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OUABAIN-INDUCED VENTRICULAR TACHYCARDIA AND ITS EFFECT ON THE PERFORMANCE AND METABOLISM OF THE DOG HEART

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At constant pressure work there was an increase in the oxygen consumption of the dog heart-lung preparation after tachycardia due to auricular stimulation and a far greater increase in consumption after ouabain-induced ventricular tachycardia, as compared with control hearts beating at their own sinus rhythm. In neither condition was the increase in coronary flow greater than the spontaneous increase in the controls. It is suggested that an increase in oxygen demand, under certain circumstances, may be met primarily by an increased desaturation of coronary blood. "Therapeutic" doses of ouabain did not improve the mechanical efficiency of the preparation. "Toxic" doses of ouabain which gave rise to ventricular tachycardia did not decrease the phosphocreatine or labile nucleotide phosphorus content of the heart provided there was no hypoxia of the heart muscle.

In intact dogs and in heart-lung preparations digitalis glycosides produce arrhythmias which usually lead to ventricular tachycardia and fibrillation. This paper deals mainly with the effect of ventricular tachycardia induced by ouabain on the performance and metabolism of the heart of the dog. Two groups of experiments served as controls: in one the ventricular rate was regulated by electrical stimulation of the auricle at the rate observed in the presence of ouabain; in the other, untreated control hearts beat at their own sinus rhythm.

METHODS

Male and female dogs were used weighing about 12 kg. Coronary flow was measured by our own modification of the Rodbard technique (Fawaz and Tutunji, 1957). This allows perfusion of both lungs with blood, direct measurement of coronary flow and oxygenation of the total "venous" blood in the reservoir. Oxygen consumption was determined by the direct Fick method. The oxygen content of the arterial and venous samples was estimated by the Van Slyke manometric method. In these experiments the lungs were ventilated with oxygen, but no oxygen was bubbled through the venous reservoir. Ouabain (1 : 100,000) was infused at the rate of 0.5 ml./min. The auricle was stimulated with monophasic impulses of 2 msec. duration from a Grass electronic stimulator. Experiments with ouabain lasted about 1 hr. and were terminated during the period of ventricular tachycardia a few minutes before ventricular fibrillation was expected. In a few experiments, blood samples were taken for analysis at the usual time and ventricular fibrillation was permitted, but in such cases the phosphorus compounds were not analysed. An experiment employing electrical stimulation followed every experiment with ouabain and the auricular stimulation was adjusted to duplicate as far as possible the changes in ventricular rate observed in the preceding experiment with ouabain. The control hearts beat at their own rhythm for 1 hr. The mean systemic arterial pressure was kept at about 100 mm. Hg and the total left ventricular output ranged from 800 to 1,000 ml./min. Other experimental details have been reported previously (Fawaz and Tutunji, 1957).

RESULTS

The results are summarized in Table I. In these experiments, unlike the control experiments reported earlier (Fawaz and Tutunji, 1957), a special attempt was made to keep the systemic arterial pressure as well as the work performed by the heart constant.

Coronary Flow and Desaturation of Coronary Blood.—It is common knowledge that coronary flow in a heart-lung preparation increases with time. In our experiments little change was observed after 20 min., but after 1 hr. the coronary flow was more than doubled. This was true of all three groups of experiments. Increased heart rate due to auricular stimulation has been reported to increase

TABLE I

EFFECT OF TACHYCARDIA ON ISOLATED DOG HEART

The numeral (1) indicates at the start of the experiment, (2) after 20 min., and (3) at the end of the experiment.

	No. of Expts.	Mean Ventricular Rate/min.			Mean Change in Arterial Pressure (mm. Hg)		Coronary Flow Mean±S.E. (ml./min.)			% Change in Work Performed Mean±S.E.		% Change in Oxygen Consumption Mean±S.E.		Mean O_2 Content of Coronary Venous Blood (vol. %)		Phosphorus Compounds of Heart Muscle Mean±S.E. (% of Total-Acid-Soluble-P)		
		(1)	(2)	(3)	(2)	(3)	(1)	(2)	(3)	(2)	(3)	(2)	(3)	(1)	(3)	Phosphocreatine	Inorganic P	Labile Nucleotide P (2/3 of ATP)
Controls . .	7	130	129	126	−0·1	−0·4	74±21	86±17	190±18	+0·46±2·2	−6·2±2·5	−0·84±2·9	−11·1±4·4	6·4	12·9	23·7±1·1	16·3±0·9	29·5±0·9
Ventricular tachycardia induced by ouabain	14	126	125	198	+1·1	−4·6	62±7	77±15	168±20	+6·3±5·1	−1·2±4·0	−0·56±4·1	+76±13·0	7·0	9·2	21·3±2·0	19·6±2·0	29·0±0·8
Tachycardia due to auricular stimulation	14	122	125	202	−0·5	−3·6	55±3	79±7	183±16	+1·6±1·2	−0·54±3·4	−0·54±2·8	+23·3±8·5	6·1	11·8	25·7±1·5	13·1±1·4	29·2±0·3

coronary flow in the intact dog (Laurent, Bolene-Williams, Williams, and Katz, 1956; Berglund, Borst, Duff, and Schreiner, 1958). It is of interest that in our experiments increased heart rate due to auricular stimulation did not increase coronary flow above the " spontaneous " increase observed in the controls. If the same heart rate was induced with ouabain, the oxygen consumption of the heart was still further increased, but this was not accompanied by a correspondingly greater increase in coronary flow. Clearly, the increased oxygen demand was met by a greater degree of desaturation of coronary blood.

It is not possible to predict in each case whether an increased oxygen demand by the heart will be met by increased coronary flow with constant arteriovenous oxygen difference, or by an increase in the latter. Both are possible and we have previously shown that increased cardiac oxygen consumption due to dinitrophenol could reduce the oxygen content of coronary venous blood to as little as 2 vol.% (Fawaz, Hawa, and Tutunji, 1957). It is generally assumed that the first response to elevated cardiac oxygen demand is an increase in coronary flow and that, when this is insufficient, an increased desaturation of coronary blood ensues. In the experiments with ouabain reported here, the latter mechanism came into play, for, though during ventricular tachycardia oxygen consumption was increased by an average of 76% in comparison with the controls, there was no greater increase in coronary flow. It may perhaps be more appropriate therefore to suggest that in the denervated heart the choice between the two mechanisms depends on the extent to which the coronary blood is desaturated at the time of the increase in oxygen demand. If the coronary venous oxygen content is high, as in the control experiments reported here, the increased oxygen demand can be met by increased desaturation without an increase in coronary flow. Further, it is possible that the nature of the stimulus to increased oxygen consumption largely determines the choice.

Oxygen Consumption and Mechanical Efficiency.—The mechanical efficiency of the control hearts, with a total left ventricular output of 800 to 1,000 ml./min., ranged between 8 and 10%. Within the first hour at least, there was no increase in the oxygen consumption of the control hearts and thus no change in " efficiency " (Table I). Starling and Visscher (1927) observed some decrease in the latter after 1 hr. However, their technique as well as their preparations differed from ours in such respects as total output (that of our hearts was twice as great as theirs) and load on the right heart.

The increased oxygen consumption in tachycardia due to auricular stimulation agreed with the findings of Laurent *et al.* (1956) and Berglund *et al.* (1958) on intact animals. However, ventricular tachycardia induced by ouabain led to a far greater increase in oxygen consumption and a corresponding decrease in mechanical efficiency.

Our experiments also throw some light on the question whether therapeutic doses of ouabain increase the mechanical efficiency of the heart. Twenty min. after the ouabain infusion, there was no change in oxygen consumption and thus no change in efficiency. Although the rate of ouabain infusion was not optimal we were still within the " therapeutic " range at 20 min. (Farah and Maresh, 1948); no irregularities were observed till then. We have repeatedly infused ouabain at this rate into heart-lung preparations to demonstrate its therapeutic potency in failure induced by a barbiturate and have convinced ourselves that, at 20 min., the " therapeutic " action of ouabain was evident. Rein (1949) reported that a heart-lung-liver preparation showed a greater mechanical efficiency than the classical preparation and he suspected the presence of digitalis-like substances in the liver which increased the efficiency of the heart. He also stated that the addition of digitalis acted in a way that resembled the inclusion of a liver in a heart-lung preparation. The experimental situation used by Rein (1949) was quite different from ours, but it was clear that under our conditions ouabain did not improve efficiency.

Phosphorus Compounds.— There was no significant change in the phosphocreatine or " labile nucleotide " phosphorus content of the left ventricular musculature after auricular stimulation or during ventricular tachycardia induced by ouabain. This is understandable when we examine the oxygen content of coronary venous blood (Table I). We have previously shown that myocardial phosphocreatine is particularly sensitive to even short periods of hypoxia produced by ischaemia or hypoxaemia (Fawaz *et al.*, 1957): in fact, we consider that a normal level of phosphocreatine indicates that the tissue has been properly handled before fixation. Wollenberger (1951) reported a decrease in the phosphocreatine content of the isolated dog heart during ventricular tachycardia induced by digitalis. However, in his experiments neither coronary flow nor coronary venous oxygen content was measured and the systemic flow was about half the value reported here. In view of the increased oxygen consumption observed after toxic doses, we suspect that an element of hypoxia was responsible for the low values for phosphocreatine found by Wollenberger (1951). Further, we had previously shown that the " resting " phosphocreatine values reported by Wollenberger (1951) for the isolated heart and particularly for the intact heart were too low (Fawaz and Hawa, 1953). The low phosphocreatine values reported by the same author for hearts at the onset of ventricular fibrillation induced by digitalis are obviously due to hypoxia (Fawaz *et al.*, 1957).

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