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THE ROLE OF BLOOD-PRESSURE LEVEL IN THE PRODUCTION OF VENTRICULAR ARRHYTHMIA IN THE RABBIT

BY

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During a study of the pressor effects of noradrenaline in normal and in hypertensive rabbits (Conway, 1955) it was found that the response to progressively increasing doses of noradrenaline by intravenous infusion was limited quite suddenly by the emergence of a characteristic cardiac irregularity (Fig. 1). This was thought to be due to a direct effect of noradrenaline on the myocardium, as had been demonstrated for adrenaline (Levy, 1913, 1914; Allen, 1934), and latterly for noradrenaline (Meek, 1941). Further study, however, showed that this was unlikely to be so, since the emergence of the arrhythmia was independent of the dose used. It was thought therefore that in the rabbit, at least, ventricular arrhythmia could be produced in circumstances in which the direct cardiac effects of adrenaline or noradrenaline could only be of secondary importance, and that the level of the blood pressure might be the essential factor.

METHODS

Nineteen normal and four hypertensive rabbits have been studied; of the hypertensive rabbits, three had been studied in their normal state and are therefore represented in both groups. Ten of the normal rabbits and the four hypertensives were studied in the conscious state and in six animals the experiments were repeated on more than one occasion. Hypertension was produced by enclosing the kidney in a latex capsule (Flasher, Drury, and Sobin, 1949). To measure the response to pressor drugs the conscious rabbits were placed in a heated box, where they remained, without restraint, until the ear artery was well dilated. After infiltration of the nerve at the base of the ear with 2% lignocaine, a needle (27 SWG) was lodged in the central artery and connected by a saline-filled polythene tube (approx. 20 cm.) to a condenser manometer and records were made with direct-writing oscillographs. The frequency response of the entire system was 30 c./sec. The diastolic blood pressure has been quoted throughout these experiments. Infusions or injections were given into the marginal vein of the same ear, and at each experiment the conditions required to produce the arrhythmia were usually produced three times.

In preliminary experiments, hexamethonium had been found to assist the production of arrhythmia by permitting a greater and more rapid rise in pressure to occur for a given dose of pressor drug without the complication of vagal slowing. In four experiments the effect of vagal section upon the production of arrhythmia has been shown. All but these four experiments were performed, therefore, after full doses of hexamethonium had been given. The initial dose of hexamethonium varied from 40 to 60 mg., with further doses of 10 mg., the criteria for which will be discussed later.

Electrocardiographic studies could not be made in conscious rabbits. Studies were therefore made in 9 rabbits under anaesthesia with pentobarbitone sodium (30 mg./kg.). Blood pressure measurements were taken from the femoral, carotid, or central artery of the ear, and an electrocardiogram was made from bipolar needle electrodes (from two fore-limbs or from one fore-limb and the chest).

Five of the normal animals and the four hypertensives were studied in the conscious state with infusions of

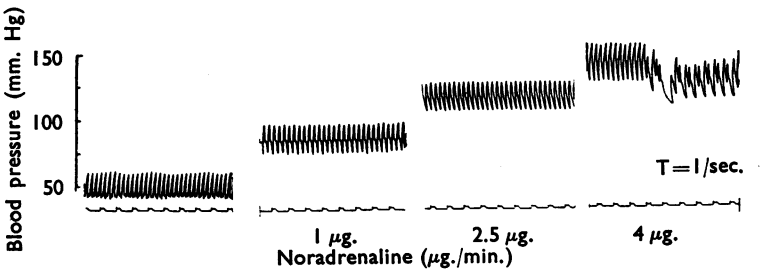

FIG. 1.—The effect of infusions of progressively increasing doses of (−)-noradrenaline after hexamethonium in a conscious rabbit.

noradrenaline alone. Increasing doses were used to produce step-wise increments of pressure until the abnormality appeared. (−)-Noradrenaline bitartrate in saline was used and doses quoted are of the base. For the remaining conscious animals, and those studied under anaesthesia, the effects of infusions of posterior pituitary extract and injections of renin were used in addition to noradrenaline either alone or in combination with the pituitary extract or renin. The posterior pituitary extract was the commercial product "Pitressin" (Parke Davis), and the renin was a lyophilized extract of hog renin kindly given by Dr. H. Goldblatt.

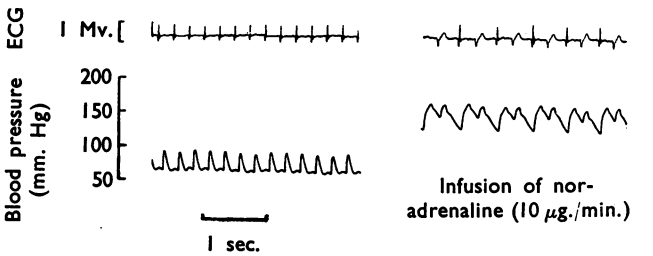

FIG. 2.—The production of ventricular arrhythmia by an infusion of (−)-noradrenaline in an anaesthetized rabbit after hexamethonium.

RESULTS

The Nature of the Cardiac Irregularity

When noradrenaline was administered by intravenous infusion the pressor response was limited, quite suddenly, by the emergence of a characteristic arrhythmia (Fig. 1). The electrocardiographic characteristics of the arrhythmia were observed therefore in the 9 experiments conducted under general anaesthesia. The effect of the arrhythmia on the blood pressure was characteristic. As the blood pressure rose the cardiac arrhythmia appeared suddenly as a premature ventricular beat occurring regularly in alternate heart beats (Fig. 2). Sometimes the premature beat was preceded by a P wave occurring normally in the cardiac cycle with consequent shortening of the P–R interval (Figs. 3 and 4). The resultant pulse wave characteristically showed bigeminal rhythm with the premature beat weaker than the normal one. When the prematurity of the ventricular beat was very slight, pulsus alternans appeared (Fig. 4). The ventricular beats arose initially from a single focus; if the abnormality was allowed to persist it became more severe, ventricular tachycardia appeared (Fig. 3) and in 4 experiments bizarre patterns arising from multiple ventricular foci appeared. In some experiments elevation of the blood pressure was accompanied by depression of the S–T segment of the electrocardiogram (Fig. 5). The importance of this change could not be ascertained, but it was not regarded as an essential feature since the ventricular arrhythmia was produced in the absence of S–T depression.

The mean diastolic pressure in the conscious rabbits at rest, measured from the dilated ear artery, ranged from 50–68 mm. Hg; this was approximately 10 mm. Hg below the aortic or carotid blood pressure. Infusions of (−)-noradrenaline (4–5 μg./min.) in the normal rabbits, after large doses of hexamethonium, produced the ventricular arrhythmia at an average blood pressure of 115 mm. Hg (Table 1A). This did not appear to distress the animals in any way. Large doses of hexamethonium were used in these experiments because the arrhythmia was produced more readily in the absence of the full action of the depressor reflexes. The adequacy of the ganglionic blockade was judged by production of maximal depression of blood pressure, fixation of the pupillary light reflex, and the absence of further potentiation of the pressor response to noradrenaline or change in heart rate.

Vagal activity was not responsible for the cardiac

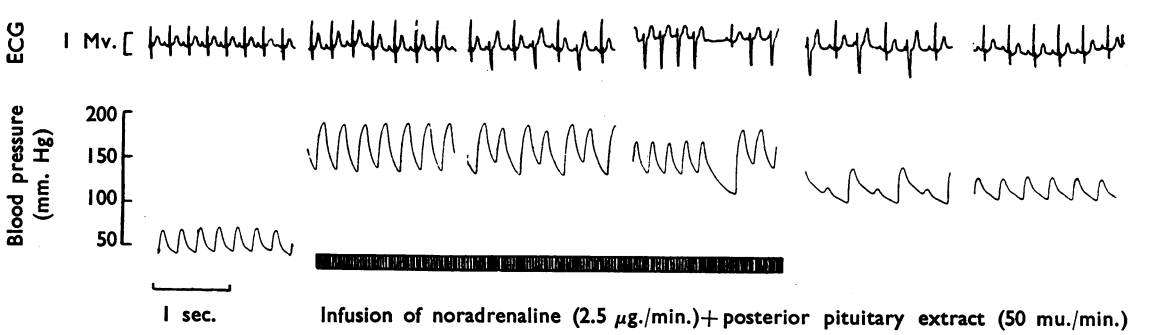

FIG. 3.—The production of ventricular arrhythmia by a mixture of (−)-noradrenaline and posterior pituitary extract, showing the increasing severity of the arrhythmia with a prolonged infusion. Sections of tracing shown were taken at one minute intervals.

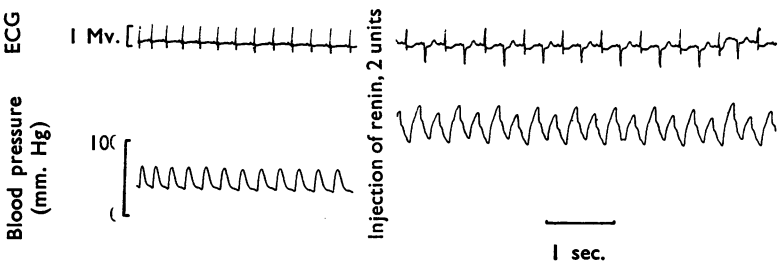

FIG. 4.—The production of ventricular arrhythmia by an injection of renin.

TABLE I

THE PRODUCTION OF VENTRICULAR ARRHYTHMIA BY INFUSIONS OF NORADRENALINE (4–5 μG.) IN NORMAL AND IN HYPERTENSIVE RABBITS

Rabbit No.	Average Pressure at which Arrhythmia Appeared (mm. Hg)
A. *Normal rabbits*	
99 (4 occasions)	124
89 (2 „)	116
78	112
88 (2 „)	108
79	116
	Mean 115 (S.D. ±6)
B. *Hypertensive rabbits*	
78 (2 occasions)	200
71	174
88 (2 „)	210
79 (4 „)	184
	Mean 197 (S.D. ±17·2)

irregularities, for in experiments under anaesthesia in 4 rabbits, section of both vagi had no effect upon the production of arrhythmia, upon the dose of noradrenaline required, or upon the level of blood pressure at which it appeared (Table II).

The Use of Different Pressor Agents

In order to determine whether noradrenaline produced these cardiac irregularities by virtue of some specific effect upon the myocardium or indirectly as a result of elevating the blood pressure, a further series of experiments was performed. When the dose of noradrenaline was reduced and the blood pressure maintained by adding posterior pituitary extract to the infusion fluid, the cardiac arrhythmia appeared at the same pressure (Table IIIA, Fig. 3). The importance of the level of pressure in the production of the ventricular arrhythmia could not be investigated further with posterior pituitary extract, since larger doses of posterior pituitary extract (100–200 mu./min.) neither produced the arrhythmia nor elevated the blood pressure to adequate levels. Injections of renin, however, raised the blood pressure to the necessary level and also provoked the cardiac arrhythmia (Table IIIA, Rabbit 91). The experiments with variations in pressor agents were performed initially in the anaesthetized animals and were extended and confirmed in the conscious animals (Table IIIB).

The evidence strongly suggested that the level of pressure was the essential feature in the production of ventricular arrhythmia, the pressor agent, and particularly noradrenaline, having no detectable action of its own. Further evidence to support this was obtained in 4 experiments when amyl nitrite, administered by inhalation, abolished the arrhythmia as it lowered the blood pressure. This is illustrated in Fig. 5, in which it may also be seen that the depression of the S–T segment of the electrocardiogram was not affected by the amyl nitrite.

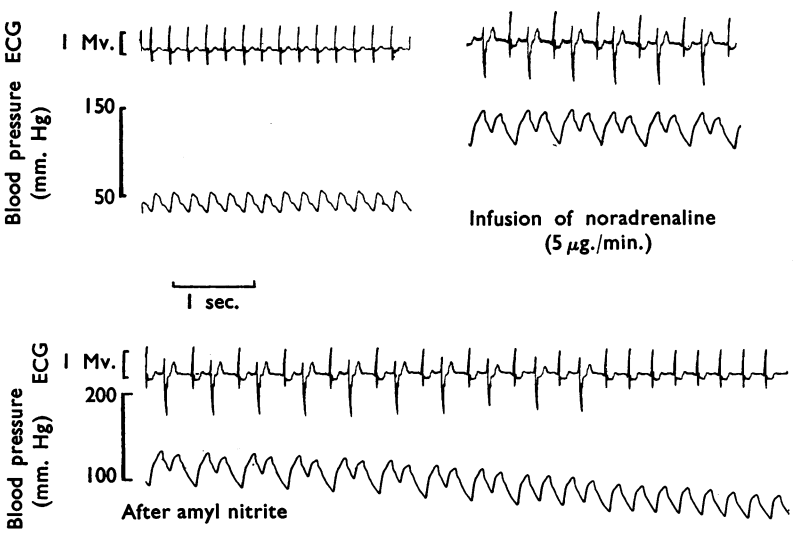

FIG. 5.—The production of ventricular arrhythmia by an infusion of (−)-noradrenaline and its abolition by the inhalation of amyl nitrite. The infusion of noradrenaline was continued after the inhalation of amyl nitrite.

TABLE II

THE EFFECT OF VAGAL SECTION UPON THE PRODUCTION OF VENTRICULAR ARRHYTHMIA IN ANAESTHETIZED NORMOTENSIVE RABBITS

Rabbit No.	Noradrenaline (μg./min.)	Average Pressure at which Arrhythmia Appeared (mm. Hg)	
		Vagi Intact	Vagi Cut
011	10	146	134
012	10	118	122
013	10	148	138
014	5	132	120

The Effect of Hypertension

Since the evidence pointed to the sudden elevation of pressure as the agent provoking the ventricular arrhythmia, a further series of experiments was performed in animals with experimental renal hypertension. In these comparative experiments precisely the same procedures were adopted in the normal and in the hypertensive animals. Conscious animals were used throughout. Noradrenaline was administered in progressively increasing doses by infusion into the marginal vein of the ear (Fig. 1) until the arrhythmia appeared.

The diastolic pressure at rest in the conscious rabbit ranged from 50–68 mm. Hg, and the mean pressure at which the arrhythmia appeared was 115 mm. Hg (S.D.±6) (Table I). In the hypertensive animals the diastolic pressure ranged from 84–102 mm. Hg, and the average pressure required to provoke the arrhythmia was 197 mm. Hg (S.D.±17.2); the difference between these means was statistically significant ($t=9$, $P<.001$).

DISCUSSION

Premature ventricular contraction and bigeminal rhythm was shown to follow a rise in systemic arterial pressure due to aortic compression by Rothberger and Winterberg (1910). This was confirmed by Levy (1914), who thought that the arrhythmia thus produced was different from the one evoked by adrenaline in cats sensitized with chloroform. The production of arrhythmias by adrenaline in sensitized dogs depends to some extent upon the level of blood pressure, since drugs which prevent the pressor response to adrenaline (F933) also suppress the arrhythmia (Shen, 1938). Evidence, however, accumulated that adrenaline-blocking drugs had a specific effect protecting against ventricular arrhythmias, and the part played by the level of blood pressure became obscure. It was shown in cats and rabbits that F933 not only suppressed ectopic ventricular beats produced by adrenaline but also those which were obtained with other agents or by electrical stimulation (Van Dongen, 1939). Furthermore, it could be shown that mechanical prevention of blood-pressure elevation could not completely prevent the arrhythmia produced by adrenaline after cyclopropane, whereas dibenamine could do so (Moe, Malton, Rennick, and Freyburger, 1948). This specific activity of dibenamine was confirmed by Nickerson and Nomaguchi (1949), who showed

TABLE III

THE EFFECT OF DIFFERENT DRUGS UPON THE LEVEL OF PRESSURE AT WHICH VENTRICULAR ARRHYTHMIA APPEARED IN NORMOTENSIVE RABBITS

Rabbit No.	Drugs	Average Pressure at which Arrhythmia Appeared (mm. Hg)
A. *Under anaesthesia*		
96 (2 occasions)	Noradr. 5 μg./min.	160
	Postpit. 50 mu./min. + noradr. 2·5 μg./min.	144
06	Noradr. 10 μg./min.	162
93	Noradr. 5 μg./min.	128
	Postpit. 50 mu./min. + noradr. 2·5 μg./min.	134
05	Noradr. 5 μg./min.	134 Abolished by amyl nitrite at 60
	Postpit. 50 mu./min. + noradr. 2·5 μg./min.	130
91	Noradr. 5 μg./min.	140 Abolished by amyl nitrite at 100
	Renin 2 units	116 Abolished by amyl nitrite at 90
		Mean 136
B. *In the conscious state*		
92 (2 occasions)	Postpit. 50 mu./min.	130
	Renin 0·5 units	96
	Renin* + noradr. 2·5 μg./min.	104
83	Renin 0·5 units	120
	Renin* + noradr. 1 μg./min.	114 Abolished by amyl nitrite at 94
01	Renin 0·5 units	114
08	Noradr. 10 μg./min.	144
	Renin 0·5 units + noradr. 1 μg./min.	126
97	Renin 0·75 units	94
	Renin* + noradr. 1 μg./min.	110
		Mean 116

* The pressor effect of an injection of renin was very prolonged. It was therefore possible, during the gradual decline in blood pressure, to give an infusion of a small dose of noradrenaline.

that larger doses of dibenamine were necessary to prevent arrhythmias than were necessary to reverse the pressor response to adrenaline. It appeared therefore that elevation of the blood pressure was not essential for the production of arrhythmias by adrenaline after chloroform or cyclopropane, yet it remained a contributory factor, since doses of dibenamine just sufficient to prevent adrenaline arrhythmia became ineffective after mechanical elevation of the blood pressure.

The role of the level of pressure in the genesis of ventricular abnormalities was described by Dawes (1952) as one of 3 main variables capable of producing arrhythmias, but not as a crucial factor under all circumstances. The present studies have shown, in the rabbit at least, that the level of pressure may readily be the sole agent responsible for the production of ventricular arrhythmias. As far as can be seen from electrocardiographic evidence, the arrhythmias are the same as, though perhaps milder than, those occurring after chloroform or cyclopropane. In these experiments a direct action of noradrenaline could not be demonstrated. Since the arrhythmias were produced in animals under the influence of hexamethonium, and have also been reported to occur in the heart-lung preparation (Moe *et al.*, 1948), the level of blood pressure must be assumed to act directly upon the excitability of heart muscle, either through the excessive tension developed in systole, or by influencing diastolic size by increasing the systolic remainder. The protective effect of continued hypertension must be due to the muscular hypertrophy it initiates.

Recognition of the part played by the level of pressure in the production of ventricular irregularities might, if it can be shown to apply to man, be of practical value in the prevention or treatment of ventricular irregularities. This aspect deserves study, since it has been suggested that circulatory obstruction is a factor in the precipitation of ventricular fibrillation in cardiac surgery (Milstein and Brock, 1954). It is also possible that sudden elevation of pressure and ventricular fibrillation could be responsible for the sudden deaths occurring tragically at minor operations.

Summary

1. The circumstances responsible for the production of ventricular arrhythmia have been studied in the rabbit in the conscious state and under anaesthesia.

2. (−)-Noradrenaline, given by infusion to conscious normal rabbits in adequate doses, provoked the arrhythmia at an average blood pressure of 115 mm. Hg. The electrocardiogram showed that the arrhythmia was ventricular in origin, usually arising from a single focus and alternating with normal beats.

3. By using other pressor agents—posterior pituitary extract or renin—it was shown that the emergence of the arrhythmia depended upon the level of blood pressure and not upon the dose of noradrenaline.

4. The inhalation of amyl nitrite temporarily abolished the arrhythmia.

5. After the production of chronic hypertension the average level of blood pressure required to provoke the arrhythmia was 194 mm. Hg.

6. The possible practical implications of these observations are discussed.

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