CONTRACTILE FUNCTION OF THE HEART IN RABBITS WITH EXPERIMENTAL THYROTOXICOSIS

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Experimental thyrotoxicosis in rabbits is accompanied by increased contractile activity of the heart and a sharp decrease in the functional reserve of the organ. The contractility of the myocardium rises to begin with and then falls to the control level.

The rapid onset of cardiac failure in untreated cases of thyrotoxicosis demands assessment of the contractile function of the myocardium at the various stages of this disease. The existing data [2, 7] are based, as a rule, on indirect indices of the contractile function of the heart. Only in a few cases [12] has myocardial function been assessed with the aid of indices having the closest correlation with the energy expenditure of the heart. Such indices, as recent work has shown, include the tension-time index [15] and the maximal rate of development of tension (pressure) in the ventricle [17].

In the present investigation indices of the contractile function of the heart were determined during the development of experimental thyrotoxicosis.

EXPERIMENTAL

Experiments were carried out on male rabbits weighing 2.5-3.5 kg. Thyroid extract was given by mouth in increasing doses for 2 and 4 weeks [5]. Under chloralose-urethane anesthesia (200 and 50 mg/kg, respectively), and under artificial respiration, thoracotomy was performed and a catheter inserted into the chamber of the left ventricle. A second catheter was inserted via the carotid artery into the aortic orifice. The pressure was recorded by means of "Barovar" electromanometers. The operational amplifier of a type NBN-1 analog computer, with calibrated output signal, was connected to the output of the electromanometer amplifier. The signals were recorded on a San Eisokki loop oscillograph. By dividing the values of each recorded index by the weight of the left ventricle, the intensity of function of the myocardial structures (IFS) [6] was calculated. Indices of contractile function were measured (A) before and (B) after total occlusion of the aortic orifice. The ratio B : A was regarded as an index of the functional reserve of the myocardium [2]. The tension-time index (TTI) was calculated on the basis of the mean intraventricular pressure, not the aortic pressure [17]. Besides the TTI, the maximal intraventricular pressure, and the maximal rate of increase of that pressure (dp/dt_{max}), Opie's index [14], the product of maximal intraventricular pressure and heart rate ($\times 10^{-3}$), was determined. The potential reserves of the heart were also characterized by means of "fatigue ladders" [1], allowing for the degree of decrease of intraventricular pressure during successive (every 5 min) and brief (30 sec) occlusions of the aorta and the number of these occlusions before the heart stopped or fibrillation began. The contractility of the myocardium, reflecting its state irrespective of myocardial function as a pump, was estimated by means of the formula

$$\frac{dp/dt_{max}}{\text{IIT}},$$

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TABLE 1. Indices of Contractile Function of the Heart in Rabbits with Experimental Thyrotoxicosis

Index studied	I control (n = 7)	II thyrotoxicosis for 14 days (n = 11)		III thyrotoxicosis for 28 days (n = 10)		
	$M \pm m$	$M \pm m$	P_{I-II}	$M \pm m$	P_{I-III}	P_{II-III}
Maximal pressure in left ventricle, P_v (in mm Hg)	110,4±10,4	165,2±10,8	<0,05	173,3±12	<0,01	>0,5
IFS based on P_v (in mm Hg/g)	23±1,6	33±2,3	<0,05	39,8±2,3	<0,001	<0,05
Function reserve of the heart based on P_v	2,4±0,27	1,48±0,1	<0,01	1,28±0,08	<0,01	>0,1
Maximal rate of increase of pressure in left ventricle, dp/dt_{max} (in mm Hg/sec)	3 488±597	6 504±724	<0,01	6 760±980	<0,05	>0,5
IFS based on dp/dt_{max} (in mm Hg/sec/g)	717±94,3	1 300±149	<0,01	1 531±272	<0,05	>0,4
Function reserve of the heart based on dp/dt_{max}	2,33±0,24	1,35±0,13	<0,01	1,45±0,11	<0,001	>0,5
Tension-time index (TTI) (in mm Hg·sec/g)	2 148±318	3 375±308	<0,05	3 404±225	<0,01	1
IFS based on TTI (in mm Hg/sec/g)	551±52	665±57	<0,05	756±54	<0,01	>0,3
Functional reserve of the heart based on TTI	4,92±0,5	1,66±0,26	<0,01	1,81±0,14	<0,001	>0,6
Opie's index (in mm Hg·beats/min·10^{-3}	26,4±3,7	59,6±6,3	<0,001	69,5±5,2	<0,001	>0,2
Index of contractility after Veragut (in sec^{-1})	60±5,8	110±15	<0,01	73±4,7	0,1	<0,05
Index of contractility after Siegel and Sonnenblick (in sec^{-2})	3 354±398	6 323±1 006	<0,05	4 210±500	0,2	0,08

where IIT denotes the integral isometric tension of the ventricle, calculated planimetrically [16], and also by the formula

$$\frac{dp/dt_{max}}{PC},$$

where P_c denotes the intraventricular pressure at the point of its maximal rate of increase [18].

EXPERIMENTAL RESULTS AND DISCUSSION

The experimental results are given in Table 1.

Experimental thyrotoxicosis in the rabbits was accompanied by an increase in the maximal pressure inside the left ventricle. However, as the pathological state becomes more severe, this index no longer increased. The dynamics of the other indices of the contractile function of the heart was similar: although increased in the relatively early, "compensated" stage of thyrotoxicosis [3], they later became stabilized at this level, despite the increased blood flow required by the animal. Although the general trend of the changes in all studied indices was the same, the degree of increase of contractile function of the heart in thyrotoxicosis differed for each of them: from 50 to 125%. This fact probably reflects differences in the degree of correlation between each index and the energy expenditure of the heart muscle in the performance of its physiological function. While recognizing the TTI as an index of contractile function of the heart, Meerson [6] rightly points out that this index is indirect in nature, because the equal pressure in ventricles of different sizes may be the result of differences in the tension in their walls. This objection can evidently be extended also to the maximal intraventricular pressure. Sonnenblick and co-workers [17] showed that under certain conditions the energy expenditures of the heart and the TTI may change in different directions. Other investigators have obtained similar data [11, 13]. Sonnenblick concluded that "with an increase in the contractile function of the myocardium, the TTI loses its value as an index of oxygen consumption by the heart; the value of dp/dt_{max} correlates more closely with the energy expenditure of the myocardium during

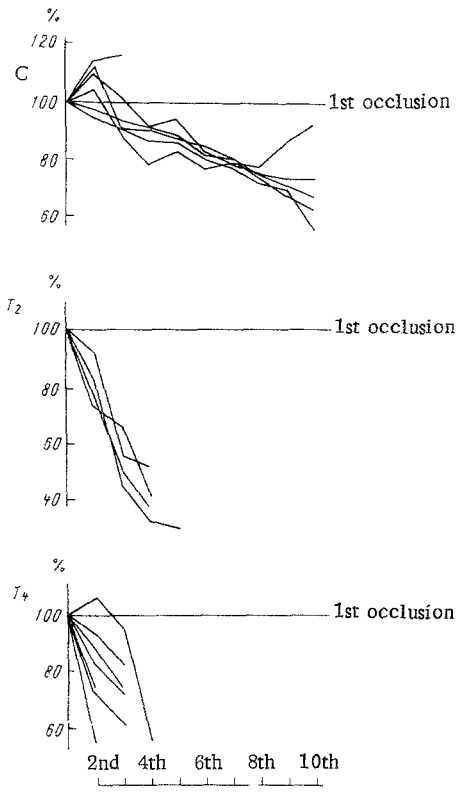

Fig. 1. Curves showing fatigue of myocardium of left ventricle during successive occlusions of aorta; ordinate, deviation of intraventricular pressure after each occlusion from its value after first occlusion (in %). C) control; T_2) thyrotoxicosis for 2 weeks; T_4) thyrotoxicosis for 4 weeks.

its function. In the modern view, the rate of shortening of the fibers of a muscle reflects the rate of formation of cross linkages between filaments of actin and myosin, i.e., the rate of liberation of energy from ATP. For that reason, the index dp/dt_{max} must determine the expenditure of energy and, correspondingly, the oxygen consumption of the myocardium in unit time. Feinberg and co-workers [10] showed that the correlation between dp/dt_{max} and the oxygen consumption of the heart persists also during isovolumic contractions. Consequently, shortening of the myocardial fibers is not essential for the maintenance of this correlation, and the index dp/dt_{max} reflects the contractile function of the myocardium, even during complete occlusion of the aorta.

It is an interesting fact that the increase in contractile function of the heart in thyrotoxicosis, judging from all indices studied, was the result of an intensification of the function of each unit of mass of the myocardium (IFS). This confirms the writers' previous conclusion regarding the insufficiency of hypertrophy of the "thyrotoxic" heart [4]. This insufficiency is evidently the reason for inability of the myocardium to recover from the emergency [6] stage of compensatory hyperfunction. Under such conditions it is natural to suggest that the functional reserve of the heart may be exhausted.

In fact, the functional reserve, which the writers define as the ratio between the maximal possible myocardial function and its actual function [2], was much smaller in animals with thyrotoxicosis than in controls, regardless of which index was used to determine it. It is curious, however, that in severe thyrotoxicosis this parameter remained at the same level as in milder or earlier ("compensated") stages.

The possibility is not ruled out that the normal function of the organ is compatible with only a certain degree of lowering of its functional reserve, and even at this "critical" level of this index, the heart can continue to function only for a certain time. Under these conditions it is evidently unable to increase its real function further, despite whatever changes took place in the needs of the organism as a whole, as was observed in the present experiments. Advanced stages of thyrotoxicosis are thus evidently a model of cardiac failure against the background of sharply intensified myocardial function.

Severe exhaustion of the functional reserves of the myocardium is confirmed by curves showing its "fatigue" (Fig. 1). With a progressive increase in the severity and duration of thyrotoxicosis, during successive occlusions of the aorta the left ventricle is able to develop an ever diminishing pressure. The number of occlusions tolerated by the myocardium is also reduced.

In thyrotoxicosis the contractility of the myocardium undergoes characteristic changes. In relatively early stages of the disease it increases, in agreement with experimental results obtained by other workers [8, 9]. Bearing in mind the decrease in the functional reserve, this evidently means that in the course of its actual function the myocardium completely exhausts the facilities which it obtains from mobilization of the inotropic mechanism. In the subsequent stages of experimental thyrotoxicosis, myocardial contractility begins to diminish, and by the end of the experiment it reaches the control level. Hyperfunction of the heart under these circumstances is evidently due to the greater stretching of the ventricle walls.

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