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The effects of physiological concentrations of noradrenaline on the coronary resistance of isolated perfused hearts of the cat, dog and monkey

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The effects of "physiological" concentrations of noradrenaline on the coronary resistance of isolated, perfused hearts of the cat, dog and monkey were determined. At the lowest active concentrations of noradrenaline (2–4 ng/ml), the preparations always responded with an increase in coronary resistance associated with an unrecordable or minimal myocardial response. As the concentration increased, the effect of the amine on the coronary resistance became biphasic. There was an initial transient increase followed by a more prolonged decrease in resistance associated with a significant myocardial response. These results support other evidence that the direct action of noradrenaline on the coronary vessels is one of vasoconstriction, and that the decrease in resistance associated with larger concentrations of noradrenaline is secondary to the myocardial stimulation, perhaps by way of vasodilating metabolites. Lack of agreement of results may well arise due to the use of concentrations of noradrenaline which also affect the myocardium.

NORADRENALINE is used as a pressor agent in cardiogenic shock due to myocardial ischaemia, although the nature of its actions on the coronary vessels is still in dispute. In man, it has been reported to cause a decrease in coronary resistance (Feinberg & Katz, 1958), an increase in coronary resistance (Yurchak, Rollett & others, 1964), or a biphasic change (Berne, 1958). Apparent disparity of this kind is found in the intact animal, including man, and in the isolated heart.

Recent investigations with the isolated mammalian heart, using a sensitive coronary resistance recorder (Proctor, 1964), suggest that the variation in results may arise, in part, from the difficulties of measuring small changes in coronary resistance, and the consequent use of concentrations of catecholamines far in excess of those found physiologically.

Experimental

Isolated hearts of the cat, dog and monkey were perfused by the Langendorff technique with Krebs solution at a perfusion pressure of 50 cm H_2O and a temperature of 37°. The Krebs solution contained in g/100 ml: NaCl 0·692, KCl 0·0354, $CaCl_2$ 0·0282, $NaHCO_3$ 0·21, KH_2PO_4 0·0162, $MgSO_4.7H_2O$ 0·0294, glucose 0·2. The solution was gassed with oxygen 95% and carbon dioxide 5%, and its pH immediately before it entered the coronary arteries was in the range 7·34–7·44. Number and weight range of animals in each species were: cats (10) (0·8–1·2 kg); dogs (8) (0·9–1·3 kg); monkeys (2) (*Cynomolgus* 1·8–1·9 kg). The perfusion apparatus was based on that of Baker (1951).

Since the coronary resistance is a function of vascular and myocardial support, kymograph recordings were also made of the amplitude of contraction (spring-loaded lever with a tension of 9 g), and heart-rate (Thorp impulse counter). The sensitivity of the coronary resistance recorder

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was such that a change in coronary resistance of 1·5% gave a deflection of 1·0 cm on the drum. Noradrenaline was injected in a volume of 0·05 ml of Krebs solution into the aortic cannula, which had a volume of 1·0 ml. At least 45 min were allowed for the heart to become steady in amplitude, rate, and coronary resistance before any injections were made.

DRUGS

Acetylcholine chloride (Hopkins and Williams). (−)-Noradrenaline bitartrate (Bayer). Doses given are in terms of the base.

Results

Early in perfusion, the coronary vessels of the isolated heart have a low tone and show an exaggerated vasoconstrictor response. However, if perfusion is maintained for 45–60 min much of the smooth muscle tone returns and the preparation will respond with a decrease in coronary resistance to doses of acetylcholine which do not significantly affect the

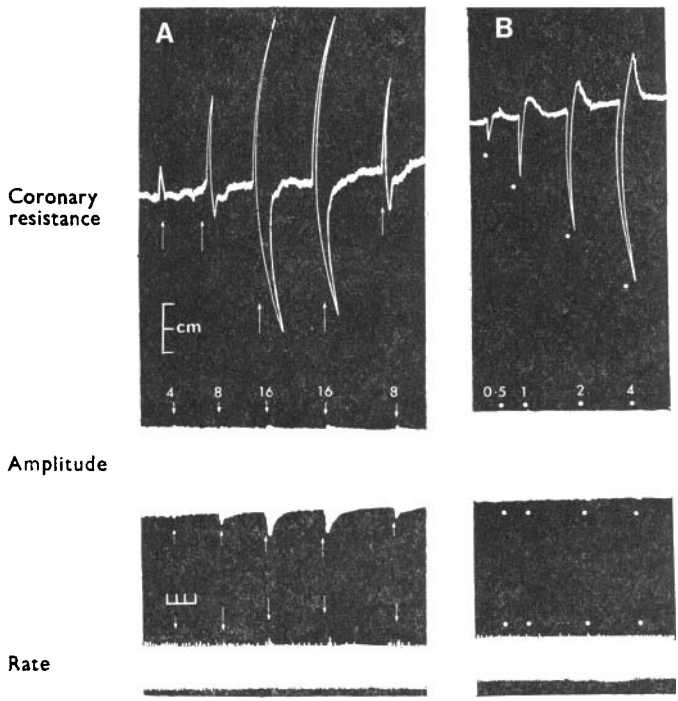

FIG. 1. Isolated perfused cat heart. Krebs solution. 37°. 1 cm≡1·5% change in coronary resistance. A. A simple increase in coronary resistance with the smallest effective dose of noradrenaline (4 ng), changes to a biphasic response as the dose is increased to 16 ng, and myocardial amplitude and rate are more affected. B. Indicating the sensitivity of the recording system, and the effect on the coronary resistance of small doses of acetylcholine which have a minimal or insignificant effect on the myocardium. Time scale: min.

myocardium (Fig. 1B). Noradrenaline is not used until this point is reached.

Cats. Fig. 1A shows the effect of very small doses of noradrenaline on the coronary resistance, heart rate and amplitude of contraction in the cat isolated perfused heart. The smallest dose of noradrenaline seen to affect the coronary resistance (4 ng) caused a transient increase in coronary resistance. At 8 ng, a biphasic response was seen in which there was first a brief increase in resistance, followed by a prolonged decrease. At 16 ng, the decrease in resistance became the larger component. The rate was unaffected until the dose reached 16 ng, and the amplitude of contraction was increased minimally at 4 ng and moderately at 16 ng.

Dog. Fig. 2A shows a similar response in the dog isolated heart, with the difference that the effect on the coronary resistance was recordable at 2 ng, and the biphasic response was dominated by the decrease in resistance at a lower dose of noradrenaline than the cat heart. The effect on the myocardium was similar to that of the cat preparation except that the heart rate was affected at a lower dose of noradrenaline.

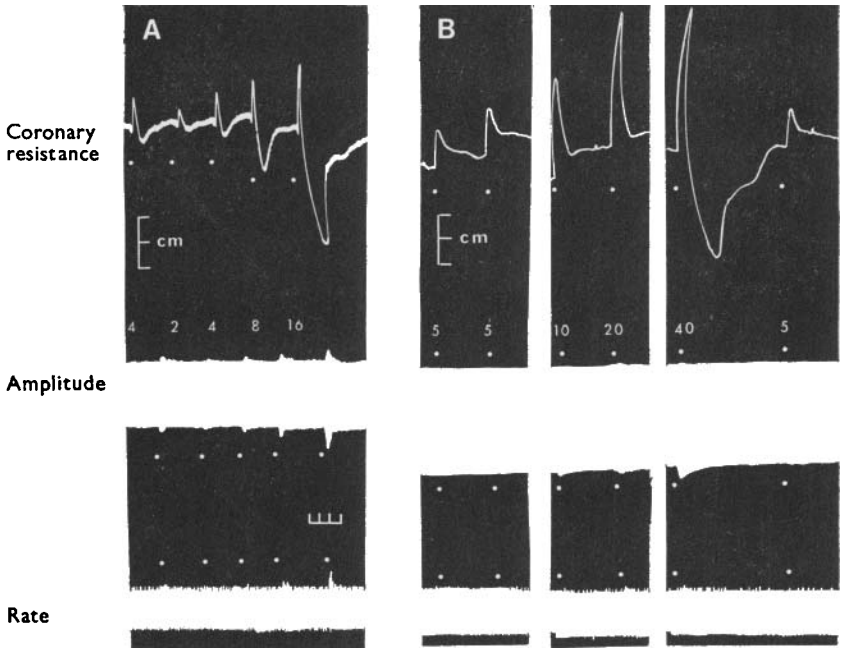

FIG. 2. A. Isolated perfused dog heart. Krebs solution. 37°. 1 cm≡1·5% change in coronary resistance. A simple increase in coronary resistance with the smallest effective dose of noradrenaline (2 ng), changes to a biphasic response as the dose is increased to (8 ng), and myocardial amplitude and rate are more affected. B. Isolated perfused monkey heart. Krebs solution. 37°. 1cm≡1·5% change in coronary resistance. A simple increase in coronary resistance with the smallest effective dose of noradrenaline (5 ng), changes to a biphasic response as the dose is increased to (40 ng), and myocardial amplitude and rate are more affected. Time scale: min.

Monkey. Fig. 2B shows qualitatively that the monkey isolated heart gave a response similar to the cat and dog preparations, but differed in that the increase in coronary resistance with the smallest dose (5 ng) was more prolonged than that seen with the cat and dog hearts, and the biphasic response did not begin until the dose reached 40 ng. The effect on the myocardium was less marked than with the other species. There was no increase in rate until 20 ng. At 5 ng it is doubtful if the slight increase in amplitude of contraction could be called significant, but a clear, though small, increase did occur at 10 ng.

In all three species, as the dose was increased towards the levels generally used (0·1–1·0 μg), the initial increase in resistance became proportionately smaller and its duration became shorter until the decrease in resistance became the predominant effect. This response would not be apparent with a summated type of record of greater than a few seconds duration, which would indicate a decrease in resistance.

Discussion

The concentration of noradrenaline in the plasma of the rabbit is about 1 ng/ml (Muscholl & Vogt, 1957), in the rat and cat it is 15 ng/ml and 27 ng/ml respectively (Farrant, Harvey & Pennefather, 1964), in the dog 2 ng/ml (Goott, Rosenberg & others, 1960), and in the whole blood of the "non-resting" man it is 5 ng/ml (Weil-Malherbe & Bone, 1953). Most recent work on the effect of catecholamines on the coronary resistance has been with dog and man. The concentrations of noradrenaline used were some fifty to two hundred times those found physiologically and caused marked stimulation of the myocardium. With a dose of noradrenaline which did not apparently affect the myocardium (Fig. 2B), or only minimally so (Figs 1A and 2A), the effect on the coronary resistance was one of transient increase. As the dose was increased the myocardium became increasingly affected and this was associated with the development of the biphasic response in the coronary resistance.

It is tempting to assume that in the lower "physiological" range of doses, in which the myocardial effect and therefore the support component of the coronary resistance was minimal, the effect on the coronary resistance arose directly from the action of noradrenaline on the coronary vessels, i.e. vasoconstriction. However, these results do not constitute proof of a direct vasoconstrictor action by noradrenaline on the coronary vessels but, taken with other reports (see below) they add to the evidence for such an action. Also, in the biphasic response seen with larger doses of noradrenaline and associated with moderate stimulation of the myocardium, it may well be that the prolonged decrease in resistance seen after the initial increase arises from the release of vasodilating metabolites associated with myocardial stimulation rather than as a direct action on the vessels, as suggested by Folkow, Frost & Uvnäs (1949).

Support for this delayed indirect action has been growing, and Krasnow, Hood & others (1964) have shown that although noradrenaline and isoprenaline stimulate the myocardium and increase myocardial oxygen

consumption, isoprenaline causes the coronary flow to rise out of proportion to demand and the coronary venous oxygen content to rise, while noradrenaline causes an increase in the oxygen extraction and a decrease in the coronary venous oxygen content. These responses were interpreted as indicating that isoprenaline has a direct vasodilating action in addition to the metabolic response it induces, and that noradrenaline must be primarily vasoconstrictor in spite of an increase in coronary flow. Further support may be inferred from the work of Szakacs & Cannon (1958) with animals treated with noradrenaline. These authors described pathological changes in the myocardium resembling sub-endocardial infarction which occurs from excessive coronary vasoconstriction.

The present results show that if the method of recording the coronary resistance is sufficiently sensitive and rapid in response, it is possible to use concentrations of noradrenaline approximating to those found physiologically, and to reduce the chance of artifact caused by excessive concentrations at which the myocardial stimulation becomes the dominant feature and two components of the coronary resistance—metabolic vasodilation and myocardial compression—are exaggerated.

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References

Baker, J. B. E. (1951). *J. Physiol.*, **115**, 30P.
Berne, R. M. (1958). *Circulation Res.*, **6**, 644–655.
Farrant, J., Harvey, J. A. & Pennefather, J. N. (1964). *Br. J. Pharmac. Chemother.*, **22**, 104–112.
Feinberg, H. & Katz, L. N. (1958). *Am. J. Physiol.*, **193**, 151–156.
Folkow, B., Frost, J. & Uvnäs, B. (1949). *Acta physiol. scand.*, **17**, 201–205.
Goott, B., Rosenberg, J. C., Lillehei, R. C. & Miller, F. A. (1960). *J. thorac. cardiovasc. Surg.*, **40**, 625–634.
Krasnow, N., Hood, W. B., Rollett, E. L., Yurchak, P. M. & Gorlin, R. (1964). *Am. J. Med.*, **37**, 514–525.
Muscholl, E. & Vogt, M. (1957). *Br. J. Pharmac. Chemother.*, **12**, 532–535.
Proctor, E. (1964). *J. Physiol., Lond.*, **177**, 4–5P.
Szakacs, J. E. & Cannon, A. (1958). *Am. J. Clin. Path.*, **30**, 425–434.
Weil-Malherbe, H. & Bone, A. D. (1953). *Lancet*, **1**, 974–977.
Yurchak, P. M., Rollett, L. E., Cohen, L. S. & Gorlin, R. (1964). *Circulation*, **30**, 180–187.