PHYSIOLOGY

Comparison of Different Cardiac Relaxation Indices

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Sensitivity (response to epinephrine infusion) and specificity (response to changes in pre- and afterload) of some cardiac relaxation indices were compared in acute experiments on cats treated with ganglionic blocker arfonad. Some new indices proposed by us provide better characteristics than widely used relaxation time constant (t) and maximum first derivative of the left ventricular pressure $(-dP/dt)_{max}$.

Key Words: *heart; diastole; indices of contractility*

The contractile function of the myocardium can be evaluated by a number of myocardial contractility indices, which are sensitive primarily to its inotropic state and less sensitive to changes in pre- or afterload [1,4,8,9]. The first contractility index $(dP/dt)_{max}$ was proposed in 1927 [13]. Less attention was paid to parameters characterizing the diastolic function of the heart, in particular, to relaxation indices (for example, relaxation rate). The first proposed relaxation index was the maximum first derivative of the left ventricular pressure under conditions of isovolumic relaxation $(-dP/dt)_{max}$ [6]. However, this index depends on aortic pressure at the moment of aortic valve closure and, hence, depends on load shifts. At present, the conventionally used relaxation index is the time constant of ventricular pressure decrease during isovolumic relaxation, τ [8, 10-12]. This index is applicable only for exponential pressure decrease, *i.e.* τ constancy througout the period of isovolumic relaxation. However, the validity of monoexponential characterization was argued and additional relaxation indices were proposed [5,6,13]. Publications of this kind are scanty, and sensitivity and specificity of the relaxation indices were not compared in experimental studies. At the same time hemodynamic load is usually applied under conditions of intact innervation to the heart. In this study we compared a number of relaxation indices under conditions of blockade of the cardiac nervous control.

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MATERIALS AND METHODS

Experiments were carried out on open-chest and artificially ventilated cats (adult males and females) under nembutal narcosis (30-40 mg/kg, intraperitoneally). Left ventricular pressure was measured with a Statham P34XL transducer inserted into the ventricle through the apex. Pressure in the aorta was recorded with an Elema-Shonander transducer via a subclavian arterial catheter. Resonance frequency of the measuring system was tested after each experiment, and was not less 300 Hz [3]. Preload was modulated by blood injection or removal via intravenous catheter in the hindlimb. Afterload was increased by occlusion of the descending aorta with a ligature loop passed through a small cut (1.5-2.0 cm) in the abdominal wall. To prevent reflex reactions, trimethaphan camsylate (Arfonad, Hoffman-La Roche), a ganglionic blocker was infused in doses of 15 mg/kg/h (loading dose) and 5 mg/kg/h (maintenance dose). The efficacy of blockade was assessed by the absence of heart rate response to electrical stimulation of the vagus nerve. Inotropic/lusi-

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tropic stimulus was infusion of epinephrine in a dose of 3 μg/kg/min. Signals passed via a 10-bit analog-to-digital converter to a 8-bit Corvette computer at discretization rate of 300-500 Hz and were processed off-line using Statistica for Windows software.

RESULTS

A total of 3335 cardiocycles were recorded in 16 experiments. Cardiocycles with aortic valve openning pressure below 45 mm Hg were ignored, because under these conditions loading stimuli can improve cardiac blood supply by increasing perfusion pressure in the coronary arteries and act as inotropic and lusitropic factors (improve relaxation).

For verification of the assumption on τ constancy, we calculated τ for 7 different intervals on the curve during the phase of isovolumic relaxation (Fig. 1, *a*). All plots ended in one point, where ventricular pressure is equal to the end-diastolic pressure (EDD)+5 mm Hg. The first plot started from the point where the absolute -dP/dt value was maximum (routine τ calculation). Other plots (*n*=6) started from points, which were distant from the first point by an integer number (1-6) of discretization intervals (Fig. 1, *b*). It was found that τ gradually declined as the start point of the plot moved to the right. The maximum difference between τ values calculated for the longest and shortest intervals was 22%. The assumption on exponential pressure decay during isovolumic relaxation was incorrect and τ calculated for different intervals within the period of isovolumic relaxation varied considerably.

Apart from τ and $(-dP/dt)_{max}$, we studied also average rate of pressure decay during isovolumic relaxation [7], isovolumic relaxation time [17], and some original relaxation indices grouped into classes of primary, primary corrected, secondary, and secondary corrected indices.

The primary indices were:

$(-dP/dt)_{45}$, or -dP/dτ calculated at left ventricular pressure P_{LV}=45 mm Hg. By contrast to (-dP/dt), P_{LV}= 45 mm Hg does not depend on aortic valve closure pressure (main disadvantage of the index $(-dP/dt)_{max}$);

τ_{45}, or τ calculated for P_{LV}=45 mm Hg. When using this index, we calculated τ for the same interval of isovolumic relaxation curve in order to avoid errors due to non-exponential pressure decay.

V_{45}, or the average rate of pressure fall from P_{LV}= 45 mm Hg to P_{LV}=5 mm Hg. We assumed that this index does not depend on the moment of aortic valve closure and the dynamics of pressure decay during isovolumic relaxation.

Thus, all calculations of primary indices used P_{LV}= 45 mm Hg. However, location of the corresponding point on the pressure curve was not stable. The higher EDP, the closer was this point to the end of isovolumic relaxation (Fig. 2, *a*). Hence, stimuli elevating EDP can lead to artefacts in calculation of primary

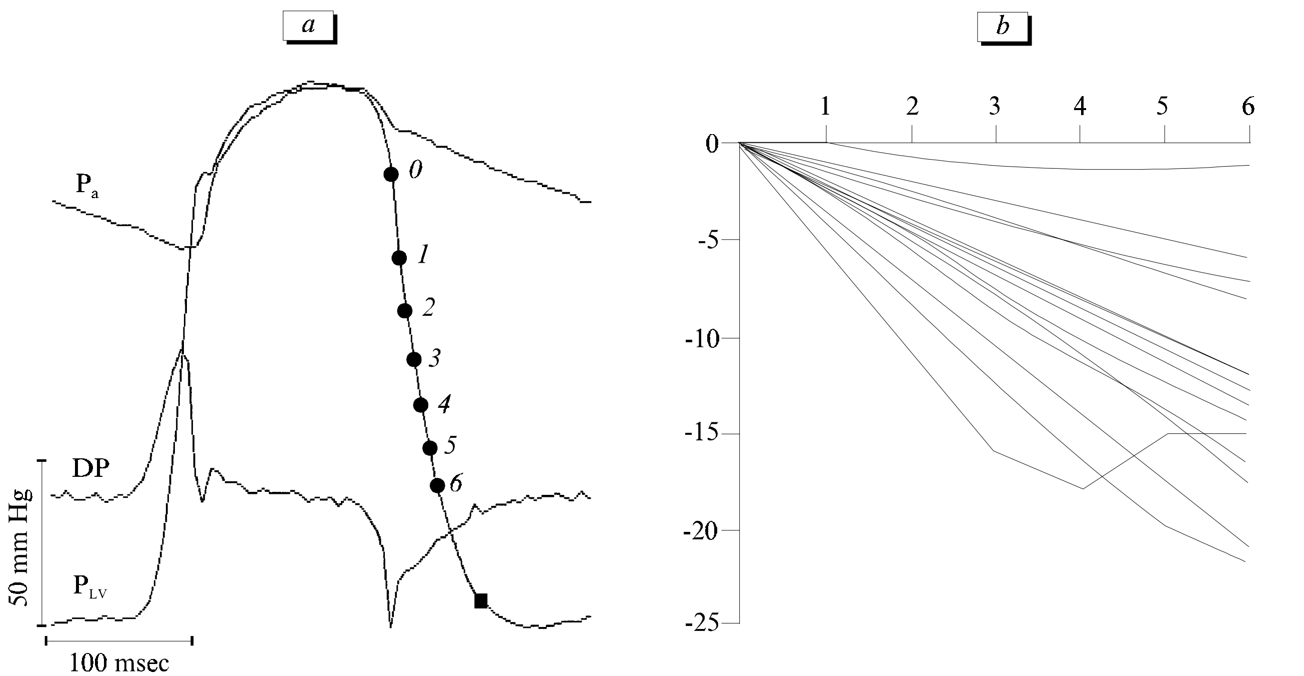

Fig. 1. Variation of t calculated for different intervals (*a*) in the period of isovolumic relaxation. Aortic pressure (P_a); left ventricular pressure (P_{LV}); first derivative of left ventricular pressure (DP); Circles in the P_{LV} curve show the beginnings of 7 intervals, and the square shows their common end. Digits next to the circles indicate the number of quantization periods. A set of t curves (*b*) obtained by shifting the beginning of interval used for calculation to the right (data of 15 experiments).

TABLE 1. Comparative Description of Relaxation Indices

Index	Definition	*M*	*S*	*m*
V_{45}	Average rate of P_{LV} fall from 45 mm Hg to P_{LV}=5 mm Hg			
	Sp	1.13	0.157	0.027
	Se	1.38	0.217	0.063
	Sp/Se	1.22		
$V_{45,rel}$	Average rate of P_{LV} fall from EDP+45 mm Hg to EDP+5 mm Hg			
	Sp	1.09	0.147	0.025
	Se	1.33	0.241	0.070
	Sp/Se	1.22		
$(-dP/dt)_{45}$	The first derivative of P_{LV} at P_{LV}=45 mm Hg			
	Sp	1.13	0.188	0.032
	Se	1.55	0.405	0.117
	Sp/Se	1.38		
τ_{45}	The time constant of P_{LV} fall calculated from P_{LV}=45 mm Hg to P_{LV}=EDP+5 mm Hg			
	Sp	1.10	0.190	0.033
	Se	1.55	0.456	0.137
	Sp/Se	1.41		
$(-dP/dt)_{45,rel}$	The first derivative of P_{LV} at P_{LV}= EDP+45 mm Hg			
	Sp	1.17	0.219	0.037
	Se	1.67	0.445	0.128
	Sp/Se	1.42		
$\tau_{45,rel}$	The time constant of P_{LV} fall calculated from P_{LV}=EDP+45 mm Hg to P_{LV}=EDP+5 mm Hg			
	Sp	1.09	0.179	0.031
	Se	1.59	0.453	0.137
	Sp/Se	1.47		
τ	The time constant of P_{LV} fall calculated from $(-dP/dt)_{max}$ to P_{LV}=EDP+5 mm Hg			
	Sp	1.03	0.165	0.028
	Se	1.57	0.371	0.107
	SP/Se	1.53		
$(-dP/dt)_{max}$	The absolute value of peak negative first derivative of P_{LV} during isovolumic relaxation			
	Sp	1.40	0.368	0.063
	Se	2.17	0.853	0.246
	Sp/Se	1.55		
V_{av}	The average rate of P_{LV} fall			
	Sp	1.36	0.310	0.053
	Se	2.22	0.955	0.276
	Sp/Se	1.64		
$(-dP/dt)_{45,rel}/\tau_{45,rel}$	See text			
	Sp	1.29	0.411	0.070
	Se	2.69	1.303	0.393
	Sp/Se	2.09		
$(-dP/dt)_{45}/\tau$	See text			
	Sp	1.17	0.320	0.055
	Se	2.49	1.092	0.315

Table 1.

Index	Definition	*M*	*S*	*m*
	Sp/Se	2.13		
$(-dP/dt)_{45,rel}/\tau$	See text			
	Sp	1.22	0.388	0.067
	Se	2.74	1.276	0.368
	Sp/Se	2.25		
$(-dP/dt)_{45,rel}/V_{av}$	See text			
	Sp	1.62	0.663	0.115
	Se	3.98	2.528	0.730
	Sp/Se	2.46		
$(-dP/dt)_{max}/\tau$	See text			
	Sp	1.48	0.551	0.094
	Se	3.64	1.950	0.562
	Sp/Se	2.46		
$(-dP/dt)_{max}/ V_{av}$	See text			
	Sp	2.00	0.998	0.171
	Se	5.38	3.471	1.002
	Sp/Se	2.69		
$(dP/dt)_{max}/R_{time,rel}$	The contractility index. Peak first derivative of P_{LV} rise during isovolumic contraction/ the time of P_{LV} rise from EDP+25 mm Hg to EDP+45 mm Hg			
	Sp	1.81	0.855	0.165
	Se	6.82	4.507	1.703
	Sp/Se	3.77		

Note. The mark "rel" in the index name means that the index is calculated using not the absolute pressure P_{LV}=45 mm Hg, but the relative pressure P_{LV}=EDP+45 mm Hg.

indices (Fig. 2, *b*). In this connection, calculation of corrected indices was based not on absolute (45 mm Hg), but on relative pressure of EDP+45 mm Hg.

The secondary indices were derived similarly to the contractility index $(-dP/dt)_{max}/R_{time}$, which, according to our previous study, provided best sensitivity and specificity compared to other contractility indices [2]. Similar to this index, which represents the first derivative divided by time parameter (R_{time} is the time of P_{LV} increase from 25 to 45 mm Hg), secondary indices were a result of division of first derivatives by τ or by average rate: $(-dP/dt)_{max}/\tau$; $(-dP/dt)_{45}/\tau$; $(-dP/dt)_{45}/\tau_{45}$; $(-dP/dt)_{max}/V_{av}$; and $(-dP/dt)_{45,rel}/V_{av}$.

Secondary corrected indices were calculated using relative pressure P_{LV}=EDP+45 mm Hg instead of P_{LV}= 45 mm Hg.

Index sensitivity was evaluated by its deviation from the baseline in response to epinephrine infusion, and index specificity by load-induced changes. The sensitivity to specificity ratio (Se/Sp) was the main parameter by which relaxation indices were ranked. They are listed in Table 1 in increasing order of Se/Sp ratio. For comparison, the best contractility index $(-dP/dt)_{max}/V_{av}$ [2] was given at the bottom of the Table. It is clearly seen that all secondary indices (from 9 to 13) are characterized by higher Se/Sp compared to primary indices. Secondary indices with the highest Se/Sp values are $(-dP/dt)_{max}/V_{av}$ and $(-dP/dt)_{max}/\tau$. However, both these indices have a disadvantage characteristic of $(-dP/dt)_{max}$ (dependence on aortic valve closure pressure), and, moreover, index $(-dP/dt)_{max}/\tau$ has an additional drawback (characteristic of τ) associated with non-exponential pressure decay. The index $(-dP/dt)_{45,rel}/V_{av}$ is free of these disadvantages.

Thus, among tested relaxation indices the best index is $(-dP/dt)_{45,rel}/V_{av}$. If experimental conditions ensure stable aortic valve closure pressure, $(-dP/dt)_{max}/V_{av}$ can be used. This index is superior to $(-dP/dt)_{45,rel}/V_{av}$ by the Se/Sp ratio.

REFERENCES

1. N. N. Alipov, I. M. Izrail'tian, T. E. Kuznetsova, and O. L. Lepetyukh, *Fiziol. Zh. SSSR*, 77, No. 1, 82-88 (1991).
2. N. N. Alipov, I. M. Izrail'tian, O. L. Lepetyukh, and A. V. Sokolov, *Ros. Fiziol. Zhurn.*, **78**, No. 10, 63-69 (1992).

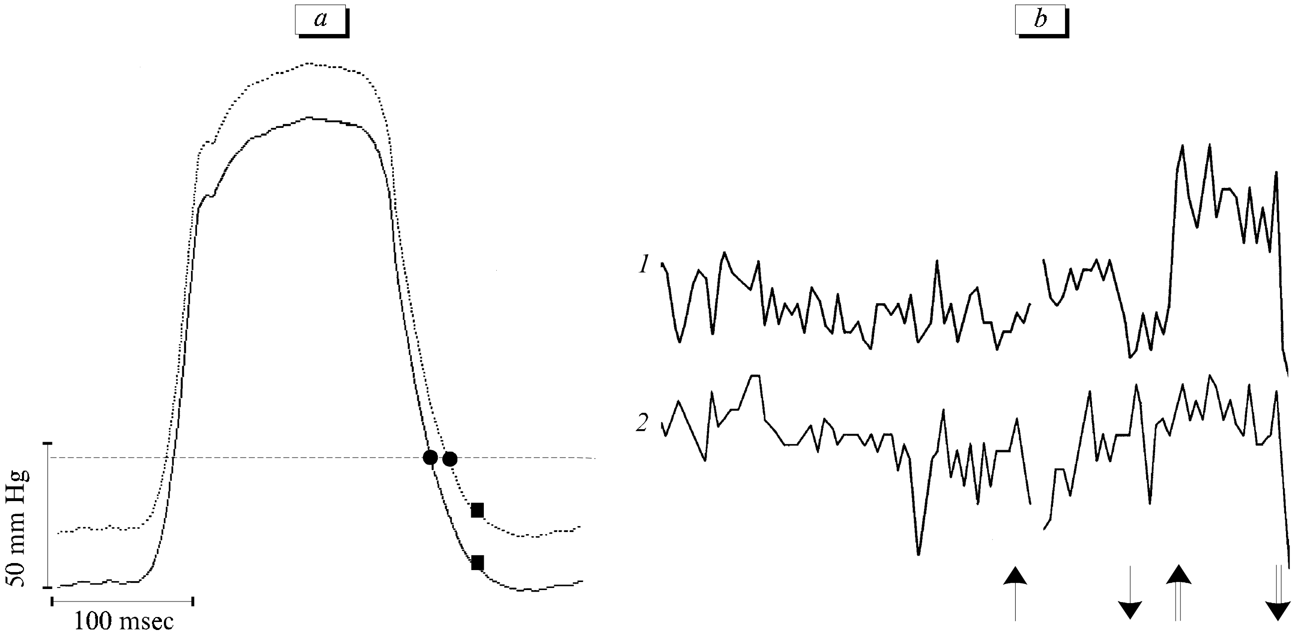

Fig. 2. Artefacts associated with non-corrected relaxation indices. Shift of the point P_{LV}=45 mm Hg in the P_{LV} curve (*a*) due to an increase in end-diastolic pressure (EDP); solid line corresponds to EDP=0 mm Hg and dashed line to EDP=15 mm Hg; dashed horizontal line corresponds to pressure level of 45 mm Hg. When EDP increases, the point P_{LV}=45 mm Hg (marked with a circle) moves towards the end of isovolumic relaxation period (marked with a squre). The behavior of $(dP/dt)_{45}$ (*1*) and corrected $(-dP/dt)_{45,rel}$ (*2*) relaxation indices. The non-corrected index was insensitive to either afterload (arrows) or epinephrine infusion (double arrows).

3. I. M. Izrail'tian, O. L. Lepetyukh, N. N. Alipov, *et al., Byull. Eksp. Biol. Med.*, **108**, No. 11, 526-528 (1989).
4. A. A. Moibenko and N. N. Orlova, *Fiziol. Zhurn.*, **24**, No. 6, 839-848 (1978).
5. Ts. V. Orlova and V. I. Kapel'ko, *Kardiologiya*, **26**, No. 6, 79-83 (1986).
6. P. F. Cohn, A. J. Leidtke, J. Serur, e*t al., Cardiovasc. Res.*, **6**, 263-267 (1972).
7. G. L. Freeman, S. D. Prabhu, L. E. Widman, and J.T. Colston, *Am. J. Physiol.*, **264**, H262- H268 (1993).
8. W. Grossman, *Cardiac Catheterization, Angiography and Intervention*, Eds. W. Grossman and D. S. Baim, Baltimore, P. 333 (1996).
9. C. R. Jr. Lambert, W. W Nichols, and C. J. Pepine, Am. Heart J., **106**, Pt. 1, 136-144 (1983).
10. W. C. Little and E. Braunwald, *Heart Disease*, Ed. E. Braunwald, Philadelphia, 421-444 (1997).
11. L. H. Opie, *Ibid*, 360-393 (1997).
12. J. L. Weiss, J. W. Frederiksen, and M. L. Weisfeldt., *J. Clin. Invest.*, **58**, 751 (1976).
13. C. J. Wiggers, J. Pharmacol. *Exp. Ther.*, **30**, 217-232 (1927).
14. Yellin E.L., Hori M., Yoran C., *et al., Am. J. Physiol.*, **250**, H620-H629 (1986).