Physiol. Res. 54: 601-610, 2005

Estimation of the Left Ventricular Relaxation Time Constant τ Requires Consideration of the Pressure Asymptote

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Received March 12, 2004
Accepted December 30, 2004
On-line available February 16, 2005

Summary

The left ventricular isovolumic pressure decay, obtained by cardiac catheterization, is widely characterized by the time constant τ (tau) of the exponential regression $p(t)= P_\infty+(P_0–P_\infty)\exp(–t/\tau)$. However, several authors prefer to prefix $P_\infty=0$ instead of coestimating the pressure asymptote empirically; others present τ values estimated by both methods that often lead to discordant results and interpretation of lusitropic changes. The present study aims to clarify the relations between the τ estimates from both methods and to decide for the more reliable estimate. The effect of presetting a zero asymptote on the τ estimate was investigated mathematically and empirically, based on left ventricular pressure decay data from isolated ejecting rat and guinea pig hearts at different preload and during spontaneous decrease of cardiac function. Estimating τ with preset $P_\infty=0$ always yields smaller values than the regression with empirically estimated asymptote if the latter is negative and *vice versa*. The sequences of τ estimates from both methods can therefore proceed in reverse direction if τ and P_∞ change in opposite directions between the measurements. This is exemplified by data obtained during an increasing preload in spontaneously depressed isolated hearts. The estimation of the time constant of isovolumic pressure fall with a preset zero asymptote is heavily biased and cannot be used for comparing the lusitropic state of the heart in hemodynamic conditions with considerably altered pressure asymptotes.

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

Introduction

Ventricular relaxation, i. e. restoring the diastolic ventricular pressure after each contraction, is the essential prerequisite for the subsequent diastolic refill. Thus a reliable quantification of this left ventricular pressure decay, an index of lusitropy, is needed. One obvious and constantly used index is given by the steepest pressure decline, peak –LVdP/d*t*. Unfortunately, this parameter depends on the actual ventricular pressure maximum and, therefore, does not characterize the lusitropic condition of the heart independently of inotropic changes.

Other well established lusitropic indexes are given by different kinds of time constants of the left ventricular decelerative pressure decay, i. e. during the isovolumic relaxation phase. The onset (t=0) of this isovolumic phase is usually assumed at the time of peak –LVdP/d*t*, that typically follows closely after zero aortic flow had occurred (Abel 1981). The time point when the end-diastolic pressure (LVEDP) of the preceding beat is

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reached again is chosen as the end point (s, subsequently) of the data sample for calculating the time constant, τ. The most popular estimate (τ_3, subsequently) for this time constant is then obtained from a three-parametric exponential regression on the time series (p_3) of pressure data,

$$p_3(t) = P_\infty + (P_0 - P_\infty)\exp\frac{-t}{\tau_3} \quad (1)$$

that additionally estimates the initial (P_0) and asymptotic pressure (P_∞) (Raff and Glantz 1981, Thompson *et al.* 1983). However, this model often yields P_∞ estimates considerably below the pressure minimum actually observed in intraventricular pressure curves of ejecting-and-refilling hearts (Yellin *et al.* 1986). Many authors, therefore, prefer a biparametric model to estimate the time constant (τ_2 throughout the following), fixing P_∞=0,

$$p_2(t) = P_0\exp\frac{-t}{\tau_2} \quad (2)$$

(originally calculated as the slope of logarithmized pressure by Weiss *et al.* 1976) or present time constants calculated from either method. Both time constants, τ_3 and τ_2, often correlate in their general behavior, but some studies report controversially reacting τ_3 and τ_2 values during the same hemodynamic intervention (see Discussion, *Time constant estimates biased*). It is a completely unsolved question how these differences between τ_3 and τ_2 are to be interpreted, and which model yields the more reliable information about the actual lusitropic condition of the heart.

Therefore, we analysed the relation between τ_3 and τ_2, first mathematically, and secondly empirically in isolated ejecting guinea pig and rat hearts, testing whether τ_3 and τ_2 can be considered as different measures of a distinct physiological entity, i. e. lusitropy. Rejecting this hypothesis provided evidence for preferring τ_3 to the much less reliable τ_2.

Methods

The biasing effect of estimating the time constants of exponential functions with different, especially non-zero, asymptotes P_∞ (Eq. 1) by the regression model with zero asymptote (Eq. 2) was analyzed mathematically as described in the Appendix. Guided by this theoretical result, the following experimental protocol was selected to provoke discordant behaviour of τ_3 and τ_2:

Isolated heart setup

Eleven guinea pigs (body mass 378 g ± 19 g S.D.) and 12 rats (383 g ± 8 g) were fully anesthetized with intraperitoneal urethane (initial doses: rat 108 mg per 100 g body mass, guinea pig 193 mg per 100 g; if necessary, additional doses were administered). All animals recieved care in accordance with the German Animal Protection Act (Tierschutzgesetz).

The hearts were excised and perfused in an artificial circulation apparatus as previously described (Langer and Schmidt 1998). Modified Krebs-Henseleit bicarbonate buffer (content 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, sodium pyruvate 2) was continuously equilibrated with 95 % O_2 and 5 % CO_2 (pH 7.4, 37 °C) and fed to the left atrium by a roller pump.

An air buffer above the aortic cannula served as a windkessel. Aortic pressure was maintained at 60 mm Hg (guinea pig) or 75 mm Hg (rat) by a variable hydraulic resistor. Right atrial electrical stimulation, set to about 20 min^{-1} above the intrinsic rate of the respective heart, ensured constant heart rate within each experiment. Coronary outflow was collected from the non-working right ventricle *via* the pulmonary artery to determine oxygen consumption. High-fidelity left ventricular pressure (LVP) data were sampled by a catheter pressure transducer (SPR-249A, Millar Instruments, Houston, Texas) introduced *via* the aortic valve, digitized at a rate of 1000 s^{-1}, and stored in four-second recordings.

Preload tests

An increasing preload was used to establish conditions in which τ_3 and τ_2 are expected to react differently. These tests were carried out in each heart by increasing left atrial inflow from about 10 ml min^{-1} in steps of 5 ml min^{-1} while mean aortic pressure was held constant by untying the hydraulic outflow resistor. One LVP recording was sampled at each step in the steady-state. This stepwise increase was terminated when imminent heart failure was apprehended.

Repetitions of the preload tests at different times after isolation allowed to use the spontaneous cardiac depression, always seen in isolated hearts, as a second varying experimental condition. In half of the experiments, the preload test was therefore repeated every 60 min until the heart became unable to maintain

constant aortic pressure due to that spontaneous depression. In the other experiments only an initial test with the freshly prepared heart and a final test were done; in the interim, the heart worked undisturbed with about 40 ml min^{-1} cardiac output. Each experiment lasted for more than 3 h (guinea pig) or 4 h (rat) after organ isolation; each first preload test consisted of at least 10 steps of inflow, the last test of at least 5 steps (duration of each preload test between 15 and 25 min).

Data Processing

Isovolumic pressure decay phases were extracted from LVP recordings from the times of peak –LVdP/d*t* until the preceding LVEDP was re-established (hereafter: standard fit interval). The data from all beats within a recording were pooled by setting t=0 at each peak –LVdP/d*t*, as previously described (Langer 2000). τ_3 and τ_2 were estimated from the models Eq. 1 and Eq. 2 using the simplex regression method (Press *et al.* 1989).

Two other possible sources of incorrect estimation, not related to the choice of the asymptote, were accounted for: Aortic valve closing and mitral valve opening both mark points of singular changes in the physical condition of the ventricular pressure decay; therefore, first and latest data points of the standard fit interval are surmised not to conform with the model assumption of a single monoexponential. Taking this into consideration, we repeated the calculation of τ_3 and τ_2 restricting the data points on a subinterval (hereafter: central fit interval) of the standard fit interval. These central fit intervals were created by discarding data points from the beginning and the end of the standard fit interval; their duration and position were individually determined from the pooled pressure data of each sample using a cluster-analytical method to find the optimal (i. e. regression-error minimizing) split (Langer 1996, 2000, 2002).

An other source of possibly systematic error in estimating the time constant is suggested by the observation that isovolumic pressure data are described by a hyperbolic tangent or (meaning the same) logistic function rather than a monoexponential in many cases (Matsubara *et al.* 1995, Senzaki *et al.* 1999, Langer 2002). To examine for such deviations, we calculated (from the standard fit interval) the shape parameter γ from the four–parametric regression

$$p_4(t) = P_\infty + \frac{P_0 - P_\infty}{\gamma + (1-\gamma)\exp\frac{t}{\tau_\infty}} \qquad (3)$$

Introducing the shape parameter, γ, turns the exponential time constant (τ_3) into the more general logistic one, τ_∞. Equation 3 becomes equivalent to Eq. 1 (i. e. $\tau_3=\tau_\infty$) if γ=0; presetting γ=0.5 yields the three-parametric logistic regression introduced by Matsubara *et al.* (1995). Thus, $\gamma>0$ is a useful indicator for such curve shape deviations from the exponential model (Eq. 1) that are independent of problems caused just by misestimating P_∞.

Statistical tests

For each preload test, the zero hypothesis states that τ_3 and τ_2 estimates differ only by chance from linear interrelation. Consequently, rejection of the zero hypothesis provides evidence for τ_3 and τ_2 being not measures of the same physical entity.

The statistical tests were performed by ranking the sequences of τ_3 and τ_2 separately within each preload test and counting the number of rank-inversions between both sequences. Let n be the number of values in each sequence (i. e. the number of levels in the respective preload test). Under the assumption that these sequences differ only by chance, the expected number of inversions is $n(n–1)/4$, because n elements allow for a maximum of $n(n–1)/2$ inversions (this maximum occurs if the sequences appear in a reverse order). The discrete (Laplacian) probability for each number of inversions can be obtained by dividing the number of permutations containing the respective number of inversions by the number $n!$ of all possible permutations of n. These probabilities are symmetrically distributed. A two-sided error probability, p, for rejecting the zero hypothesis was calculated for each preload test by summing the probabilities of those numbers of inversions that differ more from the mean number of inversions than the number actually found. A zero hypothesis was rejected at $p<0.01$. Data are presented as numbers of significant and non-significant cases.

Results

Theoretical analysis

Figure 1 shows the results of the theoretical analysis according to the Appendix, covering numerical values that usually occur in isovolumic pressure decay curves. The time constant τ_2, estimated by Eq. 2, underestimates the actual time constant τ_3 (Eq. 1) if the asymptote P_∞ is negative; the opposite holds if $P_\infty>0$. Obviously, the relative incorrect estimation is severe,

especially for small τ_3. Practically, values below 20 ms are most often observed; shifting of P_∞ by ± 4 mm Hg then causes errors of ± 20 % in estimating the time constant τ_2 instead of τ_3.

These results suggest that conflicting, i. e. reverse, responses of τ_3 and τ_2 may be provoked by increasing preload. This may occur in cases of cardiodepression, from whatever cause, when the Starling mechanism no longer counteracts the increasing end-systolic (residual) volume.

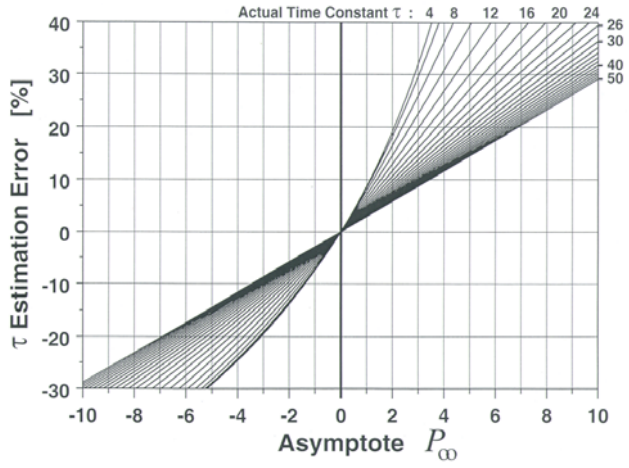

Fig.1. Relative error of the time constant estimated by the mono-exponential regression function with fixed asymptote (text Eq. 2) applied to a monoexponential function with non–zero asympto-te. Curves belong to exponential functions (Eq. 1 with fixed P_0=50) with variable asymptote (abs-cissa) and are parametrizised by different actual time constants $\tau=\tau_3$. The relative estimation error (ordinate) is $100(\tau_2-\tau_3)/\tau_3$. All units are arbitrary but the numbers are chosen to reflect typical values seen in cardiac isovolumic pressure decays (mmHg and ms). The length of the regression period is fixed to 40 (ms), beginning at the time of P_0.

Time constant changes during the preload tests

This situation was realized by the preload tests in the fresh and especially in the spontaneously depressed hearts. Table 1 summarizes the outcome of significance tests on the parallelism of τ_3- and τ_2-estimates during increasing preload in isolated small animal hearts.

Concerning the standard fit interval, most of the first preload tests (i. e. in the fresh preparation) presented with τ_3 and τ_2 measurements significantly progressing in the same direction (column "+s." in Table 1), namely a decrease. This pattern changed in subsequent tests and completely reversed in the last preload tests, performed more than 3 h (guinea pig) or 4 h (rat) after the preparation was completed, i. e. in the depressed heart. The total number of significant differences decreased, and in most of the remaining non-random outcomes the τ_3 and τ_2 series changed in opposite direction (column "–s." in Table 1), usually falling τ_3 but increasing τ_2 at rising preload.

Estimating the time constants from the central fit interval yielded fewer significant parallelism between τ_3 and τ_2 than the calculation from the standard fit interval did (Table 1). The obtained significant outcomes are distributed between parallel and reverse order in the same pattern as found from the standard fit intervals; this holds especially for the characteristic differences between first and subsequent preload tests, as mentioned above.

The underlying phenomenon is revealed by typical preload tests of an undepressed heart and a heart after spontaneous functional loss (data from standard fit intervals):

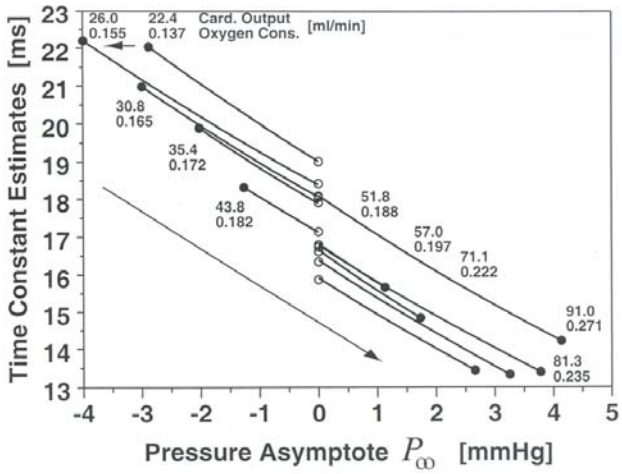

Fig. 2. Changes of time constants and pressure asymptotes of isovolumic pressure decays during increasing cardiac inflow (preload test, arrows indicate sequence of measurements) in an undepressed isolated ejecting guinea pig heart (left ventricular wet mass 1048 mg, aortic pressure 60 mm Hg, heart rate 255 min^{-1}, 37 °C). Rising inflow increases cardiac output, oxygen consumption (values given in the panel; ambient air pressure 754 mm Hg), and the pressure asymptote P_∞ (abscissa). Filled circles represent τ_3 estimates (ordinate) with estimated P_∞ (abscissa), open circles the corresponding τ_2 estimates with preset P_∞=0. Data points from both methods are connected by curves representing the theoretical time constant estimates with P_∞=0 at different interponed actual P_∞ values. Thus, the open ends of the curves give the respective precalculated estimates which are in high accordance with the observed estimates (open circles). Note that some quite different τ_3 values are connected with almost identical τ_2 estimates.

The freshly prepared, well performing heart (Fig. 2) manages cardiac outputs from 22 to 45 ml min^{-1} with P_∞ ranging from –4 to –1 mm Hg and further up to 91 ml min^{-1} output with P_∞<4 mm Hg. Energy demand increases, as indicated by the oxygen consumption noted in Fig. 2. τ_3 and τ_2 estimates concomitantly change; however, the parallelism remains poor. For instance,

τ_2 values estimated with zero asymptote (Eq. 2) pretend same lusitropy at lowest and highest P_∞ ($\tau_2 \approx 18.2$ ms), whereas the three-parametric exponential reveals a much shorter relaxation time constant in the latter case (τ_3 falling from 21 ms to 14.4 ms).

In the spontaneously depressed heart (Fig. 3), rising atrial inflow, increasing cardiac output from 23.4 to 44.5 ml min^{-1}, causes the pressure asymtote P_∞ to increase about twice as fast as in the undepressed case, whereas the time constant τ_3 still decreases (energy demand increases, as before). Contrary to this, the τ_2 values increase. This means that the series of time constants estimated with zero asymptote instead of a coestimated asymptote yields completely reverse results about lusitropy.

Throughout the study, shape parameter γ (Eq. 3) remained less than 0.2, indicating fairly exponential shape of the pressure decay curves (ideally, γ=0).

Table 1. Comparison of isovolumic pressure fall time constants estimated with variable and with zero pressure asymptote in sequences of preload tests in isolated ejecting hearts.

Species	Preload test		Standard fit +s.	n.s.	–s.	Sum	Central fit +s.	n.s.	–s.
Guin. Pig	*First*	*n*	6	3	2	11	4	6	1
		%	55	27	18	100	36	55	9
		%s.	75	—	25	100	80	—	20
	Subsequent	*n*	3	28	4	35	2	31	2
		%	9	80	11	100	6	88	6
		%s.	43	—	57	100	50	—	50
	Last	*n*	0	8	3	11	0	10	1
		%	0	73	27	100	0	91	9
		%s.	0	—	100	100	0	—	100
Rat	*First*	*n*	7	5	0	12	2	10	0
		%	58	42	0	100	17	83	0
		%s.	100	—	0	100	100	—	0
	Subsequent	*n*	3	17	3	23	1	21	1
		%	13	74	13	100	4	92	4
		%s.	50	—	50	100	50	—	50
	Last	*n*	1	10	1	12	1	11	0
		%	8	84	8	100	8	92	0
		%s.	50	—	50	100	100	—	0
Both	*First*	*n*	13	8	2	23	6	16	1
		%	56	35	9	100	26	70	4
		%s.	87	—	13	100	86	—	14
	Subsequent	*n*	6	45	7	58	3	52	3
		%	10	78	12	100	5	90	5
		%s.	46	—	54	100	50	—	50
	Last	*n*	1	18	4	23	1	21	1
		%	4	79	17	100	4	92	4
		%s.	20	—	80	100	50	—	50

Standard fit refers to the usual regression interval, beginning at the time of peak –LVdP/dt and ending when the former LVEDP is reached again. Central fit refers to a subinterval of the former with discarded first and latest data points (see Methods). Values are numbers (n) and percentages of preload tests found with significant (p<0.01) synchrony (+s.), non-significance (n.s.), and significant reversion (–s.) between the series of time constant estimates τ_3 (text Eq. 1) and τ_2 (Eq. 2). %s.: percentages of significant cases.

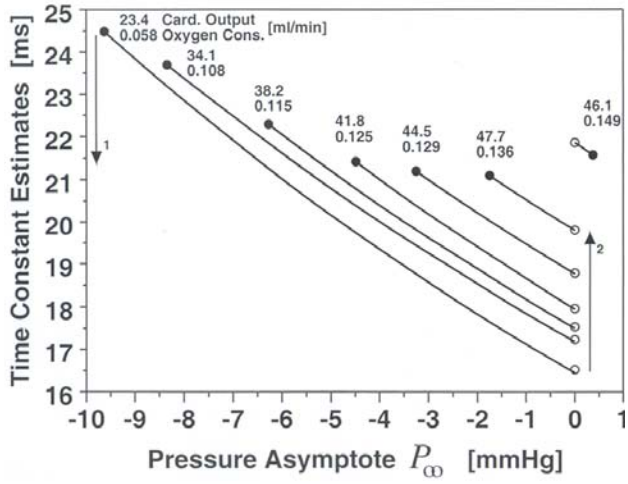

Fig. 3. Changes of time constants and pressure asymptotes of isovolumic pressure decays during increasing cardiac inflow (preload test) in a spontaneously depressed ejecting guinea pig heart, 3 h after isolation (left ventricular wet mass 1080 mg, aortic pressure 60 mm Hg, heart rate 260 min^{-1}, 37 °C). Rising inflow increases cardiac output, oxygen consumption (values in the panel; ambient air pressure 764 mm Hg), and the pressure asymptote P_∞ (abscissa). Obtaining the time constants τ_3 (ordinate, filled circles), with estimated P_∞, results in a decrease (arrow 1), whereas the time constants τ_2 (open circles), estimated with preset P_∞=0, progressively increase (arrow 2).

Discussion

This study challenges the questionable use of two similarly calculated time constant concepts for the left ventricular isovolumic pressure decay, the monoexponential regression model with zero asymptote against that with coestimated pressure asymptote. It demonstrates opposing changes of these time constant estimates atspecific hemodynamic conditions, e. g. the preload changes in depressed hearts. Evidently, one of the concepts produces false results. We recommend to abstain from the two-parametric monoexponential pressure decay model with preset zero asymptote.

Theory

The mathematical analysis shows that the zero-asymptote estimate τ_2 of the actual time constant τ_3 changes in the same direction with τ_3 if the actual asymptote P_∞ remains constant or also changes in the same direction as τ_3. If the latter does not hold, τ_2 may proceed in an opposite direction to τ_3. In order to determine the (patho)physiological relevance of this mathematical result, it was necessary to investigate if such inverse changes of τ_3 and P_∞ actually occur *in vivo* or in isolated hearts.

Time constant estimates biased by varying pressure asymptote

The performed preload tests provide evidence that τ_3 and τ_2 must not be conceived as equivalent measures of one physical entity. This became apparent in the spontaneously depressed hearts.

In the freshly prepared, well performing heart, increasing cardiac inflow, causing LVEDP to rise, enhances the subsequent contraction, thus keeping the residual (end-systolic) volume almost constant or even decreasing it. Consequently, the pressure asymptote of the following relaxation, which is determined by the residual volume (Brecher 1958), remains constant or decreases. This meets the first above mentioned condition, parallel change of τ_3 and P_∞, because positive inotropic interventions are mostly linked with positive lusitropic changes (Eichhorn *et al.* 1992, Vittone *et al.* 1994), reflected by a decreasing relaxation time constant τ_3. However, over time, this Starling mechanism becomes ineffective in the isolated organ. Now, rising cardiac inflow elevates P_∞, due to increasing residual volume, while the positive lusitropic effect of rising preload remains effective as indicated by decreasing τ_3. In contrast, τ_2 not only fails to detect this lusitropic effect but increases. Therefore, τ_2 is not a reliable alternative measure of the actual time constant of isovolumic pressure decay.

This observation explains, at least partly, the conflicting results obtained on the lusitropic influence of LVEDP in previous studies. Such conflicting results became particularly evident from studies that provide time constants calculated from both Eq. 1 and Eq. 2. Elevating LVEDP in closed-chest dogs by dextrane infusion yielded unaffected τ_3, but considerably increased τ_3, and a shift of P_∞ (Perlini *et al.* 1988) as expected by the present analysis. In similar experiments, Kettunen *et al.* (1986) detected no change of τ_2 but an increasing τ_3, whereas Raff and Glantz (1981) reported a "consistent" increase of both during volume loading. Increasing τ_3 was confirmed in open-chest dogs (Aubert *et al.* 1994), but no increase of τ_3 was seen in pig hearts (Myrmel *et al.* 1995). Methoxamine and nitroprusside infusions in humans did not induce significant changes in either τ_3 or τ_2 (Starling *et al.* 1987). Moreover, no change in τ_3 was observed during volume infusion in dogs at neurohumoral blockade (Cheng *et al.* 1990), whereas Prabhu (1999) reported that the response of τ_3 during vena cava occlusions changes with the absolute LVEDP

level. All these observations confirm that the two- and three-parametrically estimated time constants lead to different results during the same hemodynamic intervention. Any interpretation of such discordant results, in terms of lusitropy, requires knowledge of the factors that influence the τ_3 and τ_2 estimate.

Proper estimate of the time constant

The time constant τ_3 (Eq. 1) can be related to the viscoelastic properties of the myocardial wall during the isovolumic relaxation period (Langer 2002). In contrast, τ_2 (Eq. 2) additionally depends on the strength of the preceding contraction that determines the subsequent residual volume (Brecher 1958) and therefore influences P_∞, which is ignored by estimating τ_2. The mathematics of this dependence is complicated (Fig. 1 and Eq. 5) and, hence, not easily accessible for practical clinical use. It is surely preferable for a reliable analysis to estimate both τ_3 and P_∞ because this method yields distinct information about the myocardial wall property during isovolumic pressure fall (by τ_3) and about factors known to depend on the contractility or other external conditions (by P_∞) (Frais *et al.* 1990).

Objection against model Eq. 1 was raised by observing unreasonably low P_∞ estimates, e. g. P_∞= –8 mm Hg down to below –30 mm Hg in humans (Thompson *et al.* 1983). Such values are far below the empirical pressure minimum reached by the ejecting ventricle but were observed by Yellin *et al.* (1986) when they prevented diastolic refill for a single beat by a lockable artificial mitral valve in canine hearts. The authors noted that forcing P_∞=0 empirically results in time constant values (τ_2) close to the true value by compensating for deviations of the pressure decay from monoexponentiality and, further, that the trends of the time constants calculated by different methods remain the same under changing conditions. However, the present study clearly demonstrates that the latter does not generally hold.

Influence of non-exponentiality in empirical pressure decay data

Two other possible sources of inconsistence in estimating the relaxation time constant are presently considered: first, the estimates are influenced by selecting the regression fit interval; second, the intraventricular pressure decay may not meet the exponential model assumption in general. Concerning the first objection, valvular bulging and action may disturb ventricular isovolumicity at the beginning and at the end of the standard fit interval. Removing these pressure values from the regression was found to cause significant differences among the estimated time constants of ventricular pressure fall in some situations (Raff and Glantz 1981, Senzaki *et al.* 1999, Langer 2000). Presently, applying the three-parametric model (Eq. 1) to the central instead of the standard fit interval typically resulted in even more negative asymptotes, thus aggravating the above mentioned problem of "unreasonably low" P_∞ (Langer 2002). Furthermore, switching from standard to central fit intervals (Table 1) only reduced the number of significantly revealable parallelism and anti-parallelism between τ_3 and τ_2; discarding of data points renders the level of significance less attainable. The present cases with proved significant parallel or reverse changes of the relaxation time constant estimates τ_3 and τ_2 during the preload tests resemble the observations based on the standard fit intervals. These results indicate that the question — whether P_∞ should be coestimated or preset to zero — is unrelated to the chosen regression fit interval.

Non-exponentiality of the pressure decay also did not influence the present results. Significant systematic deviations of the pressure decay from Eq. 1 occur in rat and guinea pig hearts (Langer 2000) but remain small for left ventricular mass below 400 mg (with Eq. 3 typically $\gamma \leq 0.2$ in the present study). This deviation is completely unrelated to the presented discordances between τ_3 and τ_2; this is proved by comparing the τ_2 values computed according to the Appendix from model Eq. 1 with those directly estimated by regression in model Eq. 2. In Figs. 2 and 3, the former are represented by the ends of the curves at zero abscissa, and the latter by open circles. No relevant differences occur, so that switching from estimated to preset zero asymptote has not compensated for model violations (non-exponentiality) in the present experiments.

However, interfering non-exponentiality of the pressure decay and concomitant incorrect estimation of P_∞ (and time constant) may become more relevant in the hearts of larger species (Matsubara *et al.* 1995, Senzaki *et al.* 1999). P_∞ is extrapolated from ventricular properties present in the chosen pressure decay phase only and, therefore, is sensitive to model violations caused by continuously changed ventricular properties (Peterson *et al.* 1991, Tobias *et al.* 1995) during that phase. This

extrapolation can be satisfyingly corrected not by fixing P_∞=0, but, on the contrary, at the expense of a fourth regression parameter. Already chosing γ=0.5 in Eq. 3 yields reasonable P_∞ estimates in canine (Matsubara *et al.* 1995) and human hearts (Senzaki *et al.* 1999), but estimating γ as a fourth parameter significantly improves the fit further and estimates P_∞ in the vicinity of zero (usually negative), as expected (Langer 2000, 2002). Therefore, one can decide either to accept the "unrealistic" extrapolated P_∞, or to enhance that extrapolation by a properly expanded regression model. Forcing P_∞=0 instead (Eq. 2) deteriorates the accuracy of the fit and introduces an additional source of error which can lead to severe misinterpretation of the lusitropic state of the ventricle, as demonstrated by this study.

Conclusions

Estimating the time constant of the isovolumic pressure decay in hearts from monoexponential regression models with preset zero *versus* estimated asymptote leads to qualitatively different results. Under certain conditions (increasing preload in depressed hearts), alternative time constants yield directly contradictory information about "lusitropy". The time constant estimated with zero asymptote is biased by increases of the end-systolic volume. Therefore it is of limited use in basic and clinical investigations. The consequent solution is to include the estimation of the actual pressure asymptote into the regression model according to Eq. 1. This provides a measure of lusitropy that is independent from changes in end-diastolic pressure, caused by varying preload or contractility.

Appendix

Given an exponential p_3 with arbitrary asymptote P_∞ as in Eq. 1, we determined the parameters b and τ_2 so that the exponential $b\exp(-t/\tau_2)$ (with implicit zero-asymptote) becomes the least squared-error sum (Gaussian) regression on p_3 over a regression interval from t=0 to s>0. Whereas practical application of the least squared-error sum always works with a definite number of discrete data points (indicating the sum by Σ), this does no longer hold for the presently performed theoreticcal analysis, utilizing "indefinitely small steps". Therefore, the usual discrete squared-error sum is to be substituted by the integral

$$\int_0^s \left[(P_0-P_\infty)\exp\frac{-t}{\tau_3}+P_\infty-b\exp\frac{-t}{\tau_2}\right]^2 dt = \int_{\frac{-s}{2}}^{\frac{s}{2}} \left[A\exp\frac{-t}{\tau_3}+P_\infty-a\exp\frac{-t}{\tau_3}\right]^2 dt \tag{4}$$

where $A=(P_0-P_\infty)\exp[-s/(2\tau_3)]$ and $a=b\exp[-s/(2\tau_2)]$ (such symmetrizing the integration limits simplifies the following mathematics).

The task of the regression is now to find those values for b and τ_2 that minimize the term in Eq. 4. This is performed in the usual way by solving for the "normal equations": establishing the two partial derivatives of Eq. 4 with respect to b and to τ_2 and determining their roots ("zeros"). This calculation is somewhat tedious but it requires only well-known calculus, especially concerning the hyperbolic functions.

Solving the first normal equation for a and substituting it in the second yields the equation

$$f(\tau_2)=\frac{A\tau_3}{\tau_3+\tau_2}\left[\left(\frac{\tau_3-\tau_2}{\tau_3+\tau_2}+\frac{s}{\tau_2}\coth\frac{s}{\tau_2}\right)\sinh\frac{s(\tau_3+\tau_2)}{2\tau_3\tau_2} - \frac{s}{\tau_2}\cosh\frac{s(\tau_3+\tau_2)}{2\tau_3\tau_2}\right] + P_\infty\left[\sinh\frac{s}{2\tau_2} + \frac{s}{2\tau_2}\left(\sinh\frac{s}{2\tau_2}\tanh\frac{s}{2\tau_2}-\cosh\frac{s}{2\tau_2}\right)\right] \tag{5}$$

(for $\tau_2 \neq -\tau_3, 0$). The root of this function, i. e. τ_2 with $f(\tau_2)$=0, is the desired error-minimizing estimate. It was numerically determined by the iterative Newton algorithm, i. e. by expanding the series $\tau_2^{(n+1)} = \tau_2^{(n)} - f\left(\tau_2^{(n)}\right)\left[df\left(\tau_2^{(n)}\right)/d\tau_2^{(n)}\right]^{-1}$ up to the desired accuracy (starting with $\tau_2^{(1)}$=1; superscript numbers in parentheses denote the respective step of the iteration). The efficient algorithm to evaluate f and its derivative is given in Table 2. The length of the regression interval was set to s=40 (reflecting the millisecond-duration of a typical isovolumic pressure decay phase) for calculating Fig. 1. In the calculations on the empirical data (Figs. 2 and 3), the length s of the regression interval was set to the actual duration of the respective isovolumic phase.

Correctness of the formulas in Table 2 was checked by supplying some arbitrary input (τ_3, P_0, P_∞)

and comparing the output (τ_2, b) with the respective results provided by a common least-squares regression program working on discrete data series generated according to Eq. 1. Both processes yielded identical results (relative differences below 10^{-4}).

Table 2. Algorithm to evaluate the function f (Eq. 5) to find the time constant τ_2 of the least–squares fitting monoexponential (zero asymptote) to the function from Eq. 1.

$$D_1 := \tau_3+\tau_2 \qquad D_2 := \tau_3-\tau_2 \qquad C := A\tau_3 D_1^{-1}$$
$$E_1 := \tfrac{1}{2}s\tau_2^{-1} \qquad E_2 := E_1\tau_2^{-1}$$
$$F := E_1+\tfrac{1}{2}s\tau_3^{-1} \qquad G := E_1\tau_3+\tfrac{1}{2}s$$
$$\mu_1 := \exp E_1 \qquad \mu_2 := \mu_1^{-1}$$
$$H_1 := \tfrac{1}{2}(\mu_1-\mu_2) \qquad H_2 := \tfrac{1}{2}(\mu_1+\mu_2) \qquad H_3 := H_1H_2^{-1}$$
$$\nu_1 := \exp F \qquad \nu_2 := \nu_1^{-1}$$
$$K_1 := \tfrac{1}{2}(\nu_1-\nu_2) \qquad K_2 := \tfrac{1}{2}(\nu_1+\nu_2) \qquad K_3 := H_3+H_3^{-1}$$

$$f(\tau_2) = C\left[\left(\frac{D_2}{D_1}+E_1K_3\right)K_1-2E_1K_2\right] + P_\infty\left[H_1+E_1(H_1H_3-H_2)\right]$$

$$\frac{\mathrm{d}\,f(\tau_2)}{\mathrm{d}\tau_2} = \frac{C}{D_1}\left\{\frac{\tau_2-3\tau_3}{D_1}K_1+E_2\left[(D_1+4\tau_2)K_2 + GK_1\left(2+(H_1H_2)^{-2}\right)-K_3\left(GK_2+(D_1+\tau_2)K_1\right)\right]\right\} + P_\infty E_2H_1\left[E_1(H_3^2-1)-H_3\right]$$

The searched for root, $\tau_2 = f^{-1}(0)$, is obtained by the Newton algorithm using the given formulas for f and its derivative.

Acknowledgements

This study was kindly supported by a grant from the Sonnenfeld Foundation, Berlin.

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