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Differential Laws of Left Ventricular Isovolumic Pressure Fall

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Summary

An attempt has been made to test for a reliable method of characterizing the isovolumic left ventricular pressure fall in isolated ejecting hearts by one or two time constants, τ. Alternative nonlinear regression models (three- and four-parametric exponential, logistic, and power function), based upon the common differential law $dp(t)/dt = - [p(t)-P_\infty]/ \tau(t)$ are compared in isolated ejecting rat, guinea pig, and ferret hearts. Intraventricular pressure fall data are taken from an isovolumic standard interval and from a subinterval of the latter, determined data-dependently by a statistical procedure. Extending the three-parametric exponential fitting function to four-parametric models reduces regression errors by about 20-30 %. No remarkable advantage of a particular four-parametric model over the other was revealed. Enhanced relaxation, induced by isoprenaline, is more sensitively indicated by the asymptotic logistic time constant than by the usual exponential. If early and late parts of the isovolumic pressure fall are discarded by selecting a subinterval of the isovolumic phase, τ remains fairly constant in that central pressure fall region. Physiological considerations point to the logistic model as an advantageous method to cover lusitropic changes by an early and a late τ. Alternatively, identifying a central isovolumic relaxation interval facilitates the calculation of a single ("central") τ; there is no statistical justification in this case to extend the three-parametric exponential further to reduce regression errors.

Key words
Ventricular relaxation • Relaxation time constant • Rat • Guinea pig • Ferret

Introduction

Impaired myocardial relaxation is a sensitive indication of the beginning of ("diastolic") heart failure (Lorell 1991, Leite-Moreira and Gillebert 1994) and myocardial hypoxia (Gillebert and Glantz 1989, Simari *et al.* 1992, Schäfer *et al.* 1996). It is therefore valuable to ascertain a lusitropic index, i.e. a measure of ventricular relaxation, especially from intraventricular pressure data that are nowadays easily obtainable. The exponential time constant τ of the isovolumic left ventricular pressure (LVP) fall is frequently used as a lusitropic index. The onset of isovolumic relaxation (t=0) is usually assumed to be the time of peak negative pressure fall velocity, min LVdP/dt; the time when the pressure fall crosses the end-diastolic pressure (LVEDP) of the preceding diastole is chosen as the end point of isovolumic relaxation (Fig. 1A). It was shown, however, that this pressure fall deviates from the exponential in animal experiments (Raff and Glantz 1981) and in humans (Sugawara *et al.* 1997, Senzaki *et al.* 1999).

Some physical considerations have lead to meaningful differential laws describing the pressure fall. During relaxation, the LVP falls to a distinct asymptotic equilibrium pressure, P_∞, which depends on the actual left ventricular residual volume (Yellin *et al.* 1986, Gilbert and Glantz 1989). P_∞ is usually negative because the end-

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systolic volume is below the equilibrium volume (Bloom and Ferris 1956, Gilbert and Glantz 1989). Opening of the mitral valve terminates the isovolumic pressure fall prematurely; P_∞ is therefore not directly observable in ejecting hearts. The leading influence of the difference between actual and equilibrium pressure on the pressure fall velocity is expressed by the general differential law

$$\frac{\mathrm{d}\,p(t)}{\mathrm{d}\,t} = \frac{-1}{\tau(t)}\left[p(t) - P_\infty\right] \qquad (1)$$

where τ is a time-dependent function with the meaning of a time "constant". This differential law is always valid because τ is allowed to become an arbitrary function that will be fixed later. Eq. 1 is solved by the general pressure function

$$p(t) = P_\infty + (P_0 - P_\infty)\, f(t) \qquad (2)$$

P_0=p(0) is the initial pressure; f is a function with f(0)=1 that asymptotically falls to zero. The usual exponential pressure fall function, $f(t)=\exp(-t/\tau)$, emerges if τ is constant.

Substituting empirical LVP curves for p in Eq. 1 and differentiating it numerically yields empirical τ-versus-*t* plots (Raff and Glantz 1981) or LVdP/d*t*-versus-LVP phase diagrams (Sugawara *et al.* 1997), both demonstrating a non-constant τ during isovolumic pressure fall. The main objection is that numerical differentiation severely aggravates the measuremental error of the original data. Furthermore, the result depends numerically on the data sampling rate and on the differentiation procedure employed. It remains therefore questionable whether changes in τ have to be attributed to measuremental error. In order to profit by well designed statistical regression methods, such as Gaussian least-squares, p in Eqs. 1 and 2 must not be replaced by any empirical LVP data sample but is to be estimated by reliable statistics.

The present study investigates some four-parametric realizations of the general model Eq. 1 in isolated ejecting small animal hearts. Table 1 displays the regression models considered. The study especially addresses the following questions: Does goodness-of-fit decide in favour of a distinct model to describe isovolumic pressure fall data? Is it justified and recommendable to discard early and late isovolumic pressure data from the regression calculation?

Methods

Preparation

Intraperitoneal anesthesia was given to one hundred guinea pigs, one hundred Sprague-Dawley rats, and twelve ferrets, according to the Tierschutzgesetz (German Animal Protection Act). Urethane was used for the rodents, initial doses containing 193 mg per 100 g body mass (guinea pig), or 108 mg per 100 g body mass (rats). Pentobarbital (initially 3 mg per 100 g) was given to the ferrets. Supplementary doses were added on demand until paw-squeezing tests revealed full analgesia.

The hearts were excised after 25 IU heparin had been given and mounted onto an artificial circulation apparatus (see Langer and Schmidt 1998) perfused with modified Krebs-Henseleit bicarbonate buffer containing (in mmol l^{-1}): NaCl 118, $NaHCO_3$ 25, KCl 4.8, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, glucose 10, and sodium pyruvate 2. The buffer was continuously equilibrated with 95 % O_2 and 5 % CO_2 (pH 7.4). It was fed to the left atrium by a roller pump, thus setting cardiac output at 40 ml min^{-1} (rat, guinea pig) and 60 ml min^{-1} (ferret). A windkessel (13 ml air buffer) located above the aortic cannula provided elasticity. Its outflow line contained a hydraulic resistor that permits the regulation of the aortic pressure to 75 mm Hg (rat, ferret) and 60 mm Hg (guinea pig) flow-independently. LVP data were sampled by a subminiature catheter tip pressure transducer, located in the ventricular cavity (*via* the aortic valve), and digitized at a rate 1000 s^{-1}, resolution 0.075 mm Hg per bin.

The number of specimens was obtained in relation to the high number of pairwise statistical comparisons (see below). This was possible without sacrifying the animals just for this purpose because the preparations were subsequently used in further experiments not mentioned here. On the other hand, the number of ferret hearts was limited since the results were seen to be comparable to those from the other species.

Another six guinea pig and six rat hearts were prepared as before, but twenty-seven distinct hemodynamic conditions were then established in each heart by independently combining three levels of aortic pressure (guinea pig: 60, 65, 70 mm Hg; rat: 70, 75, and 80 mm Hg), end-diastolic pressure (approximately 2 to 5 mm Hg below and above its individual value at control

conditions, varied by different inflows to the left atrium), and heart rate (atrial pacing, initial value slightly above the intrinsic rate of the individual heart and then increased in two steps of 25 beats per minute each).

Table 1. Variants of the general differential law of isovolumic pressure fall according to different settings of the time "constant" function $\tau(t)$.

	General differential law	$\frac{\mathrm{d}\,p(t)}{\mathrm{d}t} = \frac{-1}{\tau(t)}\left[p(t) - P_\infty\right]$	
	General solution	$p(t) = P_\infty + (P_0 - P_\infty)\, f(t)$	
Model	**$\tau(t)$**	**$f(t)$**	**Parameters**
Exp3	$\tau = \text{const.}$	$\exp\frac{-t}{\tau}$	P_0, P_∞, τ
Power	$\tau_0 + r_\tau t$	$\left(\frac{\tau_0 + r_\tau t}{\tau_0}\right)^{-r_\tau^{-1}}$	$P_0, P_\infty, \tau_0, r_\tau$
Exp4 σ	$(\sigma_0 + r_\sigma t)^{-1}$	$\exp\left[-\left(\sigma_0 + \frac{r_\sigma}{2} t\right)t\right]$	$P_0, P_\infty, \sigma_0, r_\sigma$
Exp4τ	$\frac{(\tau_0 + r_\tau t)^2}{\tau_0} = \tau_0 + 2r_\tau t + \frac{r_\tau^2}{\tau_0} t^2$	$\exp\frac{-t}{\tau_0 + r_\tau t}$	$P_0, P_\infty, \tau_0, r_\tau$
Logis3	$\tau_\infty\left(1 + \exp\frac{-t}{\tau_\infty}\right) = \tau_\infty\left(1 - \frac{1}{2}\frac{p(t) - P_\infty}{P_0 - P_\infty}\right)^{-1}$	$\frac{2}{1 + \exp\frac{t}{\tau_\infty}}$	$P_0, P_\infty, \tau_\infty$
Logis4	$\tau_\infty\left(1 + \frac{\gamma}{1-\gamma}\exp\frac{-t}{\tau_\infty}\right) = \tau_\infty\left(1 - \gamma\frac{p(t) - P_\infty}{P_0 - P_\infty}\right)^{-1}$	$\frac{1}{\gamma + (1-\gamma)\exp\frac{t}{\tau_\infty}}$	$P_0, P_\infty, \tau_\infty, \gamma$

Data processing

LVP records of four seconds each were partitioned into individual beat intervals. The median of pressure values at min LVdP/dt and the median time the pressure falls needed to cross the LVEDP level of the respective preceding beat were calculated from all individual beats in the four-second LVP record. Relaxation subintervals of this median duration were taken from each beat, beginning with the median pressure at min LVdP/dt. The relaxation phases of all beats were pooled by adjusting to zero abscissa (Fig. 1B). This relaxation interval, sometimes denoted as the decelerative phase of pressure fall (Leite-Moreira and Gillebert 1994), is subsequently referred to as the standard interval of isovolumic pressure fall, *StdI*. Nonlinear least-squares regressions (simplex algorithm, Press *et al.* 1989, pp. 289-293) were then performed using each of the regression functions displayed in Table 1.

Central subintervals of isovolumic pressure fall were additionally calculated by a data-dependent interval partition previously described in detail (Langer 1997). In short, the standard interval *StdI* was extended by 5 ms before the beginning of *StdI* and by 5 ms after *StdI* had ended. These pooled extended intervals were partitioned into three subintervals; all possible tripartitions were

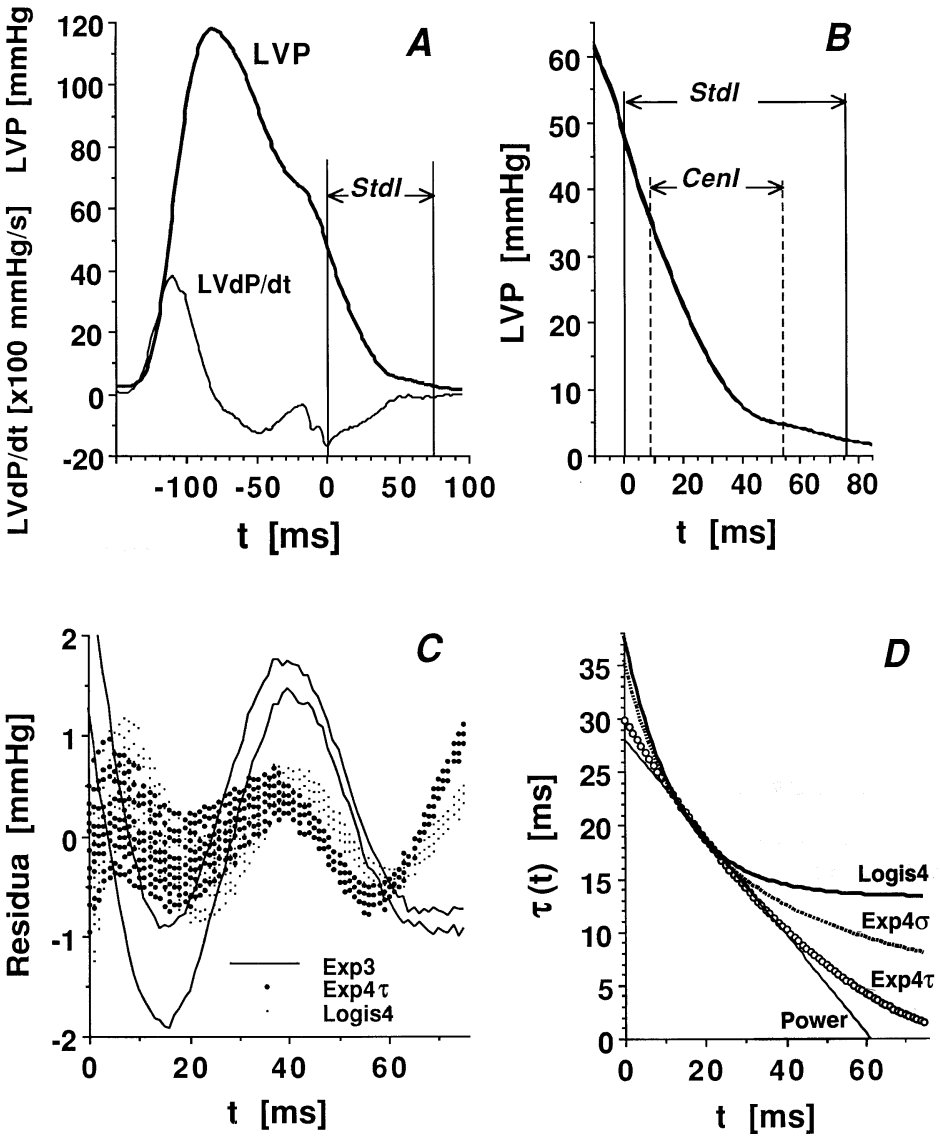

Fig. 1. *Fitting left ventricular isovolumic pressure fall of an isolated ejecting ferret heart at 37 °C, heart rate 206 min^{-1}, aortic pressure 75 mmHg, cardiac output 63 ml min^{-1}.* ***A****: Pressure curve* (LVP) *of the second beat from a four-second data record. Standard isovolumic rela-xation interval (StdI) begins at* min LVdP/d*t, after the pressure notch that indicates aortic valve closing. StdI terminates when the end-diastolic pressure of the preceding cycle is re-encountered.* ***B****: All 13 consecutive pressure falls from the data record are overlayed, adjusted to zero abscissa. Pressure values differ by less than 1 mm Hg at early t; these differences decrease further at later t. CenI indicates the central subinterval of isovolumic relaxation, calculated by regression error minimizing interval partition of StdI using method* Exp4τ*, see text.* ***C****: Plot of regression residua from the overlayed 13 consecutive pressure fall curves; fitting of different pressure fall models (Table 1) to the standard isovolumic relaxation interval StdI. Double lines indicate the range of residua obtained from model* Exp3*. Bold dots mark the residua obtained from model* Exp4τ*, tiny dots those from* Logis4*. Many points are multiple due to the digital resolution. Residua of models* Exp4σ *and* Power *are similar to* Exp4τ*.* ***D****: τ functions obtained from the different pressure fall models, each with best-fitted regression parameters. The τ estimates coincide 10 to 25 ms after* min LVdP/d*t instead in the center of the regression interval because the variance of the residua is greater at early t; the regression procedure therefore takes more attention to fit the early part of data (this may be redressed by performing a χ^2 minimizing regression instead of minimizing the usual squared error sum).*

considered successively. The model in question was fitted separately to each subinterval. The central part of that tripartition with the least total squared regression error sum was selected. It was always a subinterval of *StdI* and is referred to as the central subinterval of isovolumic pressure fall, *CenI*, see Fig. 1B.

Statistical hypotheses

The global zero hypothesis claims that no significant differences in regression errors occur among the different fitting functions from Table 1. The individual zero hypotheses of paired comparisons claim that each two fitting models do not differ in regression error. The preconditions of the usual parametric analysis

of variance are not met by the present data because the regression errors (input data) are small and unable to cross below zero. A non-parametric analogon of the analysis of variance, the weighting rankings test of Quade, was therefore used to test the global zero hypotheses. Multiple individual comparisons between the six models were additionally performed. The calculation is given in the Appendix B.

The influence of the hemodynamic parameters LVEDP, max LVP, and beat interval length (BI) on regression errors and on relaxation parameters was checked in the variable hemodynamic experiments by a stepwise regression using the SPSS statistics package (Norusis 1988). Regression errors were logarithmized to obtain a normal distribution. A quadratic regression model, including squares and products of the hemodynamic parameters, was applied because nonlinearity had been previously detected.

Table 2. Basal data of one hundred isolated ejecting guinea pig, one hundred rat, and twelve ferret hearts at control conditions: 37 °C, aortic pressure 60 mm Hg (guinea pig) and 75 mm Hg (rat, ferret), cardiac output about 40 ml min^{-1} (guinea pig, rat) and 60 ml min^{-1} (ferret). Data are medians ± median of absolute deviation from the median.

	Guinea Pig	**Rat**	**Ferret**
Body Mass [g]	366±22	370±15	725±128
Left Ventricular Mass [mg]*	837±124	779±54	2386±81
Beat Interval [ms]	231±11	190±14	260±18
LVEDP *[mmHg]*	4.0±2.5	3.1±1.8	2.8±1.5
max LVP *[mmHg]*	84.3±4.5	109.9±6.2	104.8±3.3
max LVdP/d*t* *[mmHg* s^{-1}*]*	2718±268	4833±455	3307±424
min LVdP/d*t* *[-mmHg* s^{-1}*]*	1740±219	2367±156	1658±110
Aortic Flow [ml min^{-1}*]*	23.5±3.7	22.1±2.6	28.1±7.9
Coronary Flow [ml min^{-1}*]*	13.7±3.1	16.1±1.3	20.7±5.3

** inclusive intraventricular septum, wet.*

Results

Comparisons under standard hemodynamic conditions

Table 2 summarizes apparent basal data of the specimens used in the "standard hemodynamics" block. Data-dependent interval partition, using method Exp4τ, determined central subintervals *CenI* with median quotient (± median absolute deviation from the median) *CenI/StdI* being 42.9 % ± 2.0 % (guinea pig), 48.5 % ± 1.5% (rat), and 48.4 % ± 4.8 % (ferret). These ratios are similar when methods Logis4 and Power are used, whereas method Exp4σ yields shorter *CenI*, about 60% of the previously given figures.

Figure 1C,D demonstrates a typical example of the fitting process on *StdI* in a single ferret heart; its lower heart rate provides high resolution of the relaxation phase. The plot of regression residua (Fig. 1C) reveals two characteristic phenomena: 1.) The variance of the pressure data from consecutive beats at the same abscissa decreases with t. 2.) The pressure fall contains a damped oscillatory component of about 20 s^{-1}. Both observations were also constantly found in the guinea pig and rat hearts (but higher oscillatory frequency, about 50 s^{-1}). Figure 1D depicts the time course of τ according to the parameters estimated by different fitting methods.

The values of the fitted relaxation parameters are listed in Table 3. The respective initial time constant $\tau_0=\tau(0)$ and the time constant τ^* from the center of the standard relaxation interval [i.e. $\tau^*=\tau(t^*)$, t^* denoting half the length of the respective *StdI*] are calculated to compare models with different parameters. It should be noted that the commonly adopted model Exp3 yields remarkably low estimates for the pressure asymptote P_∞ but too high estimates for the central time constant τ^*. Figure 2 shows the concomitant standard errors of regression obtained from *StdI* and also from *CenI*.

The differences between these residual errors, concerning *StdI*, are found to be significant ($p<0.01$) in each of the species by the Quade tests, F_Q values were

Table 3. Estimated parameters from different pressure fall models (Table 1) in one hundred guinea pig, one hundred rat, and twelve ferret hearts, working under standard conditions (see Table 2).

	P_0	P_∞	τ_0	τ^*	Other parameters
Guinea Pig					
Exp3	40.7±5.5	-3.0±5.1	21.0±5.2	$=\tau_0$	
Logis3	39.7±5.4	1.2±2.9	24.3±4.6	14.1±3.4	τ_∞=12.2±2.3
Exp4τ	39.9±5.1	1.0±3.1	21.7±4.1	14.7±3.4	r_τ = -0.180±0.148
Exp4σ	39.9±5.2	-0.4±3.0	21.9±4.8	16.6±3.5	$r_\sigma=0.43\cdot10^{-3}\pm0.57\cdot10^{-3}$
Logis4	39.8±5.1	-0.9±3.0	22.6±5.3	17.5±3.6	τ_∞=15.6±3.1; γ=0.342±0.204
Power	40.0±5.2	2.0±2.8	21.1±3.3	13.6±3.1	r_τ = -0.347±0.206
Rat					
Exp3	47.5±5.2	-3.9±5.2	16.8±3.2	$=\tau_0$	
Logis3	46.2±5.0	0.2±3.8	19.3±2.8	11.2±1.7	τ_∞ = 9.7±1.4
Exp4τ	46.9±5.2	0.2±3.7	16.6±2.8	11.0±2.1	r_τ = -0.147±0.134
Exp4σ	46.7±5.1	-0.9±3.6	17.9±3.5	11.9±2.3	$r_\sigma = 1.12\cdot10^{-3}\pm0.86\cdot10^{-3}$
Logis4	46.6±5.1	-1.6±3.4	17.8±3.5	12.8±2.2	τ_∞=11.6±2.4; γ = 0.341±0.211
Power	47.1±5.3	0.4±3.6	16.0±2.5	10.5±2.2	r_τ = -0.323±0.225
Ferret					
Exp3	43.7±5.4	-4.0±5.3	24.4±1.7	$=\tau_0$	
Logis3	42.2±5.5	1.2±4.2	29.6±2.7	16.9±1.4	τ_∞ = 14.8±1.3
Exp4τ	43.2±5.7	-1.4±5.2	26.6±3.9	13.4±1.7	r_τ = -0.225±0.083
Exp4σ	43.1±5.5	0.4±5.0	26.2±3.1	14.9±1.4	$r_\sigma = 0.94\cdot10^{-3}\pm0.21\cdot10^{-3}$
Logis4	43.0±5.3	-3.2±4.2	27.9±4.5	15.9±1.0	τ_∞=14.4±0.8; γ=0.478±0.143
Power	43.2±5.7	-1.0±5.2	25.4±2.9	13.0±1.7	r_τ = -0.383±0.090

Data are medians ± median of absolute deviation from the median. τ^* is the local time constant obtained from the center of StdI. Units: P [mm Hg]; τ [ms]; r_τ, r_σ, γ [1].

greater than: 68 in guinea pigs, 69 in rats, and 11 in ferrets. Comparing the four-parametric models on *CenI*, the Quade statistic also indicates significance (F_Q > 14, 19, and 4.6 respectively). Results of the paired comparisons, already converted to error probabilities, are shown in Table 4A. A clear advantage of the four-parametric models over the three-parametric ones is proved: regression errors are about 20 to 30 per cent less in the latter. On *StdI*, Exp4τ is best fitted in rat and ferret hearts; model Power is insignificantly better in guinea pig hearts. However, most of the paired comparisons between the four-parametric models do not reveal significant differences. On *CenI*, models Exp4σ and Logis4 are superior to Exp4τ.

Comparisons under variable hemodynamic conditions

As expected, standard errors of regression and median absolute deviation of all models increased (by about 50-80 %) when the hemodynamic conditions were variable instead of remaining constant (see Fig. 2). No systematic influence of distinct hemodynamic variables on the (logarithmized) standard errors is revealed by the quadratic regression analysis. Rat hearts exhibit no significant hemodynamic influence on standard errors at *StdI* as well as *CenI* ($r^2\approx0.06$). In guinea pig hearts, eight of the nine factors and their products are included in the regression (reaching $r^2\approx0.5$), again indicating that none of them preponderates. However, the standard regression errors in this species tend to decrease with the heart rate.

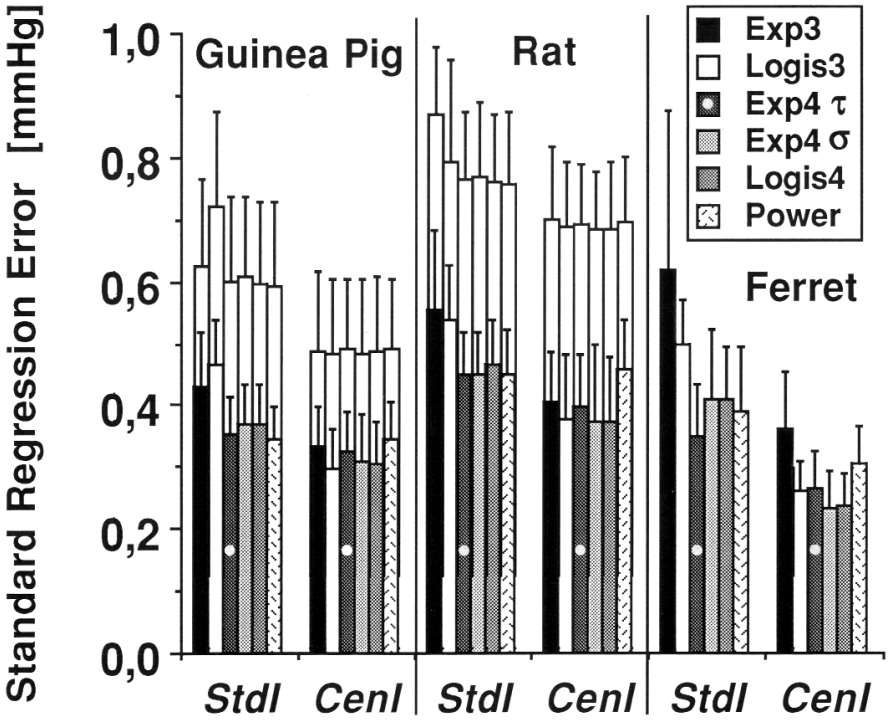

Fig. 2. *Median of standard errors of regression (columns) and median of absolute deviation from the median (error bars) of different pressure fall models (Table 1).* ***Lower columns*** *refer to data from one hundred guinea pig, one hundred rat, and twelve ferret hearts, working at standard conditions (notice that mean aortic pressure is less in guinea pig preparations). Fitting calculations were performed using the standard relaxation interval StdI and the central subinterval CenI. The three-parametric models* Exp3 *and* Logis3 *are not suitable for data-dependent interval partition; the respective data shown for CenI were obtained by applying these models to the CenI calculated by a piecewise fit of method* Exp4τ. ***Higher light columns*** *show additional data from six guinea pig and six rat hearts, each working under 27 different hemodynamic conditions (see text).*

These results are the same among all of the four-parametric models.

The Quade test reveals significant ($p<0.01$) differences of goodness-of-fit between the four-parametric models applied to *StdI* in guinea pig hearts ($F_Q=22$) but not in the rat hearts ($F_Q=2.2$, $p>0.09$). Comparisons on *CenI* yield significant differences in both species ($F_Q=12$ in the guinea pig, $F_Q=5.4$ in the rat). However, most paired comparisons do not reach significance (Tab. 4B).

The quadratic regression analysis, considering initial τ_0 and central time constant τ^*, does not reveal a noteworthy hemodynamic influence on the τ estimates (typically $r^2<0.25$). Factor LVEDP·BI on the *StdI* and factor EDP^2 on *CenI* tended to increase τ_0 and τ^*.

Discussion

The reliability of the model fitted to the empirical data is crucial in calculating parameters to describe physiological facts. Such parameters are mainly relevant in correlation to other physiological phenomena to infer scientific conclusions. An inadequately chosen model leads to parameter values that are biased in an obscure way; thus, well designed experiments may yield unclear results. For example, Perlini *et al.* (1988) obtained contradictory results by investigating the influence of changing preload on the relaxation time constant τ by two models, Exp3 (with empirically estimated P_∞, as presently), and the same model with a fixed asymptote $P_\infty=0$.

The present study gives a physical motivation only of the general differential law of pressure fall, Eq. l. Suitable models for the hitherto undetermined function $\tau(t)$ are heuristically proposed and tested purely empirically. The discussion focusses on these two points and finally demonstrates the different behavior of early and late relaxation constants in a physiological example.

Table 4. Results of Quade tests and error probabilities of paired comparisons between different pressure fall regression functions (see Table 1). Most negative *S* values indicate best fits. Upper left-hand triangles present data obtained from the standard intervals *StdI*, lower right-hand ones those from central subintervals *CenI* (using only four-parametric models). Table entries are error probabilities of the zero hypotheses "no difference in goodness-of-fit".

A. Standard hemodynamic conditions

Guinea Pig	S_{StdI}	Power	Logis4	Exp4σ	Exp4τ	Logis3
Exp3	9472	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	0.128
Logis3	7658	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	
						S_{CenI}
Exp4τ	-5890	0.329	0.002	0.001		1406
Exp4σ	-1960	$<10^{-3}$	0.823		$<10^{-3}$	-2744
Logis4	-2227	$<10^{-3}$		0.270	0.003	-1640
Power	-7053		$<10^{-3}$	$<10^{-3}$	0.117	2978
Rat	S_{StdI}	Power	Logis4	Exp4σ	Exp4τ	Logis3
Exp3	9798	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	0.120
Logis3	7951	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	
						S_{CenI}
Exp4τ	-6237	0.170	0.003	0.084		937
Exp4σ	-4181	0.719	0.219		$<10^{-3}$	-2395
Logis4	-2723	0.113		0.977	$<10^{-3}$	-2423
Power	-4608		$<10^{-3}$	$<10^{-3}$	0.003	3881
Ferret	S_{StdI}	Power	Logis4	Exp4σ	Exp4τ	Logis3
Exp3	164	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	0.344
Logis3	117	$<10^{-3}$	0.012	$<10^{-3}$	$<10^{-3}$	
						S_{CenI}
Exp4τ	-149	0.085	0.007	0.069		24
Exp4σ	-58	0.919	0.343		0.013	-83
Logis4	-11	0.294		0.064	0.482	-5
Power	-63		0.100	0.001	0.334	64

B. Variable hemodynamic conditions

Guinea Pig	S_{StdI}	Power	Logis4	Exp4σ	Exp4τ	S_{CenI}
Exp4τ	-543	$<10^{-3}$	0.208	$<10^{-3}$		2401
Exp4σ	10112	$<10^{-3}$	0.015		$<10^{-3}$	-9466
Logis4	3077	$<10^{-3}$		0.004	0.253	-959
Power	-12646		0.003	$<10^{-3}$	0.056	8024
Rat	S_{StdI}	Power	Logis4	Exp4σ	Exp4τ	S_{CenI}
Exp4τ	286	0.592	0.245	0.200		3084
Exp4σ	3801	0.070	0.015		0.002	-5586
Logis4	-2904	0.530		0.135	0.091	-1520
Power	-1183		0.042	$<10^{-3}$	0.730	4022

The basal differential law of isovolumic pressure fall

Calculating a time constant from the isovolumic left ventricular pressure fall during normal cardiac action was introduced and is understood as being a purely empirical index (Raff and Glantz 1981, Thompson *et al.* 1983, Yellin *et al.* 1986). The basal differential law (Eq. l) is, however, physically motivated by the Law of Laplace and elementary linear viscoelasticity (see Appendix A with Fig. 5). Especially the pressure asymptote P_∞ must be estimated from the data instead of preset to zero for reasons also discussed in Appendix A.

The models compared in the present study (Table 1) extend the general differential law heuristically by allowing τ to become a non-constant function of time. This was motivated by observing that, compared with the exponential, pressure always falls faster than expected late in isovolumic relaxation (Raff and Glantz 1981). Model Exp4σ considers a linear change of the exponential constant, *i.e.* the inverse of τ, in the pressure function p during the relaxation period. A linear change of τ itself in p is chosen for model Exp4τ. A time-linear change of τ in the differential law (instead in pressure function p) leads to the Power model. The logistic model Logis3 (Matsubara *et al.* 1995) is characterized by the property that τ can be expressed as a function of the actual pressure, $\tau=\tau(p(t))$; in fact, τ^{-1} depends linearly on p, see Table 1. The linear factor is fixed at $\gamma=0.5$ in model Logis3; Logis4 overcomes this unmotivated restriction by estimating γ empirically. Table 3 confirms $\gamma<0.5$ in the small hearts of guinea pig and rat, whereas the larger hearts of ferrets allow for $\gamma\approx0.5$.

Proper fit of isovolumic pressure fall

The quality of fit is often discussed in passing, if at all, in the physiological literature that uses the index τ. Although many different mathematical methods have been proposed and employed (see six methods compared by Senzaki *et al.* 1999), literature concerning isovolumic pressure fall has not yet focused the fundamental scientific concept of goodness-of-fit in defining meaningful parameters to describe real phenomena. For instance, only a very few residual plots (or equivalent graphics) are found out of more than two hundred papers on the topic, though inspecting the residuals is a well-known and important suggestion in any regression procedure. Neglecting this prerequisite may easily lead to misleading conclusions.

Establishing a method to fit isovolumic pressure decay therefore involves three formal steps before a physiological interpretation may be started: 1.) defining and identifying the time interval to be fitted, 2.) selecting the mathematical pressure decay model (purely numerical execution is not discussed here) and 3.) comparing the regression residua or other indices of goodness-of-fit.

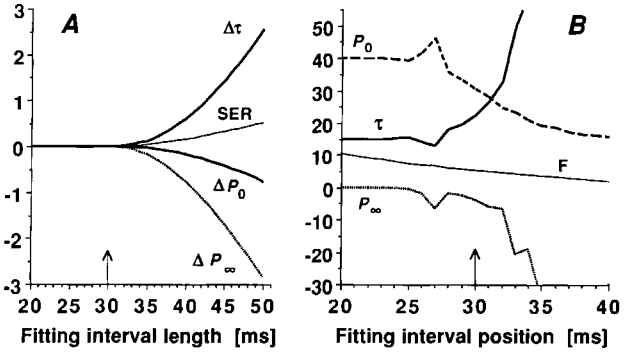

Fig. 3. *Effect of late violations of monoexponentiality on the estimates of the regression variables. A function* F *(partly shown in panel* ***B****) is defined by smooth concatenation of* $F(0\le t\le30)=40\cdot\exp(-t/15)$ *and* $F(30<t\le50) = F(30)+ \dot{F}(30)\cdot(t-30) = 5.41-0.36(t-30)$. F *resembles empirical pressure fall data which become properly fittable to linear rather than exponential regression in the late part (arrows mark concatenation point).* ***A****: Parameters were estimated by model* Exp3 *from intervals each beginning at* $t=0$ *and ending at the respective abscissa. Deviations* $\Delta\tau=\tau-15$ *and* $\Delta P_0=P_0-40$ *remain moderate in the relative sense, whereas the variable asymptote* P_∞ *falls remarkably from zero to negativity.* ***B****: Parameters were estimated by model* Exp4τ *from gliding intervals of length 21, centered around each abscissa* $t\pm10$. *Transition from exponential to linear part changes the parameter estimates considerably. The common three-parametric model* Exp3 *is numerically unstable in this situation; the* τ *estimate, in particular, becomes unpredictable.*

Effect of different starting and end-points on τ *estimation*

Different choices of the end-point of the fitted interval in the literature (to LVEDP of the preceding beat or some mm Hg above) are not expected to bias the relative τ estimate substantially (contrary to P_∞): Fig. 3A shows the effect in a model calculation. Such considerations led to the inclusion of *StdI* in the present

study. Similarly, changing the lower pressure cut-off point in normal human pressure fall curves, Senzaki *et al.* (1999) have obtained an insignificant change of τ (model Exp3) but this effect has been markedly increased in cardiomyopathic patients.

In contrast, Fig. 3B reveals considerable changes in the parameter estimates when a subinterval of fixed duration is moved (changing starting point) through a data set that imitates the time interval of isovolumic pressure decay. This phenomenon was also seen in LVdP/d*t*-versus-LVP diagrams from open-chest dogs (Sugawara *et al.* 1997). Violations of the regression model in the vicinity of the time of min LVdP/d*t*, i. e. the transition from accelerating to decelerating pressure fall, severely distort the relaxation index. It is therefore necessary either to take the pressure data from a later subinterval or to adopt an extended model capable of considering the differences between relaxation at the time of min LVdP/d*t* and at later times.

Interval tripartition

The example below (τ_0 in Fig. 4) demonstrates that the immediate pressure data after min LVdP/dt may not provide information about the lusitropic state of the heart in terms of a time constant if the shape of the pressure curve is changed by other means, e.g. pharmacological intervention. It is therefore acceptable to perform a data-dependent tripartition (Langer 1997), using only the central subinterval *CenI* to calculate the lusitropic time constant. Figure 2 shows that *CenI*, in contrast to *StdI*, already fits the three-parametric models Exp3 and Logis3 properly. So it is justifiable to choose these models in fitting *CenI*. Early and last parts of the tripartition must nevertheless be fitted by four-parametric models to avoid numerical instability. The results of these parts should be discarded; only τ estimated from *CenI* is retained as the lusitropic index searched for. The loss of possibly valuable information from the early and the late pressure data may be a drawback of this method; the computational effort is another. As a special advantage, this method is insensitive to possible early volume (and therefore P_∞) changes, mentioned in Appendix A.

Four-parametric models

Another method of attenuating unwelcome effects of model violations at early and late pressure falls is to adopt a four-parametric model to *StdI* and calculate the central time constant $\tau*$ or the initial and asymptotic time constants, τ_0, τ_∞. Differences in goodness-of-fit between the four four-parametric models investigated are relatively small in *StdI* (Fig. 2). Figure 1C shows that further improvement has to consider a mechanical oscillation that appears in the pressure fall data, initiated most probably by the retrograde blood momentum suddenly stopped at aortic valve closure; this is beyond the topic of lusitropy. Furthermore, this oscillatory amplitude is very small compared to the total pressure fall range. Hence, it is justified to assume an exponential main component of the isovolumic pressure fall.

Table 4 and Fig. 2 show that Exp4τ provides the best fit of *StdI* in most cases, but its statistical benefit over the other four-parametric models is rather small. It is therefore reasonable to consider two disadvantages: 1.) Exp4τ assumes a falling τ (Fig. 1D) until a singularity occurs (Table 1), which is physically impossible. Logis4 reasonably proposes an asymptotic τ_∞ instead; the local $\tau(t)$ does not differ substantially from τ_∞ in the whole second half of the isovolumic pressure decay. 2.) Exp4τ estimates a considerably higher asymptotic pressure P_∞ than Logis4 does. This may counteract the numerical effect of supposing τ falling to zero. Although P_∞ must not be assumed to equalize the empirical pressure minimum even in a non-filling heart (Appendix A), a considerably negative P_∞ is nevertheless expected at small end-systolic residual volume by the concept of the difference between residual and equilibrium volume (Bloom and Ferris 1956).

By these considerations, Logis4 appears to be, theoretically and practically, the most satisfactory model. Goodness-of-fit studies in canine (Matsubara *et al.* 1995) and human hearts (Senzaki *et al.* 1999) have already shown the advantage of Logis3 among other three-parametric models. However, Logis3 is not an alternative to the four-parametric models that all do fit better the pressure fall in small animal hearts (Table 4).

Effect of isoprenaline on early and late relaxation

Administering catecholamines is a common standard method to enhance lusitropy. This effect was first described by an increase in min LVdP/dt but it also appears in τ (Blaustein and Gaasch 1983, Martin *et al.* 1984, Burwash *et al.* 1993, Schäfer *et al.* 1996, Langer and Schmidt 1998). A recommendable method for obtaining τ must therefore provide a high sensitivity to catecholamine-induced changes.

Figure 4 shows the effect of isoprenaline obtained from a rat heart using methods Exp3 and Logis4

on *StdI*. Notably, the initial time constant τ_0 (Logis4) does not change. This is not unexpected because the

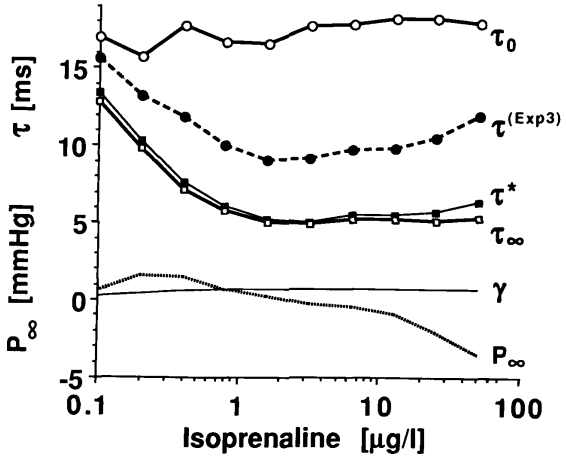

Fig. 4. *Effect of isoprenaline on left ventricular relaxation, determined by methods* Exp3 *and* Logis4 *from the standard relaxation interval StdI. Isolated ejecting rat heart, left ventricular mass 689 mg, mean aortic pressure 75 mmHg, cardiac flow 41 ml min^{-1}, heart rate 240 to 256 min^{-1}, 37 °C. Method* Exp3 *indicates a decrease in time constant* $\tau^{(Exp3)}$ *by about 35 %. Method* Logis4 *reveals a constant initial pressure fall time constant* τ_0*, but a decrease in the terminal (asymptotic) time constant* τ_∞ *by more than 60 %. The local time constant* τ^* *from the center of the relaxation interval is already the same as* τ_∞*. This demonstrates that the positive lusitropic effect of isoprenaline is related to an accelerated decrease in* τ *during the isovolumic period rather than to an initially decreased myocardial viscosity. The increase in the factor* γ *along with isoprenaline administration directly reflects this effect. The positive inotropic effect of isoprenaline causes the residual volume (not measured) to decrease because the cardiac inflow was held constant. This is detected by considerably decreasing pressure asymptote* P_∞ *(Martin et al. 1984) which demonstrates that estimating* P_∞ *rather than fixing it at zero is necessary to obtain reliable results.*

myocardium is not yet fully relaxed at t=0 (when min LVdP/dt occurs); this condition appears to remain true during β-adrenergic stimulation. The latter increases max LVP even if the mean aortic pressure is held constant, thus the lusitropic effect of isoprenaline may be outweighed in the initial time constant τ_0 by stronger residually contracted myocardium. Therefore, the very early pressure data do not contribute to a useful lusitropic index in this situation. In contrast, τ_∞ reacts with a large decrease from 13 down to 5 ms. It is considerably more sensitive than τ calculated from Exp3 (16 to 9 ms); furthermore, τ from Exp3 increases again at higher doses. The central time constant τ^*, calculated from Logis4, is almost equal to τ_∞; this was to be expected from Fig. 1D. Isoprenaline administered to open-chest dogs only caused a decrease in τ (Exp3) from 23 to 18 ms (Blaustein and Gaasch 1983). Another study reports a decrease in τ from 40 to 15 ms in decentralized canine hearts (Burwash *et al.* 1993). However, τ was calculated with P_∞ preset to zero in that study. Additionally, τ is an inverse index of lusitropy; ratios of any changes are only comparable from the same starting-value.

Calculating the central time constant τ^* from model Exp4τ results in values very similar to those obtained from Logis4.

Limitations and Conclusions

The present study is limited to three species of small animals. The pressure fall curve of greater hearts, and therefore the adequacy of the compared models, may differ with respect to heart size. The studied conditions were also restricted to a "laboratory standard" and some simple (but multivariate) hemodynamic changes. Especially the effect of pharmacological interventions (except the example in Fig. 4) and pathologic conditions on the τ models remain uncovered. It is thus possible to conclude that:

1) Isolated hearts allow the overlaying of multiple consecutive pressure fall intervals with great accuracy to enhance the statistical basis of the nonlinear regression procedure. A statistically well-founded procedure (Gaussian error minimization) to fit the original pressure fall data is preferred to biasing data transformations (*e. g.* logarithmizing or differentiating). Two effective ways of preventing the lusitropic index τ from being biased by improperly fittable very early and late parts of the isovolumic pressure fall are demonstrated in this study; further experience is necessary to decide finally on the alternatives.

2) Isolating a central subinterval of pressure fall by data-dependent interval partition supplies a reasonable and non-arbitrary way of identifying a scarcely biased central subinterval of isovolumic pressure fall. Fitting the common, unextended monoexponential Exp3 to that subinterval is justified and sufficient in terms of the goodness-of-fit.

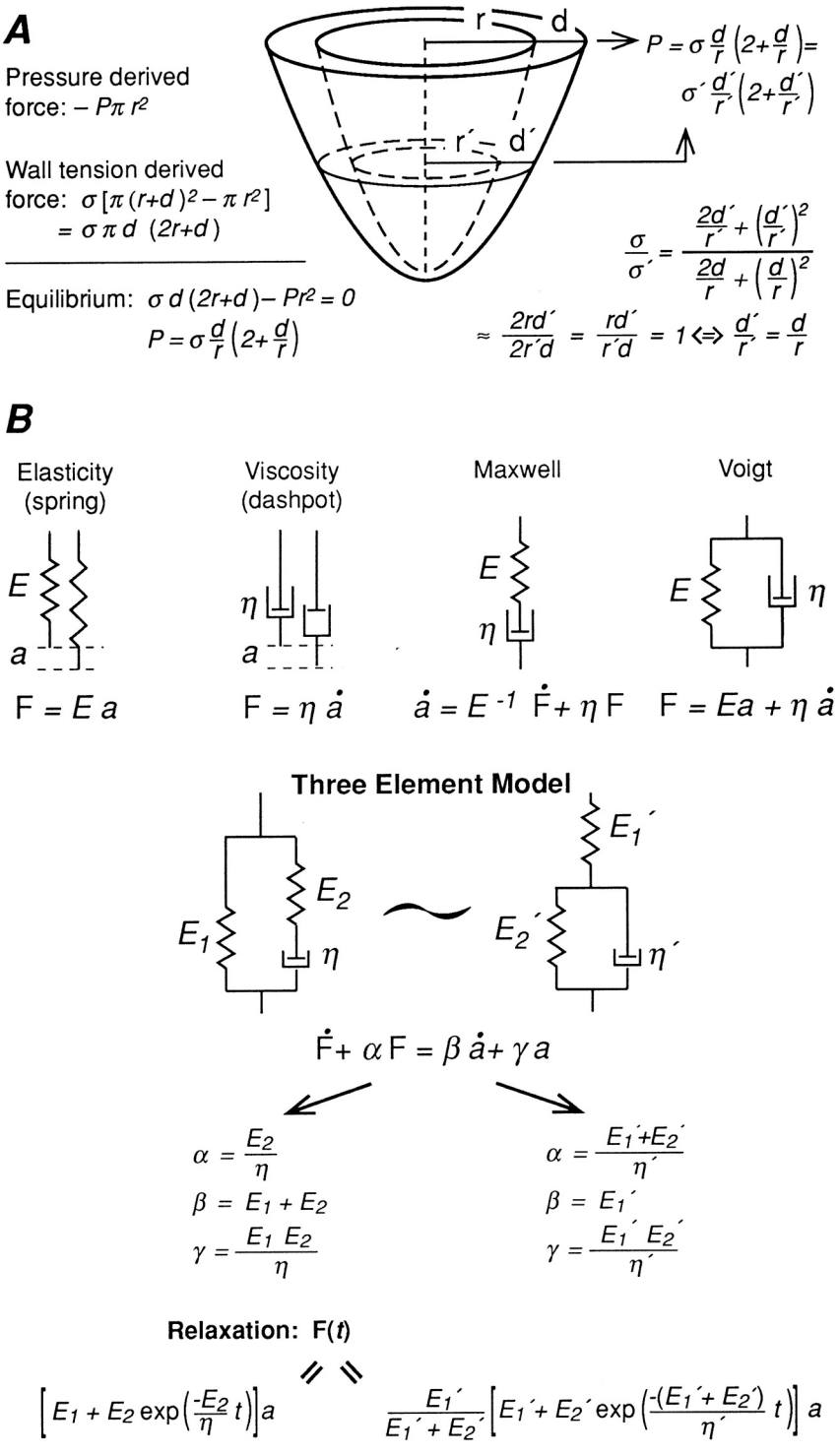

Fig. 5. *Motivating differential laws of isovolumic pressure fall.* ***A****: By the Law of Laplace, static wall stress* σ *and transmural pressure P are proportional in an elastic hollow sphere (left hand side). This remains valid in an elliptic paraboloid if* σ *means the perpendicular wall stress and d<<r holds (right hand side).* ***B****: The theory of linear viscoelasticity provides a simple three-element elastic model to describe the behavior of a muscle fiber (Bland 1960, Gilbert and Glantz 1989). The two representations given in the figure are equivalent. The time course of force during isometric relaxation at elongation a is given by the "relaxation function"* F. *Force declines exponentially by a time constant, which is a ratio of viscosity and elasticity [notice that* E_2/η *and* $(E_1'+E_2')/\eta'$*, respectively, are the inverse time constants].*

3) Fitting a four-parametrically extended model (allowing τ becoming a time-variant function) to the standard isovolumic pressure fall is another way how to effectively overcome the empirical deviations from mono-exponentiality. More complicated models are not expected to provide essentially better goodness-of-fit (unless an overlying damped oscillation with small amplitude is taken into account). The exact formulation of such four-parametric extensions is of minor importance although significant differences are seen in sufficiently large samples. On the basis of some

physiological considerations, the logistic model seems to be the most rewarding.

Acknowledgements

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Appendix

A. Motivating the differential law of isovolumic pressure fall

Time constant as ratio of viscosity by elasticity

First, intraventricular pressure is, at static equilibrium, a proportional measure of perpendicular intramural wall tension (Fig. 5A). Employing the linear viscoelasticity theory (Bland 1960) in order to understand the behavior of such perpendicularly stressed ventricular wall elements yields a monoexponential tension fall (Fig. 5B) and thus, by combining the results, the differential pressure fall law Eq. l with $\tau(t)$=const.

There are undeniably many objections. The shape, wall thickness, and sarcomere orientation of the ventricle are not as simple as assumed. Relaxation is a successive process spreading from apex to the base. Isovolumicity does not mean isometric relaxation of individual fibers. Different fiber properties may lead to a spectrum of time constants (Bland 1960) instead of a single one obtained by Fig. 5B. Nonlinearity of relaxation may be caused by non-isovolumic conditions (Ruttley *et al.* 1974), blood momenta (Sugawara *et al.* 1997), ventricular interaction (Gilbert and Glantz 1989), additional effects of early intrafibrillar restoring force (Parsons and Porter 1966), the bending of previously relaxed fibers at the end of the isovolumic change of the ventricular shape (Ruttley *et al*. 1974), changes in oxygen supply (Schäfer *et al.* 1996), or vascular engorgement (Salisbury *et al.* 1960, Gilbert and Glantz 1989). However, the very multitude of such objections would suggest that none of them can be taken too seriously. There are in fact two possibilities to be decided empirically: Either Eq. l is useless, or the effects of the different model violations more or less compensate each other. Wide experience in different studies (Thompson *et al.* 1983, Martin *et al.* 1984, Yellin *et al.* 1986, Langer and Schmidt 1998) and the results of the present study clearly speak in favor of the latter because of the excellent goodness-of-fit. This in turn permits the above consideration to be applied and to conclude that the time constant of isovolumic pressure fall is the quotient of some kind of average viscosity and elasticity of the ventricle during the relaxation phase.

The ventricular viscosity changes, of course, during the cardiac cycle because the contracted myocardium is stiffer. However, only the present statistical comparisons by pairs between three- and four-parametric models prove that a completely constant viscosity of the ventricle cannot be assumed even during the isovolumic relaxation phase. It is surmised that partially contracted fibers still exist in the early isovolumic relaxation phase: the myofibrils do not relax synchronously throughout the whole ventricle, and the intracellular Ca^{2+} handling, responsible for the relaxation of individual fibers, is also a time-consuming multi-compartmental process.

Role of pressure asymptote

P_∞, the asymptotic pressure, reflects the difference between the residual and equilibrium volume of the ventricle (Bloom and Ferris 1956, Gilbert and Glantz 1989); the more the residual volume of the individual beat diminishes, the more negative it becomes. The former is variable and usually not equal to the equilibrium volume, that means $P_\infty \neq 0$ (see example Fig. 4). Therefore, the pressure asymptote must be estimated from the data (Thompson *et al*. 1983, Langer and Schmidt 1998).

Nevertheless, many authors have performed a two-parametric fit by model Exp3 with a preset asymptote P_∞=0, sometimes explicitly in spite of acknowledging the superior goodness-of-fit obtained by empirically estimating P_∞ (Martin *et al.* 1984, Yellin *et al.* 1986, Gillebert and Lew 1989, Simari *et al.* 1992). This has been motivated by the finding that minimum ventricular pressure reached by isovolumically beating dog hearts is considerably higher than the estimated P_∞ (Yellin *et al.* 1986). Figure 4A demonstrates a methodical explanation of this effect. The exponentiality of the pressure fall is barely detectable from the late relaxation interval where low pressure is considerably affected by measurement error or violations of the exponential model. The fitting procedure estimates P_∞ as more negative as later pressure data are included in the fitted relaxation interval. Table 3 confirms that method Exp3 always estimates the most negative P_∞, but also shows that the four-parametric models overcome this drawback.

Furthermore, P_∞ is extrapolated from the ventricular properties during the normal relaxation period, and one must not expect it to describe the pressure in the fully relaxed non filling ventricle. For these reasons, no models with fixed P_∞ =0 were investigated in the present study . It is to be pointed out that the τ estimate is biased by varying hemodynamic conditions in an unclear way when P_∞ is fixed at a preset value, see Perlini *et al.* (1988).

B. Weighting rankings test of Quade

Calculations were performed according to Conover (1980). Let N=100 (rat, guinea pig) or N=12 (ferret) be the number of hearts, and k=6 the number of different fitting models. The k standard regression errors of each individual heart were ranked, yielding individual ranks R_{ij}, i=1 to N, j=1 to k. The spans of the standard errors obtained from the individual hearts were also ranked from 1 to N; Q_i may denote the rank of heart i. Indices S_{ij} were then calculated as the Q_i-weighted deviation of an individual rank R_{ij} from the mean rank: $S_{ij}=Q_i[R_{ij}-(k+1)/2]$. These indices were summed for each fitting model, $S_j=\Sigma^N_{i=1}\, S_{ij}, j=1, \ldots,k$. Finally the test index

$$F_Q = \frac{(N-1)\sum_{j=1}^{k} S_j^2}{N\sum_{i=1}^{N}\sum_{j=1}^{k} S_{ij}^2 - \sum_{j=1}^{k} S_j^2} \qquad (3)$$

was compared with the critical limits of the F-distribution with k-1 degrees of freedom (numerator) and (N-1)(k-1) degrees of freedom (denominator) using an error probability of 0.01. This approximative test is valid if Nk>40; this condition was met throughout the study.

Multiple individual comparisons (with adjusted error probability) between the six models were performed by formula

$$t = \Delta S \left(\sqrt{2\,\frac{N\sum_{i=1}^{N}\sum_{j=1}^{k} S_{ij}^2 - \sum_{j=1}^{k} S_j^2}{(N-1)(k-1)}} \right)^{-1} \qquad (4)$$

where ΔS is the difference of S_j values of the compared models (Conover 1980). The error probability p of hypothesis ΔS=0 was determined by equalizing t to the theoretical t-distribution, $t=t_{[(N-1)(k-1);\, p/2]}$, and calculating p with the incomplete beta function (Press *et al.* 1989, p. 189).

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