Whether Independent Regulation of Myocardial Contractility and Diastolic Relaxation Rate Is Possible?

N. N. Alipov, A. V. Sokolov, L. V. Trubetskaya, and T. E. Kuznetsova

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In acute experiments on cats neural inotropic and lusitropic reactions of the heart to enhancement of pre- and afterload were assessed by changes in contractility and relaxation indices, which were preliminary chosen for their maximum specificity and sensitivity. The control cardiac responses to increased pre- and afterload were measured after treatment with ganglionic blocker arfonad. The myogenic component of these responses assessed under the action of arfonad was highly pronounced, therefore the neural inotropic and lusitropic reactions were measured as the difference between load-induced changes of indices in experiments with and without arfonad. Increased preload produced similar negative inotropic and lusitropic effects, while increased afterload produced a more pronounced negative inotropic effect, which indicated independent regulation of contractility and diastolic relaxation of the heart.

Key Words: *heart; neural regulation; inotropic influences; lusitropic influences; diastole; contractility indices*

Filling of the heart depends, among other things, on the rate of diastolic relaxation, which is affected by neural and humoral regulatory factors and by pharmacological preparations [7,8,10]. It remains unclear whether individual lusitropic influences (*i.e.* selective modulation of diastolic relaxation rate) exist or the rate of diastolic relaxation varies in parallel with contractility. Some pharmacological agents can produce predominantly inotropic or lusitropic effects [4-6], but this does not prove existence of intrinsic and independent neural inotropic and lusitropic influences. Few attempts to reveal these influences by stimulation of efferent cardiac nerves [3,9,11] also could not solve this problem, since electrical stimulation of the distal nerve end is an artificial event never occurring under natural conditions. The existence of independent inotropic and lusitropic influences can be experimentally proved only under conditions of modified natural neural traffic, *e.g.* stimulation of sensory nerves and reflexogenic areas. Any influence on the heart is accompanied by changes in preload and afterload. These changes, in turn, modulate contractility and relaxation parameters. To eliminate these influences, special contractility indices (CI) are used in the studies of neural regulation of the cardiac contraction force, which ideally are not affected by changes in the heart load, but are sensitive to inotropic effects including the neural ones. In reality, all available CI do not comply to this idealized performance. As for relaxation indices (RI), their number is low, and they are little studied. Some evidently improper RI were used previously (for example, dP/dt_{min}), which depended too heavily on the load influences, while purely myogenic reactions to pre- and afterload characteristic of pharmacologically denervated heart were not used as the control.

In this paper we studied lusitropic and inotropic reactions of the heart to the changes in pre- and afterload with preliminary chosen optimal CI and RI [1,2]. Since even the best indices are slightly sensitive to the loads, some experiments were made under conditions of ganglionic blockade. Comparison of the reactions

Department of Normal Physiology, Russian State Medical University, Moscow

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observed with and without blockade allows evaluation of the effect of direct neural influences on contraction and the rate of diastolic relaxation of the heart.

MATERIALS AND METHODS

Experiments were carried out on 45 cats. Blood pressure was measured in aortal orifice and in the left ventricle with a catheter inserted via the heart apex. Preload was modulated by rapid injection and aspiration of 10-20 ml blood via a catheter inserted into a hindlimb vein. Afterload was modulated by short-term complete clamping of the descending aorta. Ganglionic blockade was modeled with trimetaphan camsilat (Arfonad, Hoffmann-La Roche). Parameters $(dP/dt)_{max}/R_{time}$ [1] and $(-dP/dt)_{45,rel} \times V_{mean}$ [2] were used as CI and RI, respectively.

The results were analyzed statistically using nonparametric tests (percentage of significant positive, significant negative, and insignificant changes of the indices induced by load stimulation) and parametric indices (ratio of mean index values during and before stimulation). The details were described elsewhere [2].

RESULTS

In arfonad-free (control) cats with intact innervation, increased preload induced a rise of both indices; in most cases, increased afterload led to elevation of RI, while CI can decrease or, more often, increase (Table 1, Fig. 1, *b*, *d*). The indices rose by, on average, 1.2-1.5 times in response to increased loads (Fig. 2, *a*, *b*).

Specific features of cardiac responses to load was revealed by comparison of innervated heart and the hearts in cats with ganglionic blockade. In most arfonad-treated (experimental) cats, the increase in pre- and afterload also elevated these parameters (Fig. 1, *a*, *c*). In denervated heart this rise could be caused only by myogenic response to load. This also confirms the absence of absolutely specific (load-insensitive) CI

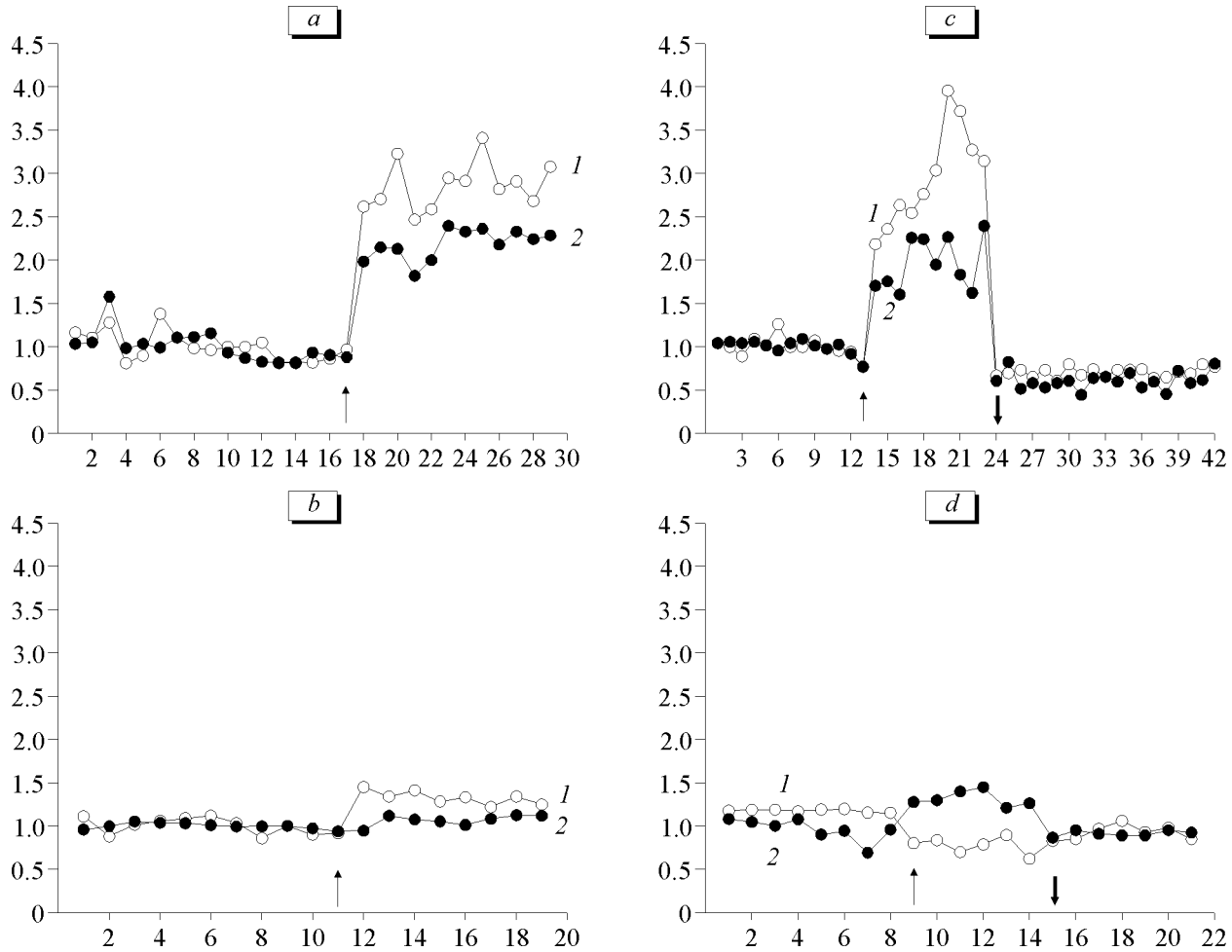

Fig. 1. Effect of arfonad on changes in contractility (CI) and relaxation (RI) indices induced by increased pre- and afterload on the heart. Ordinate: CI (*1*) and RI (*2*) in relative units (the mean values of CI and RI before modulation of pre- and afterload were taken as 1). *a*) preload+arfonad; *b*) preload without arfonad; *c*) afterload+arfonad; *d*) afterload without arfonad. The thin arrow marks the moment of load application, the thick arrow shows the moment of load termination.

TABLE 1. Effect of Arfonad on Fraction of Positive, Negative, and Insignificant Changes of CI and RI Induced by Increased Pre- and Afterload on the Heart (*M*±*m*, %)

Load	CI			RI		
	increase	decrease	insignificant changes	increase	decrease	insignificant changes
With arfonad						
preload (*n*=12)	67.00±13.57	17.00±10.84	17.00±10.84	75.00±12.50	8.00±7.83	17.00±10.84
afterload (*n*=21)	62.00±10.59	0	38.00±10.59	67.00±10.26	0	33.00±10.26
Without arfonad						
preload (*n*=52)	56.00±6.88	10.00±4.16	35.00±6.61	40.00±6.79	0	60.00±6.79
afterload (*n*=75)	35.00±5.51	20.00±4.62	45.00±5.74	44.00±5.73	3.00±1.97	53.00±5.76

Note. *n* is the number of responses to load.

and RI. Evidently, this myogenic component should be taken into consideration in the analysis of the data obtained in experiments with intact innervation. Therefore, we compared the responses of CI and RI to load both in intact and arfonad-treated cats.

In arfonad-treated cats, the indices rose more frequently (Table 1) and more pronouncedly (Fig. 2, *a*, *b*) than in control cats. Thus, in experimental cats, in which only myogenic response to load can be realized, CI and RI rose to the great extent, than in control cats, where both myogenic and neurogenic components participate in cardiac regulation. It means that the neurogenic component of cardiac response to loads is opposite to the myogenic component. In other words, neural inotropic and lusitropic reactions to pre- and afterload are negative. Therefore, the increase of CI and RI in intact heart masks the negative neural inotropic and lusitropic effects. This is possible only because myogenic rise of indices prevails over their neurogenic fall. Probably, such paradoxical behavior

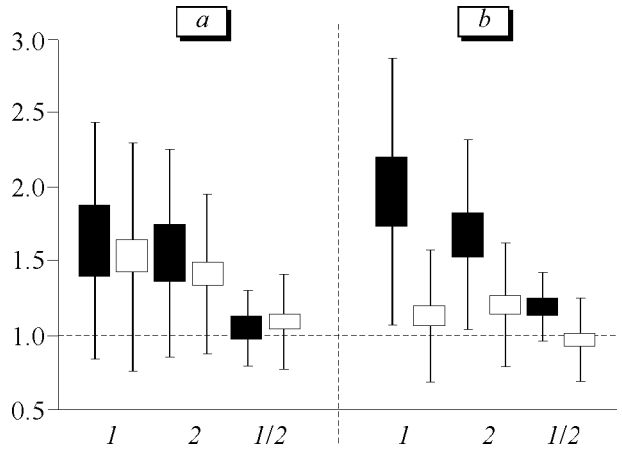

Fig. 2. Changes in CI (*1*) and RI (*2*) in response to increased pre- (*a*) and afterload (*b*) against the background of arfonad (dark bars) and without arfonad (open bars). Ordinate: ratio of mean value under the experimental influence to mean background value.

was provoked by high loads used in our study. Although increased pre- and afterload produced negative reflex inotropic and lusitropic reactions, it is possible, that lower loads would change the direction of these reactions as takes place with response of the heart rate to strong or minor increase of preload (Bainbridge reflex).

For evaluation of the possibility of existence of independent neural lusitropic influences, we compared the ratio of inotropic and lusitropic reactions to both kind of loads. If in both cases these ratios were the same, it would prove the absence of independent lusitropic influences. The data suggest that neural mechanisms can finely regulate contraction and relaxation of the heart: under some conditions, they exert predominantly lusitropic effect, while under other conditions their prevailing effect is inotropic. On the whole, reaction to increase of preload was similar in control and experimental cats: increase of both indices was observed more frequently than their decrease (Table 1). The changes induced by afterload were different: in arfonad-treated cats elevation of the indices also markedly prevailed over their decrease, although in control cats this feature was observed only for RI, while the percenage of reactions where CI dropped increased dramatically and was comparable to that of the responses where CI increased (35 and 20%, respectively). The difference between the changes in the corresponding index in experimental (only myogenic reaction) and control (myogenic and neural response) cats was taken as a factor of neural inotropic and lusitropic influences. This difference was not pronounced for preload, and it was equal for both indices: the increase in preload induced similar negative neural inotropic and lusitropic effects (Fig. 2, *a*, *b*). In the preload tests, the ratios of the changes in CI and RI in experimental and control cats were similar (1.05 and 1.09, respectively, difference insignificant). In afterload tests, the difference between the changes in CI in

experimental and control cats was significantly greater than that of RI. In this case, the negative neural inotropic reaction was far more pronounced that the negative neural lusitropic reaction, which is seen from the differences in the ratios of the changes in CI and RI (1.16 and 0.93 in experimental and control cats, $p<0.01$). Thus, preload produced similar negative neural inotropic and lusitropic effects, while afterload induced predominantly negative neural inotropic effect. These findings suggest the existence of independent regulatory influences on contraction and diastolic relaxation of the heart.

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