NERVOUS REGULATION OF VENTRICULAR CONTRACTILITY

I. M. Izrail'tyan, N. N. Alipov, A. V. Sokolov, Yu. R. Mukhtarova, O. L. Lepetyukh, T. E. Kuznetsova, and P. I. Drokhanov

UDC 616.124.2].3-092.07

KEY WORDS: contractility indices; heart; nervous regulation of the heart.

Estimation of the inotropic component of reflex effects on the heart when the circulation is intact is quite a difficult problem, because these influences are often accompanied by hemodynamic changes, which themselves independently affect myocardial contractility. To solve this problem, attempts have been made either to stabilize hemodynamic parameters [2, 15], or to use indices of myocardial contractility, on the grounds that they are insensitive to changes in these parameters [12-14]. However, with the first approach, the conditions of functioning of the heart are disturbed (and, moreover, the more reliable the stabilization of the hemodynamics, the greater the disturbance), whereas the second approach is not sufficiently accurate, because none of the existing contractility indices are absolutely independent of hemodynamic parameters [3, 4, 8, 9]; attempts to find reliable regression relationships between indices and these parameters have not yet proved successful [12].

The aim of this investigation was to study reflex influences on contractility of the cardiac ventricles with the aid of myocardial contractility indices.

EXPERIMENTAL METHOD

Experiments were carried out on 25 cats weighing 3-4 kg under pentobarbital anesthesia (30-40 mg/kg). Under open chest conditions the ventricles of the heart were catheterized through the apex, and the orifice of the aorta and pulmonary artery through peripheral arteries of the systemic and pulmonary circulation. The blood pressure measuring systems consisted of "Cournand 8-9F" catheters, EMT-34, EMT-35, and P23XL manometric transducers, and a 1187 polygraph ("O.T.E. Biomedica"), with a natural frequency of not below 300 Hz for the ventricles [5]. The findings were recorded on an 8-bit word-length PK-8020 computer and an original 16-channel 10-digit analog to digital converter with discretization frequency of 300-500 Hz, depending on the concrete experiment. The pH and blood gas concentrations were determined on a "Corning 178" analyzer (USA). In the first stage of the work, the approach to identification of the optimal contractility indices (CI) for concrete hemodynamic conditions of the experiments was developed. For this purpose responses of 50 different CI [1, 9, 12-14] to an inotropic agent (infusion of adrenalin, 1-3-10 ng/kg/min) and to a change in the conditions of the pre- and after-load (infusion of 10-30 ml blood or a change in lumen of the descending aorta) were compared. The load-dependent changes were assessed by means of parameters of the end-diastolic pressure (EDP) and mean systolic blood pressure (MSBP). Inotropic nervous influences were abolished by bilateral vagotomy and continuous infusion of the ganglion blocker Arfonad (15 mg/kg/h until saturation and 5 mg/kg/h thereafter). In the second stage of the investigation, by means of the chosen CI approaches to the study of inotropic reflex influences during electrical stimulation of the central ends of the divided vagus nerves were analyzed (parameters: 10 Hz, 2 msec, stimulus amplitude chosen to give minimal response threshold). Parameters of the cardiac cycle were used to calculate CI [1]. An original semiautomatic rejection program removed from the calculation a group of CI associated with possible artefacts in any interval of the cycle. The data were processed on PK-8020 and IBM PC/AT computers. Statistical methods were used: Student's test,

Department of Normal Physiology, N. I. Pirogov Second Moscow Medical Institute. (Presented by Academician of the Russian Academy of Medical Sciences A. D. Ado.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 7, pp. 8-10, July, 1992. Original article submitted October 20, 1991.

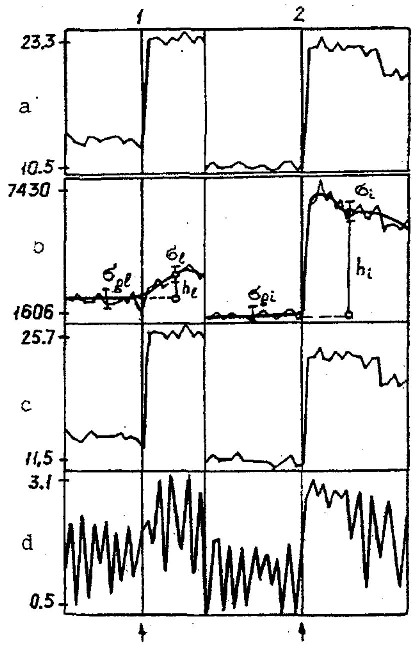

Fig. 1. Fluctuations of MSBP and three different contractility indices (CI) in response to loading (1) and to inotropic (2) influences. a) Control change in MSBP (in kPa); b) one of the better CI (DP/PVP$_{time}$, kPa/sec^2); c) "bad" CI with low specificity (PVP, in kPa); d) "bad" CI with high variability (IIT/PVP$_{time}$, in kPa). Constituent criteria of optimality given in text.

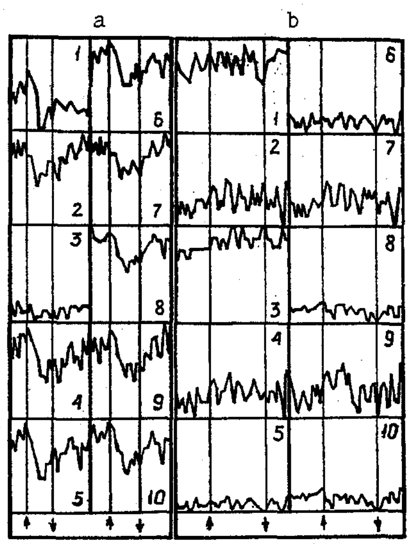

Fig. 2. Changes in 10 optimal contractility indices in response to marked (a) and weak (b) reflex effects on contractility: 1-10) serial numbers of 10 better indices of left ventricle, least dependent on fluctuations of afterload (group 2 in Table 1). Arrows indicate beginning of electrical stimulation of afferent fibers of vagus nerve and its ending.

TABLE 1. Optimal Contractility Indices (CI) and Their Mean Ranks (MR) for Left and Right Ventricles of the Cat Heart, Least Dependent on Fluctuations of Pre- (1) and Afterload (2) and Their Simultaneous Fluctuations (3)

№	Left ventricle					
	1		2		3	
	CI	MR	CI	MR	CI	MR
1	DP/Rtime	6,8	DP·HR/MSAP	7,8	DP·HR/MSAP	6,5
2	PVP/Rtime	7,3	P1/PVPtime	8,6	1/ST	7,0
3	1/ST	7,3	1/ST	8,7	DP/Rtime	7,5
4	DPTI·HR	8,0	DP/PVPtime*	9,9	DP/PVPtime	8,4
5	DP·HR/MSAP	8,3	DP2	10,9	P1/PVPtime	8,7
6	DP	9,1	DP/Rtime*	12,0	PVP/PVPtime	10,6
7	DP 2	10,0	DP*	12,1	DP	10,7
8	DP/PVPtime	10,2	PVP/PVPtime	14,8	DP 2	10,7
9	P1/PVPtime	11,4	PVP/Rtime*	16,1	PVP/Rtime	12,3
10	— DP	13,0	DP/DPtime	16,2	DP/DPtime	13,4
	Right ventricle					
1	DP·HR/MSAP	6,4	DP·HR/MSAP	4,6	DP·HR/MSAP	4,9
2	1/ST	11,8	1/ST	6,6	DP	7,8
3	DP 2	12,6	DP/PVPtime*	9,1	DP 2	9,8
4	PVP/Rtime	12,9	DP/Rtime*	9,8	1/ST	9,8
5	DP/PVPtime	13,8	DP*	9,9	DP/Rtime	11,5
6	DP/Rtime	13,9	Rtime	10,0	DP/Rtime	13,3
7	DP	14,1	DP/DPtime	11,5	DP/DPtime	13,6
8	DP/DPtime	15,8	DP 2	12,1	PVP/Rtime	16,0
9	Rtime	16,7	DP 8	13,9	DP 8	16,7
10	PVPtime/Rtime	16,7	PVP/Rtime*	13,9	Rtime	17,3

Legend. For physical meaning of CI, see in [1, 12]; asterisk indicates most stable CI compared with ICC (explanation in text).

and a second order autocorrelation model of Fisher's φ transformation. The results were significant at the $p < 0.05$ level.

EXPERIMENTAL RESULTS

The aim of the experiments of series I (15 animals) was to find a single criterion which could be used to identify optimal CI for concrete experimental conditions, i.e., those corresponding to the following conditions (Fig. 1a): 1) high sensitivity (h_i – the absolute value of the reaction of the index to the inotropic agent); 2) high specificity (h_l – the absolute value of the response to loading); 3) low variability (random fluctuations from the mean before the reaction (δ_{gl}, δ_{gi}) and during its course (δ_l, δ_i), making allowance for its trend, described by a second order regression function [11]; high repeatability of the results in different experiments. On the basis of the first three conditions a criterion of optimality (CO) was calculated:

$$KO = \frac{|h_i| - |h_l|}{\sqrt{\delta_{gl}^2 + \delta_l^2 + \delta_{gi}^2 + \delta_i^2}}.$$

With the aid of this criterion it was possible to assess the difference between the response of CI to the inotropic agent and to loading, in average standard deviations, taken as the unit of measurement. The better the index, the higher its sensitivity compared with specificity and variability, and the higher its value of CO (compare Figs. 1b and 1c, d). The indices in the experiments were ranked according to the value of the criterion. The better indices were characterized by a lower rank. The average rank of each index for all experiments was the final index for determination of optimal CI for each ventricle under concrete experimental conditions (Table 1). The indices thus selected possessed one other important feature: they responded in the same direction to a change in inotropic and loading influences.

In the experiments of series II (10 cats) an attempt was made to find an approach to the discovery of nervous influences on myocardial contractility with reflex influences on the heart intact. In most responses to stimulation of the central end of the divided vagus nerve the end-diastolic pressure (EDP) was stable (82.2 ± 10.5% of cases),

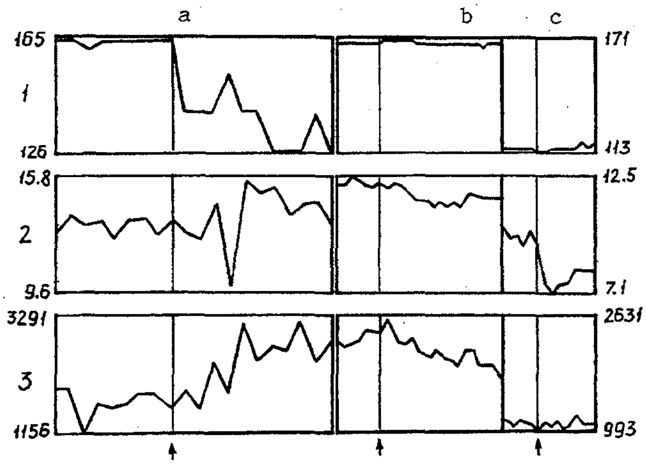

Fig. 3. Evaluation of reflex inotropic effects relative to CI in the case of stable MSBP (a) and during changes (b) requiring comparison with control influences causing a similar change of BP (c) 1) HR (beats/min); 2) MSBP (in kPa); 3) CI (DP/PVP_{time}, in kPa/sec^2). Arrows indicate beginning of reflex or loading stimulus.

whereas MSBP was changed (70.0 ± 4.3% of responses). We therefore used CI of the left ventricle, which was least dependent on the afterload (group 2 in Table 1). Two demonstrative cases of behavior of CI under reflex influences are given in Fig. 2: a) all CI but one deviated strongly and unidirectionally; b) CI either showed no significant change or responded weakly and in different directions. An orientation to one CI in the first example could accidentally lead to the choice of absence of inotropic influences, whereas in the second example it could lead to opposite judgments regarding the change of contractility. This state of affairs led us to consider the use of a special integral criterion of contractility (ICC) to assess inotropic effects, and which would take account of fluctuations of all optimal CI. Fisher's φ-transformation used for this purpose enabled us, on the one hand, to rule out any random omissions of the response of certain CI, and on the other hand, to exclude the reactions of the group of CI with multidirectional behavior as not being inotropic. Comparison of the direction of deviations of each index from the ICC enabled highly stable CI (indicated by an asterisk in Table 1) to be distinguished, the frequency of disagreement of their responses from this parameter not exceeding 15%.

During evaluation of reflex influences on stimulation of afferent nerves, only in half of the experiments were responses of CI observed in which HR and BP remained unchanged, or one or both of these parameters deviated in the opposite direction to CI (Fig. 3a). In these cases changes of contractility could be unambiguously judged, but the frequency of discovery of these inotropic reactions was not high (10.5 ± 5.0%). In most reactions consideration had to be paid to accompanying fluctuations of BP, which could not only directly affect the values of the indices, but could also cause a reflex change of contractility. In each experiment it was therefore necessary to compare reactions of CI to stimulation of the nerves and to control changes of BP caused by constriction of the aorta and corresponding in magnitude to fluctuations of BP during stimulation. If the deviation of CI in the first case exceeded its changes during the second reflex response, it could be concluded that the inotropic influences in response to nerve stimulation were stronger, and could not have been mediated through fluctuation of the hemodynamic parameters. By analysis in this way we were able to detect these influences in 80% of experiments, and we were able to increase the detectability of inotropic reactions by more than 3.5 times (up to 36.8 ± 7.8%).

The wider use of these approaches could prove advantageous in the analysis of various nervous regulatory influences on the inotropic function of the different chambers of the heart.

LITERATURE CITED

1. N. N. Alipov, I. M. Izrail'tyan, T. B. Kuznetsova, et al., Fiziol. Zh. SSSR, 77, No. 1, 82 (1991).

2. D. Z. Afanas'ev, "Effect of the vagus nerve on different parts of the heart," Author's Abstract of Dissertation for the Degree of Candidate of Medical Sciences, Moscow (1981).
3. V. Ya. Izakov, G. P. Itkin, V. S. Markhasin, et al., Biomechanics of Heart Muscle [in Russian], Moscow (1981).
4. K. Yu, Bogdanov, S. I. Zakharov, and L. V. Rozenshtraukh, Usp. Fiziol. Nauk, **14**, No. 2, 116 (1983).
5. I. M. Izrail'tyan, O. L. Lepetyukh, N. N. Alipov, et al., Byull. Éksp. Biol, Med., No. 11, 526 (1989).
6. G. P. Konradi, Physiology of the Heart. Physiology of the Circulation [in Russian], Leningrad (1980), pp. 400-419.
7. G. I. Kositskii, Afferent Systems of the Heart [in Russian], Moscow (1975).
8. F. Z. Meerson, Texbook of Cardiology [in Russian], Vol. 1, Moscow (1982), pp. 112-143.
9. A. A. Moibenko and N. N. Orlova, Fiziol. Zh. (Kiev), **24**, No. 6, 839 (1978),
10. A. A. Moibenko and V. M. Shaban, Physiology of the Circulation. Physiology of the Circulation [in Russian], Leningrad (1986), pp. 186-229.
11. N. N. Chentsov, Statistical Solving Rules and Optimal Conclusions [in Russian] (1972).
12. F. L. Abel, J. Appl. Physiol., **40**, No. 2, 196 (1976).
13. R. W. Lambert, Circulat. Res., **40**, 221 (1977).
14. K. G. Nuel, J. Physiol. (London), **48**, 465 (1914).
15. K. Scheuffler and H. Opitz, Wiss. Z. Martin Luther Univ. Halle-Wittenberg, Math. Naturwiss. Reihe, **36**, No. 6, 115 (1987).