ACCELERATION DEVELOPED BY THE MYOCARDIUM AS A CRITERION OF ITS CONTRACTILITY

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Evaluation of cardiac contractility is currently a topic for lively discussion, in the course of which the role of pre- and postloading in the regulation of the contractile function of the myocardium is gradually beginning to be recognized [2]. The search for a universal parameter of contraction, which will adequately reflect the level of mobilization of this property of heart muscle [1-5], also is continuing.

In this paper the writer has attempted to identify a parameter of contractility when the heart is exposed to the combined influence of several factors.

EXPERIMENTAL METHOD

The test object was cat heart–lung preparation (n = 12), sustaining a load at 38°C calculated at 40 ml/min/kg body weight, against a mean aortic pressure of 80 mm Hg. The heart was cooled to 25°C and the hemodynamics of the preparation studied during an increase of 1.5 times in the load by volume or resistance. In the course of the experiments the ECG, phonocardiogram, pressure in the aorta and left ventricle, and the first derivative of left-ventricular pressure were recorded on an N338 automatic writer, and the aortic fraction of the cardiac output was recorded continuously by means of P. M. Starkov's flowmeter [7], located between the Starling resistance and the venous reservoir of the preparation.

EXPERIMENTAL RESULTS

Cooling is a reliable method of revealing adequate and inadequate parameters of contractility (Table 1). In particular, if this property is assessed on the basis of the stroke work of the heart, it is possible to reach the paradoxical conclusion that myocardial contractility is increased by cold. However, this is not so, for any attempt to cool the heart below 25–23°C causes sudden inhibition of its activity, evidence that all its functional reserves are exhausted. In addition, the erroneous nature of this conclusion is due to the fact that values of the parameter obtained as a result of simultaneous action of two factors are being compared: the direct effect of temperature on contractility and lengthening of the contraction time, due to the action of cold on the excitation process. In order to make changes in stroke work comparable with its initial value, it is therefore necessary to normalize them with respect to time, i.e., to transform work into power, the time course of which gives unambiguous evidence of depression of cardiac contractility in hypothermia. The same conclusion can also be drawn by analysis of temperature shifts of stroke volume and of force and amplitude of contraction, which characterize the volume of the contractile act [5]. Hence, it follows that the velocity (i.e., normalized with respect to time) parameters more adequately reflect the state of contractility than volume parameters, which are arbitrary in character during cooling. This conclusion also means that isotropic effects do not always correlate with true changes of contractility, and for that reason there can be no justification for identifying these concepts, as is often done in the literature.

Temperature analysis of cardiac activity, thus, sharply reduces the range of parameters which adequately reflect myocardial contractility. However, even among the velocity parameters, by no means all of them satisfy the demands of universality. For instance, the volume velocity of ejection cannot be measured during contraction of the papillary muscle, and the power index is completely worthless under conditions of isotonic or isometric contraction when the work done by the muscle is zero. Accordingly, the most acceptable criterion of contractility remained the maximal rate of contraction of the myocardium, which has become widely used in experimental and clinical practice [1-6,8]. It is evident that the justification of this choice necessitates

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TABLE 1. Parameters of Activity of the Cooled Heart during Volume and Resistance Loading (M±m, P < 0.01)

Parameter determined	Conditions of work of the heart	Temperature, °C			
		38	35	30	25
Duration of cardiac cycle, msec	I	287±9	348±9	502±16	837±48
	V	289±7	348±9	502±17	852±49
	R	293±10	345±9	517±17	868±59
Isometric contraction, msec	I	46±1	52±1	55±2	61±4
	V	41±1	44±1	47±2	52±4
	R	48±1	51±1	56±3	62±3
Ejection time, msec	I	89±2	125±4	221±11	370±20
	V	96±3	136±4	232±11	404±23
	R	101±4	139±4	241±10	421±34
Stroke volume, $ml \cdot 10^{-2}$	I	57±2	67±4	82±8	105±9
	V	86±3	99±5	121±8	156±11
	R	50±3	59±4	70±6	88±11
Stroke work, $J \cdot 10^{-4}$	I	61±2	72±5	88±8	112±9
	V	96±3	112±6	136±10	173±12
	R	80±4	94±6	112±10	141±14
Power, $W \cdot 10^{-4}$	I	685±15	576±31	398±28	303±28
	V	1000±18	824±34	586±33	428±38
	R	792±49	676±37	465±40	335±40
Maximal rate of rise of pressure, mm $Hg \cdot sec^{-1}$	I	2488±109	2242±110	1959±110	1631±135
	V	2817±141	2588±109	2296±115	1862±118
	R	3442±157	3079±160	2729±156	2214±174
Volume velocity of ejection, $ml \cdot sec^{-1} \cdot 10^{-1}$	I	64±1	54±3	37±3	28±3
	V	90±2	73±3	52±3	39±3
	R	50±3	42±2	29±3	21±3
Acceleration developed by myocardium, mm $Hg \cdot sec^{-2} \cdot 10^{2}$	I	529±45	431±32	338±32	247±39
	V	704±64	575±38	459±39	332±49
	R	717±63	592±55	447±46	335±53

Legend. I) Initial conditions, V) volume loading, R) resistance loading.

making absolutely sure that changes in the maximal rate of contraction are identical when the heart is acted upon by different factors that are equivalent in the degree of mobilization of contractility. Volume and resistance loading, enabling the energy expenditure of the myocardium to be accurately graded, were chosen as these factors. It must be pointed out that the small decrease in cardiac ejection into the aorta observed during resistance loading does not contradict the control conditions, for it reflects an associated increase in the coronary fraction of the cardiac output under the influence of a mean intra-aortic pressure increased by 1.5 times. Nevertheless, as Table 1 shows, equivalent influences on the heart have different effects on the maximal rate of rise of pressure in the ventricle, from which it follows that this criterion likewise does not fully satisfy the demands of universality.

Meanwhile, careful analysis of the experimental conditions showed that simple comparison of maximal velocity during volume and resistance loading is not absolutely correct in character, for the first derivative of pressure in the ventricle as a rule does not reach its expected level during auxotonic contraction because of premature opening of the semilunar valves [8]. The peak of the first derivative of pressure recorded in our experiments therefore always coincided with the end of isometric contraction, the duration of which differed significantly with a change in load. Consequently, to compare shifts of the first derivative of pressure under different technical conditions, repeated normalization of pressure relative to time is essential, i.e., the acceleration developed by the myocardium must be calculated. This is the only criterion which showed virtually identical shifts in response to equivalent loads, despite the fact that the background values of acceleration itself varied more than twofold in the course of cooling (Table 1).

When the physiological significance of the acceleration developed by the myocardium is analyzed, attention must be paid to the fact that the peak of the first derivative of muscle tension coincides with the maximum of the calcium transition [2, 6], a key stage in electromechanical coupling in the myocardium. Hence, it follows that the acceleration developed by the myocardium (the second derivative of pressure) correlates with the rate of rise of the calcium level in the myoplasm (the first derivative of the calcium transiton), determining the rate of activation of the contractile element, i.e., the ability of the myocardium to contract, or its contractility, directly.

We can reach the above conclusion in another way, on the basis of Newton's second law, whereby, by contrast with the other principles of estimation of contractility, it is possible to take into account the role of preloading and postloading. Let us assume that $P = am$, when $a = \Delta V_S/\Delta t$, where P is the force developed by

the muscle in time Δt, Δv_S is the rate of shortening induced by it under these circumstances, a denotes acceleration, and m is a measure of inertia of the muscle + loading factor system. Analysis of the force–velocity relationship shows that momentary values of the rate of shortening V_S and the rate of development of tension V_T correlate closely with each other, i.e., with a certain approximation, $\Delta V_S = k\Delta V_T$, where k = const, and considering that $\Delta V_T = P/\Delta t$ and $a = k\Delta V_T/\Delta t^2$. But since k = const, the value of $P/\Delta t^2$ is perfectly suitable for use as the criterion of myocardial contractility, equally with acceleration of shortening a.

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EFFECT OF A 3-HYDROXYPYRIDINE DERIVATIVE MEMBRANE MODULATOR ON PHARMACOLOGICAL ACTIVITY OF SOME PSYCHOTROPIC DRUGS

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An intensive search for physiologically active compounds among the group of 3-hydroxypyridine derivatives is currently being undertaken and the mechanism of their action is being studied [12]. 3-Hydroxypyridine derivatives have been shown to be a promising class of neurotropic compounds with an original spectrum of pharmacological activity and mechanism of action that differs from those of other known preparations [5, 7, 11]. Antistressor, antiisochemic, antiarrhythmic, and anticonvulsant types of action have been found among 3-hydroxypyridine derivatives [8, 10]. Some workers [1, 10] associate the pharmacological activity of 3-hydroxypyridine derivatives with their ability to inhibit lipid peroxidation in biological membranes. Slowing oxidative reactions in membrane lipids by 3-hydroxypyridine derivatives has been shown to lead to changes in the composition and properties of the lipids [3]. This, in turn, is reflected in the structure of the membrane and its sensitivity to the action of xenobiotics and noxious factors, and it is also accompanied by changes in membrane function.

There is evidence in the literature that changes in phospholipid composition cause changes in activity of membrane-bound enxymes and, in particular, of adenylate cyclase and phosphodiesterase [2]. For example, administration of phospholipid liposomes, causing modification of the phospholipid composition of plasma membranes, modifies the conformation of adenylate cyclase, recognition and binding of hormones, and affinity of the enzyme for ATP [13]. These changes lead to an increase in activity of adenylate cyclase and its sensitivity to hormones. These results suggested that preliminary modification of the phospholipid composition of membranes by synthetic antioxidants of the 3-hydroxypyridine class could have a significant effect on the pharmacological activity of the psychotropic drugs.

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