experiment 17, from this monkey, is illustrated by figure 4. The heart was beating rhythmically before this experiment but within a minute after the epinephrin injection went into partial block, from which it never recovered. After a number of further injections with epinephrin had all yielded constriction, 0.025 of a cubic centimeter of amyl nitrite was injected. The marked flow increase illustrated in figure 5 (experiment 22) was the result. This indicates that the coronaries of the monkey, as of other animals, respond to amyl nitrite by dilatation.

DISCUSSION.

Our results greatly enhance the value of Barbour's earlier experiments upon isolated human coronaries, by annulling all the objections to the theory of coronary constriction by epinephrin in man, which are based upon analogy with other classes of mammalia. There exists, we believe, between certain primates, on the one hand, and certain of the lower mammalia on the other, a previously unsuspected difference in innervation. It has been detected by means of an agent which is already known to exhibit variations in its action upon the uterus of different species. Examples of this, with the literature, will be found in a recent paper by Gunn.[10]

As regards man, the constricting influence of epinephrin upon the coronaries, while having a possible bearing upon the therapy of anginal attacks, may also prove to be related to their etiology. In view of the work of Cannon[11] and others upon the discharge of epinephrin into the blood stream in certain emotional states, an explanation may be found for the frequent association of anginal attacks with excitement.

A factor which is common to all species and which operates against coronary constriction has been purposely omitted from the present work; namely, the decided increase in arterial pressure.

[10] Gunn, J. A., and Gunn, J. W. C., *Jour. Pharmacol. and Exper. Therap.*, 1914, v, 527.

[11] Cannon, W. B., and de la Paz, D., *Am. Jour. Physiol.*, 1911, xxviii, 64.

With stationary perfusion pressures of 50, 75, or 100 millimeters of mercury, which were never changed during an epinephrin experiment, no essential differences were seen in the results. When the pressure was raised or lowered between two experiments a corresponding increase or diminution in coronary flow was, of course, noted. Central effects of epinephrin, which are presumably of minor importance, have also been excluded from this work.

The factor of heart activity is important and has been dealt with to some extent. The earlier experiments upon each animal were all made upon actively beating hearts; many of the later ones upon hearts which were quiescent and remained so. We can say with certainty that the action of epinephrin upon the coronary flow was constant under both sets of conditions. We gained further the impression that the constrictor effect was more marked in resting than in active hearts, which may have been due to the lack of the non-volatile metabolites referred to by Starling and Markwalder. The variation in dosage in the present work precludes decision in this matter.

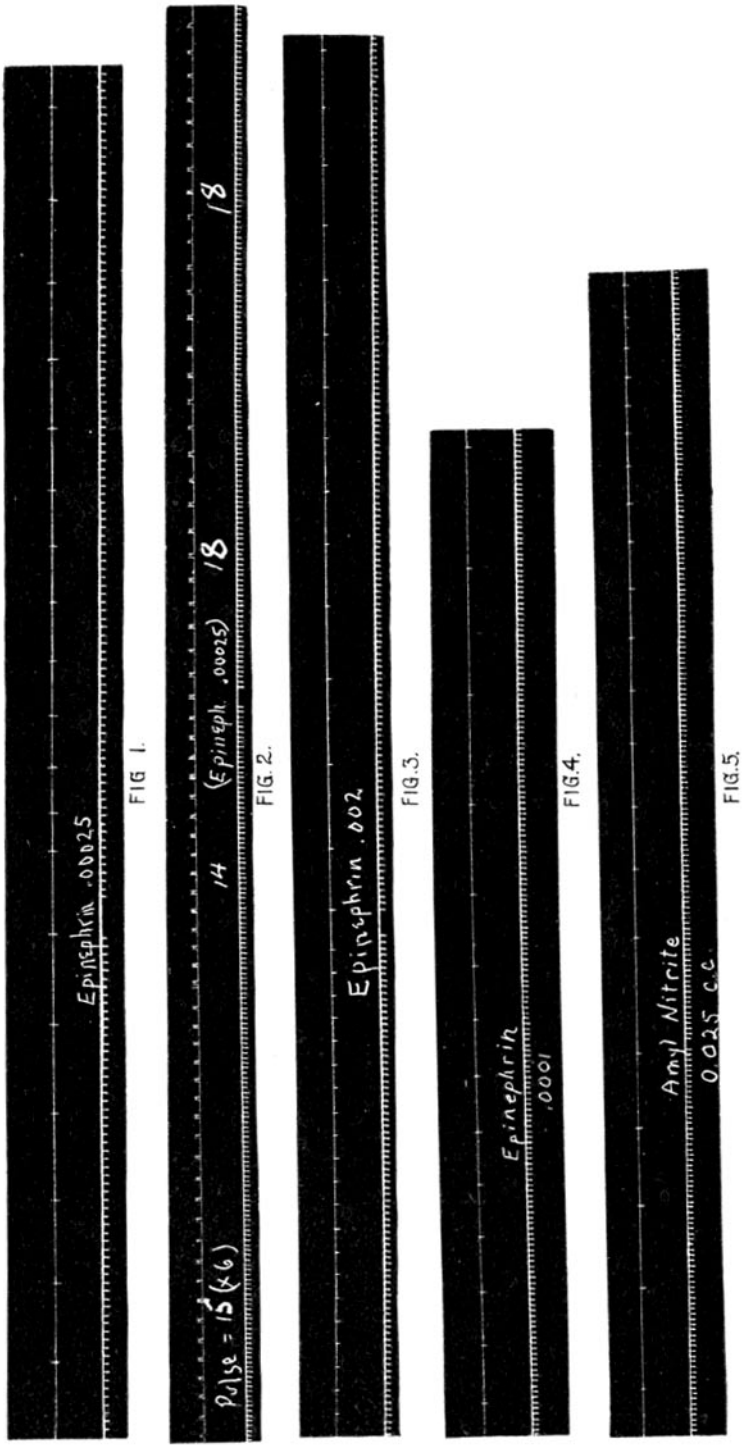
The dose was varied in the monkey from 0.025 of a milligram, which was ineffective in one experiment (not tabulated), up to two milligrams. Qualitatively our results were constant. The data are not sufficient to warrant quantitative deductions.

CONCLUSIONS.

Decrease in coronary flow was the constant response of freshly isolated monkey hearts to epinephrin. These hearts were perfused with autogenous hirudinized blood diluted with Locke solution. The results were constant at high or low perfusion pressures, in beating or resting hearts, and with all adequate doses. Increased coronary flow was obtained constantly in rabbit hearts under identical conditions.

In the light of previous work upon isolated human coronary arteries, the general conclusion is drawn that, while actively dilating the coronary vessels in the dog, cat, rabbit, ox, sheep, and pig, epinephrin constricts the coronary vessels in man and the monkey.

The coronary arteries of the last two species are presumably supplied with constrictor nerves of true sympathetic (thoracicolumbar) origin.



(Barbour and Prince: Influence of Epinephrin upon Monkey.)

EXPLANATION OF PLATE 22.

Records of coronary perfusion. Upper line = perfusion units; lower line = time in five second intervals.

FIG. 1. Rabbit 1, 0.25 mg. of epinephrin.

FIG. 2. Monkey 1, 0.25 mg. of epinephrin. The numbers indicate the heart rate per ten seconds.

FIG. 3. Monkey 2, 2 mg. of epinephrin.

FIG. 4. Monkey 3, 0.1 mg. of epinephrin.

FIG. 5. Monkey 3, 0.025 c.c. of amyl nitrite.