Ransacking the Curve of Cardiac Isovolumic Pressure Decay by Logistic-and-Oscillation Regression

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Abstract: The decelerative part of the left ventricular isovolumic pressure decay is an important phase to make the heart ready for diastolic refill (lusitropy). Its widely used characterization by an exponential regression with zero pressure asymptote or coestimated asymptote provides empirically biased time constant estimates because of significant deviations of the pressure decay from exponentiality. We systematically analyzed the regression residua of these pressure decays in isolated ejecting rat, guinea pig, and ferret hearts. A four-parametric logistic (tangens hyperbolicus) function, together with a superimposed acustomechanic oscillation, yields normally distributed residua with standard regression error typically less than one per cent of the initial pressure; this is the first model with proved unbiased and statistically complete regressive extraction of the information provided by the time course of pressure decay. Equal values of the lusitropic parameters (logistic time constant and pressure asymptote) were estimated even after the oscillatory component was removed from the regression model. Reliable estimates of the frequency, but not of the amplitude, can be obtained by fitting the oscillation model to the residua provided by the logistic; this two-step method is statistically weaker than the full one-step model, but it reduces computational effort. In conclusion, the four-parametric logistic, but not a three-parametric exponential or logistic model, suffices to obtain unbiased lusitropic parameters characterizing the left ventricular isovolumic pressure decay of small animal hearts. [The Japanese Journal of Physiology 54: 347–356, 2004]

Key words: myocardial relaxation, logistic time constant, rat, guinea pig, ferret.

Myocardial relaxation is crucial to prepare the ventricle for diastolic refill. The time constant, $\tau$, of the decelerative part of the left ventricular isovolumic pressure decay is widely used as a lusitropic index, i.e., to quantify the phase of ventricular relaxation. A multitude of models and numerical methods developed during the past decades to estimate time constants of the isovolumic pressure decay, including different selections of the regression interval and digitizing rates, have brought discredit on this lusitropic parameter by yielding inconsistent and noncomparable results.

$\tau$ was originally obtained by a (so-called) semilogarithmic fit on the pressure decay data, assuming an exponential decay to zero pressure [1]; this method is still in use. It was extended by coestimating the actual pressure asymptote empirically [2], yielding the most popular three-parametric monoexponential regression with coestimated (variable) asymptote. Others prefer the semilogarithmic $\tau$ estimate, assuming that fixing a zero asymptote may compensate for misestimation caused by the nonexponentiality of the actual pressure decay [3]. Goodness-of-fit was improved in canine [4] and human hearts [5] by substituting the exponential with a logistic model that is given by the following regression equation with fixed $\gamma = 0.5$:

$$d(t) = P_{\infty} + \frac{P_0 - P_{\infty}}{\gamma + (1-\gamma)\exp\left(\frac{-t}{\tau_{\infty}}\right)}$$

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estimating the initial \( (P_0) \) and asymptotic pressure \( (P_\infty) \), and the asymptotic time constant \( \tau_\infty \). However, this model with preset \( \Delta = \gamma = 0.5 \) was found not to properly describe the pressure decay of small animal hearts, whereas an extended, four-parametric logistic model (Eq. 1) with empirically coestimated shape parameter \( \gamma \), yields excellent regression fits with standard errors typically below 2% of \( P_0 \) [6].

That study [6] compared six different three- and four-parametric models, including exponential, power, and logistic formulas, by means of differences in the regression error sum. A significant superiority of the four-parametric models over all three-parametric ones became evident; the differences in between the four-parametric models remained small. By excluding of those models that contain physically unsound properties, we hold that the logistic model, Eq. 1 with coestimated \( \gamma \), is the most appropriate. Moreover, this fourth parameter yields additional lusitropic information that is missed by the common exponential as well as by the asymptotic logistic time constant. Both the latter indicate some different hemodynamic interventions to cause similar effects on the relaxation phase, whereas the combination of \( \tau_\infty \) and \( \gamma \) reveals qualitative differences (see DISCUSSION, 4.).

However, neither the statistical significance nor the physiological relevance of the fourth parameter guarantees for a complete exploitation, or ransacking, of the empirical pressure decay curve. The important question remains whether the regression residua of that logistic model just reflect random fluctuations or contain any further potentially meaningful information about the pressure decay.

The present study investigates the empirical adequacy of the four-parametric logistic model, Eq. 1, in describing the isovolumic decelerative left ventricular pressure decay in ejecting small animal hearts by searching for such systematic deviation. A preliminary inspection of exemplary residua from model Eq. 1 have revealed an oscillatory component; therefore, we added the damped oscillation

\[
s(t) = A \exp(-\beta t) \cos(\omega t + \varphi)
\]

(\( \beta \), damping factor; \( \omega = 2\pi v \), angular velocity; \( \varphi \), phase shift) to that logistic model, thus performing the eight-parametric regression \( d + o \) on pressure decay data. The distributions of the obtained residua were statistically tested on normality.

The results evince that the combined logistic-and-oscillation model provides an empirically correct description of the deceleratively decaying part of the left ventricular pressure curve that does not miss further nonrandom components. Furthermore, the asymptotic time constant, \( \tau_\infty \), together with the logistic shape parameter \( \gamma \) (or, equivalently, the initial time constant \( \tau_0 \)), reliably extracts the lusitropic core information provided by the isovolumic intraventricular pressure curve.

**METHODS**

1. **Material and preparation.** One hundred mixedbreed guinea pigs, 100 Sprague-Dawley rats, and 12 ferrets were anesthetized with intraperitoneal urethane or pentobarbital (ferrets) and examined for full analgesia by paw-squeezing tests. Animal care and preparation complied with the German Animal Protection Act. We administered 25 IU heparin, then excised the heart, and mounted it to an artificial circulation apparatus in ejecting-left-ventricle mode (details in [7]). This preparation took four to five minutes, while the heart was arrested in ice-cold buffer, and an additional 10 to 20 minutes with retrograde coronary perfusion. The median left ventricular mass was 837 mg (guinea pigs), 779 mg (rats), and 2,386 mg (ferrets), respectively. Modified Krebs-Henseleit bicarbonate buffer was pumped to the left atrium. The buffer contained (in mM): NaCl 118, NaHCO3 25, KCl 4.8, KH2PO4 1.2, MgSO4 1.2, CaCl2 2.5, glucose 10, and sodium pyruvate 2, and was continuously equilibrated with 95% \( \text{O}_2 \) and 5% \( \text{CO}_2 \) (pH 7.4) at 37 ± 0.1°C. Cardiac output was set at about 40 ml min\(^{-1}\) (guinea pig and rat) or 60 ml min\(^{-1}\) (ferret). Mean aortic pressure was maintained at 60 mmHg in guinea pig and 75 mmHg in rat and ferret hearts by an adjustable hydraulic resistor in the aortic outflow line; 13 ml air buffer above the aortic cannula was substituted for aortic elasticity. We introduced a high-fidelity subminiature catheter-tip pressure transducer SPR249A (Millar Instruments, Houston, Texas) through the aortic valve to sample a four-second period of left ventricular pressure data from each heart and digitized it at a rate of 1,000 s\(^{-1}\), resolution 0.075 mmHg per bin. These sample periods were taken in steady-state, regular sinus rhythm, intrinsic heart rate of the specimen. After we obtained these samples, the preparations were used for further investigations not mentioned here.

2. **Data processing.** A processing algorithm partitioned each data record into individual beat intervals, identified the points of peak pressure decay velocity, and calculated the median of pressure values at these points and the median time to re-encounter the end-diastolic pressure of the preceding beat from all individual beats in the four-second recording. The subintervals of this median length were extracted...
from each beat interval (beginning with the median pressure at peak pressure decay velocity) and pooled by adjusting it to zero abscissa (Fig. 1a); each sample contained more than 500 points. We fitted the regression models $d$ (Eq. 1) and $d + o$ (Eqs. 1 and 2) to these data samples by using the iterative downhill simplex method [8] to minimize the sum of squared regression errors.

3. Statistical tests. We counted the number of residua from each regression in bins with 0.1 mmHg width and checked for deviations from a Gaussian normal distribution (whose parameters were estimated from the sample itself) by one-sample Kolmogoroff-Smirnov tests [9]. Significant non-normality is stated if error probability holds $P < 0.05$. The data are presented as numbers of cases with significantly non-normally distributed regression residua.

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**Fig. 1. Regression analysis of the left ventricular isovolumic pressure decay.**

**a:** Sixteen consecutive decelerative pressure decay phases are extracted from the left ventricular pressure (LVP) curve of an isolated ejecting rat heart ($n = 688$ data points). **b:** Performing a four-parametric logistic fit (text Eq. 1), the residua disclose a superposed oscillatory component and show a non-normal, bimodal distribution (bold line represents a suitable binormal distribution). **c:** Fitting the data (panel a) to the eight-parametric regression $d + o$ (text Eqs. 1 and 2) yields normally distributed residua without relevant systematic error. Notice the overlapping of curves as a result of digitizing granularity in the right-hand panels b and c.
RESULTS

1. Residua analysis. Figure 1 shows a typical result of the individual regression analysis. The isolated ejecting hearts allowed the extraction and overlay of the left ventricular decelerative isovolumic pressure decays from consecutive beats with perfect accuracy (Fig. 1a). Fitting with the four-parametric logistic regression model $d$ (Eq. 1) yields oscillating pressure residua below 1 mmHg; consequently, the residua display a non-normal, bimodal distribution (Fig. 1b). The eight-parametric regression model $d + o$ (Eqs. 1 and 2) removes the oscillatory component and almost halves the regression residua; the distribution of the latter turns into a normal shape (Fig. 1c). The Table 1 summarizes the results of the Kolmogoroff-Smirnov tests on normal distributions of the regression residua. The distribution of residua from the regression model $d$ differs significantly from normality in most specimens, whereas the opposite holds for those from the extended model $d + o$. An inspection of the residua plots with indicated non-normality verified only decent deviations, as slightly skewed or flattened bell-shaped distributions without hints at considerable nonrandom components.

The Kolmogoroff-Smirnov test does not cover time-dependent trends in the regression residua. As seen from the right panel of Fig. 1c, the remaining standard error diminishes from the beginning to the end of the pressure decay periods. This is a general finding: We determined the standard errors for each time lag after the beginning of the decelerative pressure decay from the respective data points of the averaged consecutive decay phases and calculated a linear regression of standard error as against time after the beginning of the decay phase. Almost all hearts presented with negative but small coefficients, typically below $2 \times 10^{-3}$ mmHg ms$^{-1}$; this means less than 0.1 mmHg reduction of residual standard error during a 40 ms pressure decay period, or less than 10% of the initial standard error. None of these individual regression coefficients could be proved significantly non-zero (individual error probability $P > 0.5$ in most cases; only one rat heart reached $P < 0.2$).

2. Parameters estimated from $d + o$. Figure 2a displays the lusitropic parameters, i.e., those describing the pressure decay, obtained from model $d + o$, in each species. Especially, the shape factor $\gamma$ is neither zero (monoeponential curve shape) nor 0.5 (logistic shape), but varies between these values. Expressing $\gamma$ as an initial value of the time constant (see DISCUSSION, Eq. 5) allows a comparison with the asymptotic time constant of the same heart. The scattergram, Fig. 3, demonstrates absent simple relations between initial and asymptotic time constants among most hearts; only a subgroup of hearts (most of them guinea pig) presents with data points on the main diagonal, i.e., with a single time constant describing the whole pressure decay. Usually, the decelerative pressure decay starts with a higher time constant that turns into a smaller asymptotic one (data points below the diagonal), with no apparent preetermination between both figures.

The oscillatory component resembles low-frequency acoustomechanical vibrations (Fig. 2b), most probably initiated by the aortic valve closing. Its frequency is lower in the ferret (left ventricular mass > 2 g in this study) than in the rodent hearts (< 1 g); most hearts came with a meaningless near-zero damping factor $\beta$, probably because of the short regression interval.

3. Reliability of parameters estimated from $d$. Because of a considerable reduction of the computational effort, one would wish to abstain from the eight-parametric regression $d + o$ in favour of a standalone four-parametric model $d$. We therefore compared the values of the parameters estimated from $d$ with the respective estimates obtained by the complete model $d + o$. All figures are found equal in the range of at most two units of the first decimal (all correlations $r^2 > 0.996$).

Furthermore, even a two-step (4+4)-parameter regression by fitting the residua supplied from $d$ to the oscillation model $o$ saves much of computation time. We compared the oscillatory parameters obtained by this process with those correctly estimated by the one-step eight-parametric regression $d + o$. Only the amplitude $A$ is severely misestimated by the two-step method, yielding values too low for an actually large A (Fig. 4). Especially, the two-step method

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<th>Table 1. Number of non-normal distributions of regression residua from isovolumic pressure decays.</th>
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<td>Regression method</td>
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Table entries are the number of specimens in which the Kolmogoroff-Smirnov tests reveal significant ($P < 0.05$) deviation from a normal distribution in the regression residua after fitting the left ventricular decelerative isovolumic pressure decay of small animal hearts by a four-parametric logistic (text Eq. 1) and an eight-parametric logistic- and-oscillation model (text Eqs. 1 and 2).
Fig. 2. Lusitropic and oscillatory parameters of isolated ejecting small animal hearts. All parameters are estimated from the eight-parametric regression \( d + o \) (text Eqs. 1 and 2); initial pressure and phase shift are omitted. Boxes represent the central parameter ranges of 80% of \( n = 100 \) rat, \( n = 100 \) guinea pig (GP), and \( n = 12 \) ferret (Fer) hearts; the inserted lines indicate the respective median. a: Lusitropic (pressure decay related) parameters. b: Oscillation parameters \( [\nu = \omega(2\pi)^{-1}, \text{frequency}] \).

Fig. 3. Relation between the initial and the asymptotic time constant of the decelerative pressure decay in ejecting small animal hearts. The asymptotic time constant, \( \tau_\infty \), was estimated by the eight-parametric regression \( d + o \) (text Eqs. 1 and 2); initial time constant, \( \tau_0 \), was calculated from the estimated regression parameters by text Eq. 5. \( n = 100 \) rat (\( \bullet \)), \( n = 100 \) guinea pig (\( \circ \)), and \( n = 12 \) ferret hearts (\( + \)).

Fig. 4. Misestimated oscillation amplitude from a two-step regression. The one-step eight-parametric regression \( d + o \) (text Eqs. 1 and 2) yields reliable amplitude (A) values that are compared with the A values from a two-step procedure, fitting an oscillation (text Eq. 2) to the residual obtained by a previous logistic decay fit (text Eq. 1). \( n = 100 \) rat (\( \bullet \)) and \( n = 100 \) guinea pig hearts (\( \circ \)).
correctly estimates the frequency of the oscillation component.

DISCUSSION

The gold standard in describing any time series by characteristic parameters is to propose a reasonable regression function that fits to the empirical data just leaving normally distributed residua. The present study shows that (1) the regression model combining a logistic decay with (small) superimposed mechanical oscillation provides an empirically correct description of the decelerative isovolumic cardiac pressure decay; (2) the logistic shape parameter \( \gamma \) is necessary to obtain a statistically reliable time-constant estimate; and (3) the oscillatory component can be reasonably neglected if one demands the lusitropic (pressure decay related) parameters only. We discuss some aspects of this reasoning in detail.

1. Disadvantages of the three-parametric pressure decay models. Several authors compared different time-constant concepts and reported inconsistent results. An increasing preload by volume infusion affected the monoeXponential \((\gamma = 0)\) time constant if, but only if, the pressure asymptote \( P_\infty \) was coestimated [10]. Compared with three other methods, the exponential time constant, calculated via pressure derivatives, failed to detect lusitropic changes during myocardial ischemia [11]. Senzaki et al. compared six three-parametric models, including a logistic, in humans [5]; they observed a systematic non-exponentiality of the pressure decay in dilated cardiomyopathy and found the estimated exponential time constant severely sensitive to the length of the chosen data-fitting interval, whereas the three-parametric logistic estimate was more stable against data-point exclusions.

Similar deficiencies were found by others and can be explained by the inappropriateness of the three-parametric models [12]. This model violation also explains why the pressure asymptote \( P_\infty \) is usually estimated too low [3, 12]. The presently observed range in shape factor \( \gamma \) (Fig. 2a) proves that neither the exponential [2] (i.e., Eq. 1 with preset \( \gamma = 0 \)) nor the three-parametric logistic model [4] (Eq. 1 with \( \gamma = 0.5 \)) meets the observations in rat and guinea pig hearts properly.

These disadvantages must not be confused with a purely numerical instability in the calculation of the regression parameters, which is sometimes accused of the problem. Certainly, choosing the rate of digitizing too low (e.g., \( 100 \text{ s}^{-1} \), yielding less than 10 data points per pressure fall interval) prevents the performance of a regression with many parameters to estimate. Presently, the rate of \( 1,000 \text{ s}^{-1} \), along with carefully selected initial parameter values in the downhill simplex algorithm, allows us to estimate the four- and the eight-parametric regression model, even from the data of a single-beat interval. We pooled pressure curves from consecutive steady-state beats just to provide enough data for the following test on the distribution of the residua.

2. Analysis of regression residua. We have different regression models with four parameters and similar goodness-of-fit [6] in our hand. Favoring the logistic (by preliminary physical reasons) requires empirical evidence for the absence of systematic deviation from the pressure decay curve it should describe. The assumption that the remaining error of the fit is caused by a multitude of only random fluctuations leads to a normal distribution of those errors. This is the prevailing criterion that prevents us from overlooking considerable information given by the empirical data curve. Because of the incident oscillatory component, there is no prospect for an immediate test on normality. Before facing the test on the normality of the residua, we must add an oscillation term to the regression model, although we do not expect it to contribute much information about the ventricular relaxation.

The Kolmogoroff-Smirnov test is an omnibus test; i.e., it is scrupulous about any given deviation from normality. Most of the present residua from the logistic-and-oscillation model withstand this test, and even the plots of the remaining cases do not reveal conspicuous deviation. In conclusion, the chosen regression model exhausts the provided pressure decay information. This reasoning does not exclude absolutely that other models with normally distributed residua and the same or even smaller variance may exist. It is rather beyond expectation that a regression, leaving already normally distributed residua, could be evinced as an inappropriate model.

However, the performed test on normality does not seize a trend in the local standard deviations apparent at successive time points during the pressure decay (RESULTS, 1.). We may ponder on applying the least \( \chi^2 \) instead of the least squares regression; the former compensates for different variances at different time points by dividing each squared error by the local variance, calculated from the respective points of consecutive pressure decay phases. Presently, there are good reasons to argue against a recommendation of the \( \chi^2 \) method. This method aims to prevent less accurate measurements from biasing the estimated parameters. But now, the present shortage of stan-
dard errors is an epiphenomenon of the decreasing absolute pressure level. An initial pressure of, for example, 50 mmHg provides freedom for larger variance as the late pressure in the vicinity of zero. Such biological variability does not justify statistical compensation because it is not an error. Furthermore, the diminution in the standard error during the pressure decay phase by about 10% is but small and not even statistically confident in the single case. This does not sufficiently motivate the proposal of another regression method. Moreover, the \( \chi^2 \) calculation would exclude single-beat analyses because local variances are obtainable only from consecutive beat intervals in a steady-state.

3. Interpreting the logistic shape parameter. To become acquainted with the meaning of shape parameter \( \gamma \), we effortlessly rewrite the regression, Eq. 1, as a generalized hyperbolic tangent function,

\[
d(t) = P_\infty + \frac{P_0 - P_\infty}{2 \gamma} \left( 1 - \tanh \frac{t - t_0}{2 \tau_\infty} \right)
\]

with \( t_0 = \tau_\infty \ln \left[ \gamma (1 - \gamma)^{-1} \right] \) being the abscissa of its inflection point. From this we see that the exponential model (\( \gamma = 0 \)) ignores the existence of an inflection, whereas the three-parametric logistic (\( \gamma = 0.5 \)) unjustly presupposes \( t_0 = 0 \), i.e., a coincidence of the estimated inflection point with the arbitrarily chosen upper cutoff point of the pressure decay. At first sight, this applies to the empirical peak negative pressure fall derivative; however, proper regression analysis nevertheless requires us to estimate this parameter because it is also subjected to random error.

These considerations provide two equivalent interpretations of the shape parameter: (1.) \( \gamma \) varies smoothly between the popular exponential and the (three-parametric) logistic time-constant concept according to the shape of the actual pressure curve; (2.) \( \gamma \) indicates the position of the estimated inflection point in relation to the beginning of the fitted time interval.

The most illustrative use of \( \gamma \) is to calculate an initial time constant in addition to the asymptotic one. By its shape parameter, the logistic has an actual or local time constant [6],

\[
\tau(t) = \tau_\infty \left( 1 + \frac{\gamma}{1 - \gamma} \exp \left( \frac{t - t}{\tau_\infty} \right) \right)
\]

(By Eq. 4, \( \tau \) is no longer constant, but it plays exactly the role of the time constant in the differential law [6].) This allows us to substitute \( \gamma \) by the more illustrative initial time constant,

\[
\tau_0 = \tau(0) = \frac{\tau_\infty}{1 - \gamma}
\]

which is valid at the beginning of the decelerative pressure decay; from that point on, the local time constant decreases asymptotically to \( \tau_\infty \). Thus the decelerative pressure decay is exactly described by the initial and asymptotic pressure together with the initial and asymptotic time constant. (Accepting a loss of information, we can also calculate a robust central time constant, valid for the middle of the decay phase [12], or any kind of average time constant by Eq. 4 without performing another regression.)

4. Physiological differences between early and late relaxation. Concerning the exponential time constant, Brutsaert and Sys stressed the non-transparent influence of timing (e.g., between pressure maximum and the maximum of pressure decay) and shape of the intraventricular pressure curve [13]. These influences become more understandable if we remember that a relaxation time constant represents physically the ratio of viscosity by elasticity [14, 6]. Viscosity is known to be elevated in the contracted ventricle and decaying during the myocardial relaxation process [15, 16]. Thus the initial time constant, \( \tau_0 \), is expected to become influenced by the preceding systolic working conditions – especially by the extent and handling of the intramyocellular calcium load [17] – and by the nonuniformity of the relaxation in different parts of the ventricle [18]. The asymptotic time constant, \( \tau_\infty \), should reflect the actual final or basal viscosity of the ventricle, which may be influenced by the global activity of the calcium sequestration process and by conditions of the myocardial wall (e.g., shape, thickness, scars).

Figure 3 confirms enhanced asymptotic relaxation by indicating \( \tau_\infty < \tau_0 \) with but few exceptions. However, isolated working guinea pig hearts often show a fairly good exponentiability of pressure decay, i.e., \( \tau_\infty = \tau_0 \). Because of its poorer performance in the artificial circulation (note higher \( P_\infty \) in spite of lower aortic pressure in Fig. 2a), guinea pig hearts are usually, as in the present study, driven at considerably reduced aortic pressure compared to the in situ value and to other small animal hearts in anisolated setting. This reduces the systolic pressure maximum and enlarges the time between that maximum and the beginning of isovolumicity [12]; thus the ventricle may have already been relaxed to its final viscoelastic state. This explanation is confirmed through an elevation of the cardiac load, which cancels that exponentiability of pressure decay likewise in guinea pig.
hearts also [19]. Figure 2a stresses again the important role of estimating the asymptotic pressure in every reasoning about the lusitropic state: Ferret hearts (double myocardial mass) master their 50% higher output at the same aortic pressure with much lower \( P_\infty \) as the rat hearts do. Neglecting \( P_\infty \) will therefore cause severe misestimations of the actual relaxation time constant; such effects especially turn any formula with preset \( P_\infty = 0 \) into a quite meaningless model.

Interindividual differences in the relaxation time constant (Fig. 3) also occur as aftereffects of the preparation; undisturbed long-term observations revealed a spontaneous decrease of \( \tau_0 \) after the preparation had been finished, but concomitant \( \tau_\infty \) changes remained small [19]. Elevating the cardiac output for about 15 min reduces this process [19]; we abstained from doing so because some heterogeneity within the material is welcomed concerning the present question of the regression’s accuracy.

Some physiological interventions may illustrate the different meaning of early and late relaxation time constants. For instance, catecholamines are highly potent positive lusitropic [20], as well as inotropic agents. When isoprenaline was administered to an isolated rat heart, the decreasing asymptotic \( \tau_\infty \) together with the increasing inotropic \( \tau_0 \) and \( P_\infty \) will both affect the contractile pressure decay. On the other hand, increasing the frequency of an ejecting rat heart by electrical pacing at constant cardiac output only causes a small decrease of \( \tau_\infty \) (by 1.5 ms), but a large decrease of \( \tau_0 \) (10 ms, from 15) and a large decrease of the exponentially estimated time constant [12]. Similarly, an elevation of cardiac inflow (preload) in rat and guinea pig hearts caused \( \tau_0 \) (and the exponentially estimated time constant) to decrease considerably, but \( \tau_\infty \) remained much less affected [6, 19]. Thus the exponential claims a similar lusitropic effect of catecholamine on the one hand and of pacing or preloading on the other, whereas the four-parametric model reveals obvious differences. We expect such a finding to become resembled by investigations on lusitropy in other conditions; thus the additional information provided by the four-parametric decay function (Eq. 1) is of outstanding value, especially if more than one hemodynamic parameter is changing at the same time, as in most situations.

5. The oscillatory component. Although related to viscoelasticity, the superposed oscillation is of minor interest in the evaluation of lusitropy. The bimodal distribution of the residua obtained from the logistic fit (Fig. 1b) and the small amplitude, compared with the range of the pressure decay, suggest that this systematic deviation from normality may scarcely influence the lusitropic parameters estimated by the four-parametric regression \( d \) alone, instead of the complete eight-parametric \( d + o \). The results confirm empirically that model \( d \) correctly estimates all lusitropic parameters without need to account for the oscillatory component. We can thus obtain reliable lusitropic parameters with much less computational effort. Even the frequency of the superposed oscillation, if of interest, is obtainable by a time-saving two-step regression, fitting the oscillation model \( o \) to the residua from \( d \).

Only the oscillatory amplitude requires the use of the complete model \( d + o \) to become reliably estimated. Figure 4 shows that the stand-alone four-parametric logistic fit \( d \) (Eq. 1) partially compensates for an apparent oscillatory amplitude, i.e., leaving a smaller amplitude in the residua delivered to the subsequent \( o \)-regression in the two-step procedure. This is explained by observing the wavelength being of the same magnitude as the whole pressure decay time (Figs. 1b, right panel, and 2b, Frequency). Thus the oscillatory elongations do not compensate for each other within the regression interval, because \( d \) is a nonlinear model. However, this distortion does not perceptibly affect a distinct one of the four regression parameters; this finding is empirical, but it holds without exception for the 212 studied hearts. Explicitly providing an amplitude parameter, \( A \), as in model \( d + o \), relieves the decay-related parameters of that distortion by appropriately ascribing it to \( A \); thus model \( d + o \) estimates (correctly) greater \( A \) values than the two-step regression procedure.

This effect of the \( d \)-component in the regression model may also partly explain the deviations of the residua, provided by \( d \), from a harmonic oscillation with constant frequency (Fig. 1b). The course of the logistic decay may cut off the waves at different ordinates. However, physically changes that may influence the frequency differently during the decay phase, probably exist, but such components can not significantly be revealed in the presence of already normal residua. Further insight would require to making an extended data sampling period available, i.e., using a nonfilling-heart preparation. This, besides the minor
lusitropic relevance, is another reason to abstain from a thorough analysis of the significance of the oscillation in the present filling-heart environment. However, the observed ranges (Fig. 2b) in frequency and amplitude provide evidence for actually present oscillations.

6. Limitations and conclusion. The present study is entirely founded on information obtainable from the intraventricular pressure curve; other biological insight is not utilized. It is further limited by the size of the specimens, the in vitro situation, and the uniform one-condition hemodynamics.

The intraventricular pressure curve emerges from myocellular processes and the ventricular superstructure, but also from the reactions of the circulation. As an effect of spatial and temporal nonuniformity within the ventricular wall, only substantial, global myocellular processes may influence the pressure curve and its parameters. Relating these processes to the observable pressure course requires a reliable characterization of the latter by unbiased parameters.

Concerning the scope of the study’s protocol, we presume that small animal hearts, because of their high heart rate, may provide the most challenging task in modelling pressure decays. The isolated setting prevents neurohumoral, respiratory (mediastinum), and interventricular (pericard) mechanisms from influencing the left ventricular pressure. These effects will greatly modulate, but not rule out, the prevailing pressure decay shape. For instance, changing hemodynamics by assigning 27 different working conditions to the heart (combining three levels of preload, afterload, and heart rate independently in isolated rat and guinea pig hearts) has only increased the standard regression error to less than 1.0 mmHg instead of less than 0.7 mmHg in the one-condition protocol [6] (also used in the present study). Such an individual examination of the regression errors allows us to confide concretely in the model’s adequacy, and it is all the more recommended because it protects from banal model violations, e.g., those caused by extrasystoles.

We conclude that the four-parametric logistic regression is generally the best method available to estimate physically reasonable and valid parameters describing the left ventricular isovolumic pressure decay.

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