Contraction and Relaxation Indices in the Study of Neural Inotropic and Loositropic Influences on the Heart

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The possibility of using contraction and relaxation indices for evaluation of inotropic and loositropic influences on the heart was studied in experiments on cats. Increased pre- and afterload were used as the stimuli, which are simultaneously loading and reflexogenic. Under conditions of preserved innervation both stimuli elevated the indices selected according to the highest sensitivity/specificity ratio. Ganglionic blocker arfonad potentiated the effects of these stimuli. This attests to a considerable contribution of the myogenic component to the changes in the studied indices in response to increased pre- and afterload and to the existence of negative inotropic and loositropic influences on the heart under conditions of preserved innervation. These conclusions were supported when more specific indices were used: in most cases they decreased during load tests. Thus, when the contraction and relaxation indices are used for evaluation inotropic and loositropic influences on the heart, it seems reasonable either to compare heart responses under conditions of preserved or blocked innervation, or to apply more specific indices. Analysis of changes in most widely used indices $(dP/dt)_{max}$ and t showed that t reliably reflects neural loositropic influences, while the use of $(dP/dt)_{max}$ without proper control can be erroneous.

Key Words: *heart; inotropic influences; loositropic influences; contraction indices; relaxation indices*

Contraction indices (CI), *i.e.* parameters depending on inotropic state of the myocardium and little depending on the pre- and afterload [1,3,4], are widely used in clinical practice for evaluation of the state of myocardium and its functional reserves. These indices are also used for evaluation of the effect of pharmacological agents on myocardium contractility and to examine the action of inotropic influences on the heart, because these influences are always accompanied by the changes in pre- and afterload. In such examination, researches attempt to reveal the neurogenic component of cardiac response to neural influences and to isolate it from myogenic reaction to the change in the load. However, all CI to a certain extent depend on the load [1,3,4] and are characterized by high sensitivity (assessed by heart response to inotropic stimulation) to specificity (evaluated by reaction to load) ratio [1,4]. In clinical practice, this dependence of CI on load is often neglected because the range of normal CI values far surpasses CI changes in response to load variations. In humans $(dP/dt)_{max}$ normally varies in the range 1610±18%, while load-induced changes are ±10% [5]. When the effects of pharmacological agents on the heart are evaluated, the load-induced changes of CI are also neglected in many cases because of overt prevalence of the direct inotropic effect over load influences. However, this relationship can be different when neural influences on the heart are examined. Stimulation of sympathetic fibers produces a potent inotropic effect far surpassing that produced by load, while in heart response to stimulation of reflexogenic zones or afferent nerves the contribution

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of neurogenic and myogenic components are comparable. This complicates data analysis and can lead to erroneous conclusions. Nevertheless, in many works various CI are used for evaluation of neural influences on the heart without proper control. This is especially true for the most frequently used index $(dP/dt)_{max}$, which is not the best index by its sensitivity/specificity ratio. All the above relates also to less frequently used relaxation indices (RI) assessing loositropic (i.e., affecting the rate of diastolic relaxation) influences [2].

The aim of the present study was to evaluate the contribution of loading influences into CI and RI changes during cardiac reflexes and the possibilities and limitations of using these indices in the study of neural regulation of the heart.

MATERIALS AND METHODS

The experiments were carried out on cats. Blood pressure in the left ventricle was measured with a catheter passed via apex of the heart and into aorta orifice. We used stimuli, which simultaneously affected the vascular reflexogenic zones and modulated heart load: intravenous injection and removal of the blood changed preload and stimulated volume receptors, occlusion of the descending aorta increased afterload and stimulated baroreceptors. In experiments with ganglionic blockade we used trimetaphan camsilat (arfonad, Hoffmann—La Roche). We analyzed cardiac cycles, in which diastolic pressure in the aorta at the moment of aortic valve opening was above 45 mm Hg.

The examined indices were divided into 3 groups. Group 1 comprised indices with high sensitivity/specificity ratio. CI was measured as $(dP/dt)_{max}/R_{time,rel}$ (ratio of maximum first derivative of left ventricular pressure to pressure rise time from initial diastolic value of +25 mm Hg to the end-diastolic value of +45 mm Hg). RI was determined as $(-dP/dt)_{45,rel}\times V_{mean}$, which is the product of minimum first derivative of left ventricular pressure and mean rate of left ventricular pressure drop during isovolumic relaxation [1,2]. Group 2 consisted of the indices with high specificity. CI was taken as $(dP/dt)_{max}/PVP_{time}$ (ratio of maximum first derivative of left ventricular pressure to the period from the start of systole to the moment corresponding to the maximum pressure in the left ventricle). RI was determined as $(-dP/dt)_{45}/\tau$, which is ratio of minimum first derivative of left ventricular pressure at the moment, when this pressure drops to 45 mm Hg during relaxation to τ.

TABLE 1. Contraction and Relaxation Indices

Indices		*M*	s	*m*
Contraction indices				
$(dP/dt)_{max}/R_{time,rel}$	SPC	1.84	0.86	0.17
	SNS	6.82	4.50	1.70
	SNS/SPC	3.71		
$(dP/dt)_{max}/PVP_{time}$	SPC	1.27	0.34	0.06
	SNS	4.61	2.51	0.73
	SNS/SPC	3.62		
$(dP/dt)_{max}$	SPC	1.35	0.41	0.07
	SNS	2.98	1.46	0.42
	SNS/SPC	2.21		
Relaxation indices				
$(-dP/dt)_{45,rel}\times V_{mean}$	SPC	1.62	0.66	0.12
	SNS	3.98	2.53	0.73
	SNS/SPC	2.46		
$(-dP/dt)_{45}/\tau$	SPC	1.17	0.32	0.06
	SNS	2.49	1.09	0.32
	SNS/SPC	2.13		
τ	SPC	1.03	0.17	0.03
	SNS	1.57	0.37	0.11
	SNS/SPC	1.53		

Note. SPC is an index inverse to specificity, which reflects myogenic response to loads; SNS is sensitivity.

TABLE 2. Distribution (in %) of Significant Changes in CI and RI in Response to Increased Pre- and Afterload (*M*±*m*)

Experimental conditions	CI			RI		
	increase	decrease	PRC	increase	decrease	PRC
Without arfonad						
Preload (52)						
group 1	56±6.88	10±4.16	85±6.12	40±6.79	0	100
group 2	27±6.16	33±6.52	45±8.94	19±5.44	29±6.29	40.0±9.8
group 3	67±6.52	6±3.29	93±4.14	8±3.76	50±6.93	13±6.14
Afterload (75)						
group 1	35±5.51	20±4.62	63±7.54	44±5.73	3±1.97	94±4.01
group 2	23±4.86	39±5.63	37±7.12	20±4.62	27±5.13	43±8.37
group 3	37±5.57	23±4.86	62±7.24	17±4.34	40±5.66	30±6.99
With arfonad						
Preload (12)						
group 1	67±13.57	17±10.84	80±12.65	75±12.50	8±7.83	90±9.49
group 2	67±13.57	17±10.84	80±12.65	50±14.43	17±10.84	75±15.31
group 3	83±10.84	17±10.84	83±10.84	50±14.43	33±13.57	60±15.49
Afterload (21)						
group 1	62±10.59	0	100	67±10.26	0	100
group 2	71±9.9	0	100	38±10.58	5±4.76	89±10.43
group 3	86±7.57	5±4.76	95±5	33±10.26	14±7.57	70±14.49

Note. In parentheses: number of reactions, in which diastolic pressure in the aorta at the moment of aortal valve opening surpassed 45 mm Hg. Positive reaction coefficient (PRC) is the ratio of the number of positive reactions (in which the index increased) to the total number of reactions, in which the indices varied significantly.

Group 3 consisted of most widely used CI=$(dP/dt)_{max}$ and RI=τ.

Statistical analysis was performed using nonparametric tests (percentage of significant positive, significant negative and insignificant changes in response to stimulating loads) and parametrical tests (ratio of mean index value during load to similar value before loading). The methodical details are given elsewhere [2].

RESULTS

The first experimental series (n=29) was performed using routine method: to assess inotropic and loositropic reactions to changes in the pre- and afterload, we used preliminary selected CI and RI characterized by the highest sensitivity/specificity ratio. Such indices were $(dP/dt)_{max}/R_{time,rel}$ for contraction and $(-dP/dt)_{45,rel}\times V_{mean}$ for relaxation (Table 1). In cases where load produced significant changes in group 1 indices, these changes were positive in the majority of observations (Table 2). This probably indicates that the loading stimulation of the heart is accompanied by positive neural inotropic and loositropic influences, especially as we used indices characterized by higher sensitivity/specificity ratio compared to widely used indices $(dP/dt)_{max}$, τ, *etc*. To prove that elevation of indices was induced by reflex neural influences and were not caused by myogenic response to the load reflected more or less by all CI and RI, in the second experimental series (n=16) the same stimulation was applied under the action of ganglionic blocker arfonad. Under these conditions, the changes in studied the indices can be induced only by myogenic reactions. Experiments with arfonad showed that the changes of group 1 indices in response to load were also positive in the same percent of cases (Table 2). Therefore, the nonparametric data (the share of positive and negative changes) cannot prove that loading stimulation triggers reflex positive inotropic and loositropic influences. Thus, we used parametric data and compared quantitative changes of the studied indices in response to loading stimulation performed with and without arfonad.

In arfonad-treated cats, pre- and especially afterload produced greater increase of both indices in comparison with arfonad-free cats (Fig. 1). Taking into consideration that in arfonad-treated animals the changes of indices reflect the myogenic component only, while in arfonad-free cats they reflect both the myogenic and neurogenic component (the reflex reactions with volume receptive and baroreceptor areas),

one can conclude that this neurogenic component is negative. In other words, enhancement of CI and RI in response to cardiac load in animals with intact innervation (without arfonad) is explained by ne-gative neural inotropic and loositropic influences. To verify this hypothesis, we studied the load-induced changes of the indices with maximum specificity (*i.e.*, minimal load-induced myogenic reaction), even if this high specificity was combined with decreased sensitivity (the response to inotropic influences). It was expected that changes of the indices would reflect predominantly neural inotropic and loositropic influences. The choice of indices was based on our previous study, in which various CI and RI were obtained [1,2]. The indices that met our requirements were $(dP/dt)_{max}/PVP_{time}$ for CI and $(-dP/dt)_{45}/\tau$ for RI. The data were digitized and these indices were calculated for the same 29 experiments, which formed the first series.

In arfonad-treated cats, changes in new indices were predominantly positive and similar to the changes of previously used indices (Table 2, the indices of group 2). However, in experiments with intact innervation (without arfonad) the results were drastically different: the changes of indices became predominantly negative. Indeed, preload decreased CI and RI in 55 and 60% cases, while afterload decreased them in 63 and 57% cases, correspondingly. Since these indices are highly specific, the myogenic contribution into their changes was significantly decreased, so it can be concluded that the load triggered predominantly the negative inotropic and loositropic reactions.

In view of pronounced difference in response to load, we tested the load-induced changes of $(dP/dt)_{max}$ and τ which are widely used as CI and RI, correspondingly. Since t is characterized by low sensitivity (Table 1), we expected that the percentage of false-negative (insignificant) responses would be higher in the experiments with intact innervation. However, we observed an opposite effect. Moreover, when *t* index was used, the percentage of these reactions somewhat decreased in parallel with significant increase in percentage of negative loositropic reactions (Table 2). Probably, it can be explained by high specificity of this index (Table 1), which minimizes contribution of myogenic component acting in opposite to the neurogenic one. By contrast, the $(dP/dt)_{max}$ index is inferior to other indexes by its sensitivity and specificity (Table 1), and this limitation is not compensated by its high specificity. The responses of this index to load were corresponding: the percentage of both false-negative and positive inotropic reactions did not decrease, and in the case of increased afterload they even increased (Table 2).

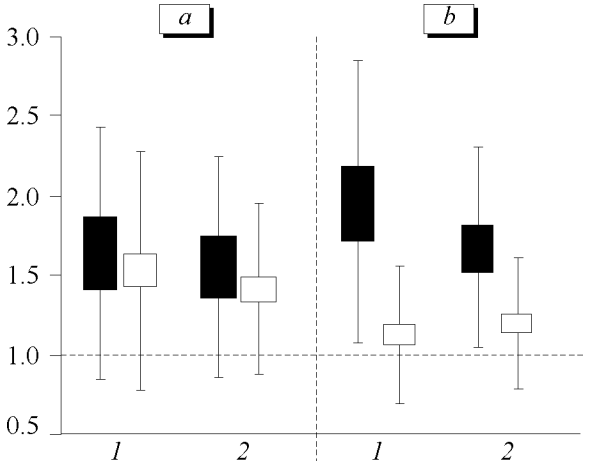

Fig. 1. Changes of contraction $(dP/dt)_{max}/R_{time,rel}$ (*1*) and relaxation $(-dP/dt)_{45,rel}\times V_{mean}$ (*2*) indices in response to increased pre- (*a*) and afterload (*b*) in arfonad-treated (dark bars) and control (light bars) cats. Ordinate: ratio of mean index value during load to baseline.

Thus, assessment of inotropic and loositropic reactions of the heart with CI and RI performed without due consideration of the myogenic component of these reactions to load can result not only in distorted, but directly erroneous conclusions. There are two ways to use CI and RI as indicators of inotropic and loositropic reaction of the heart *in situ*: first, examination paradigm should include the control tests with chemical denervation (ganglionic blocker) and comparison of quantitative changes in the studied indices under conditions of intact and blocked neural traffic; second, the use of the most specific (although possibly less sensitive) indices and assessment of the percentage of positive (or negative) changes in the studied indices in respect to the total number of significant reactions. The τ index can be used with certain limitations for evaluation of loositropic influences on the heart [2], although the use of $(dP/dt)_{max}$ for evaluation of inotropic reactions raise serious objections. Increased pre- and afterload induces not only myogenic changes in contraction and relaxation, but also negative inotropic and loositropic reactions.

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