Half-Logistic Time Constants as Inotropic and Lusitropic Indices for Four Sequential Phases of Isometric Tension Curves in Isolated Rabbit and Mouse Papillary Muscles

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Summary
The waveforms of myocardial tension and left ventricular (LV) pressure curves are useful for evaluating myocardial and LV performance, and especially for inotropism and lusitropism. Recently, we found that half-logistic (h-L) functions provide better fits for the two partial rising and two partial falling phases of the isovolumic LV pressure curve compared to mono-exponential (m-E) functions, and that the h-L time constants for the four sequential phases are superior inotropic and lusitropic indices compared to the m-E time constants. In the present study, we tested the hypothesis that the four sequential phases of the isometric tension curves in mammalian cardiac muscles could be curve-fitted accurately using h-L functions. The h-L and m-E curve-fits were compared for the four phases of the isometric twitch tension curves in 7 isolated rabbit right ventricular and 15 isolated mouse LV papillary muscles. The isometric tension curves were evaluated in the four temporal phases: from the beginning of twitch stimulation to the maximum of the first order time derivative of tension (dF/dt_{max}) (Phase I), from dF/dt_{max} to the peak tension (Phase II), from the peak tension to the minimum of the first order time derivative of tension (dF/dt_{min}) (Phase III), and from dF/dt_{min} to the resting tension (Phase IV). The mean h-L correlation coefficients (r) of 0.9958, 0.9996, 0.9995, and 0.9999 in rabbit and 0.9950, 0.9996, 0.9994, and 0.9997 in mouse for Phases I, II, III, and IV, respectively, were higher than the respective m-E r-values (P < 0.001). The h-L function quantifies the amplitudes and time courses of the two partial rising and two partial falling phases of the isometric tension curve, and the h-L time constants for the four partial phases serve as accurate and useful indices for estimation of inotropic and lusitropic effects. (Int Heart J 2009; 50: 389-404)

Key words: Myocardium, Inotropism, Lusitropism, Half-logistic function, Curve fit
The waveforms of myocardial tension and left ventricular (LV) pressure curves in the mammalian heart provide significant information regarding myocardial and LV performance, and are especially useful for evaluation of inotropism and lusitropism. In this paradigm, the myocardium and left ventricle are viewed as nonlinear oscillators that generate the output, i.e., myocardial tension and LV pressure as a function of time.\(^1,2\) Nonlinear regression and curve-fitting may contribute to resolution of the mechanism, summarize information, remove noise, allow speculation regarding unmeasured data, and separate the effects of multiple factors. In an effort to maximize the amount of useful information that can be extracted from the waveforms of the tension and LV pressure curves, these curves have been studied by curve-fitting with mathematical models including sinusoidal,\(^3\) polynomial-exponential,\(^4\) hybrid-logistic,\(^5-10\) and hybrid-Weibull functions.\(^11\)

Many attempts have also been made to derive reliable lusitropic indices from the minimum of the first order time derivative of LV pressure (dP/dt\(_{\text{min}}\)). A mono-exponential (m-E) function has been put forth as a reasonably good fit for the isovolumic LV pressure decrease from dP/dt\(_{\text{min}}\) in the excised, cross-circulated canine heart,\(^12\) and the m-E time constant (P\(_E\)) for the LV pressure decrease has been widely used as a reasonable lusitropic index in animal models\(^13\) and clinical settings.\(^14\) The physiological and clinical significance of P\(_E\) and the coefficients derived from the m-E curve-fits have been established to provide a basis for LV analysis and clinical decision making. However, the m-E curve-fit does not completely represent underlying effects due to mismatches between the original waveform and the modelled curve.\(^15,16\) Therefore, we have found that a half-logistic (h-L) function, which is half of the sigmoidal, logistic function with a boundary at the inflection point, fits the isovolumic LV pressure decrease more accurately than the conventional m-E function in the excised, cross-circulated canine heart,\(^17\) and the h-L time constant (P\(_L\)) has been proposed as a better lusitropic index than P\(_E\).\(^17-19\) The h-L curve-fits have been used in assessment of animal\(^20-24\) and human LV pressure decreases.\(^25\) Moreover, the h-L time constant (F\(_L\)) for the isometric relaxation tension curve from the minimum of the first order time derivative of tension (dF/dt\(_{\text{min}}\)) in the papillary muscle\(^26,27\) has been proposed as a better lusitropic index than the standard m-E time constant (F\(_E\)).\(^28,29\)

The concept of P\(_L\) has also been applied to analysis of partial isovolumic LV pressure curves acquired during contraction and relaxation.\(^6\) Specifically, the maximum of the first order time derivative of pressure (dP/dt\(_{\text{max}}\)) and the peak LV pressure have been used as LV inotropic indices, and dP/dt\(_{\text{min}}\) and the LV end-diastolic pressure (LVEDP) have been used as LV lusitropic indices,
respectively. The isovolumic LV pressure curves, ie, one oscillation for each cardiac cycle, were divided into four distinct phases with boundaries set at $dP/dt_{\text{max}}$, peak LV pressure, $dP/dt_{\text{min}}$, and LVEDP resulting in the rising phase from the point corresponding to QR on the electrocardiogram to $dP/dt_{\text{max}}$; the rising phase from $dP/dt_{\text{max}}$ to the peak LV pressure; the falling phase from the peak LV pressure to $dP/dt_{\text{min}}$; and the falling phase from $dP/dt_{\text{min}}$ to LVEDP. We found that $P_L$ for the four sequential phases of the LV pressure curve provided useful indices of velocity for estimation of alterations in the two partial rising and two partial falling phases. Each phase had its own particular $P_L$ value and is influenced by the physiological, pharmacological, and pathological conditions. Moreover, in the myocardial tension curve, the maximum of the first order time derivative of tension ($dF/dt_{\text{max}}$) and the peak tension have been used as myocardial inotropic indices, and $dF/dt_{\text{min}}$ and the resting tension have been used as myocardial lusitropic indices. The quantitative contribution of different calcium ($Ca^{2+}$) handling to contraction and relaxation as well as myosin isoform composition varies among animal species.

It would be of value to compare h-L and m-E fits for the four sequential phases of the myocardial tension curves with boundaries set at $dF/dt_{\text{max}}$, the peak tension, $dF/dt_{\text{min}}$, and the resting tension in different animal species. In the present study, we tested the hypothesis that h-L functions more accurately represent the two partial rising and two partial falling phases of acquired papillary muscle tension curves in different animal species compared to the currently used m-E function and that each of the four phases has h-L characteristics.

**Methods**

This study protocol was approved by the Animal Investigation Committee of the Jikei University School of Medicine. All procedures were conducted in conformity with the Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences endorsed by the Physiological Society of Japan. **Surgical preparation:** Seven albino rabbits (Japan White, body weight 2.0 - 2.5 kg) and 15 mice (C57BL/6, body weight 25 - 30 g) were anesthetized with intravenous (1.5 - 2.0 mg/kg) and intraperitoneal (15 - 20 mg/kg) pentobarbital sodium, respectively. After the heart was removed, the aorta was cannulated with a blunted 18 G needle and the heart was mounted on a Langendorff apparatus. The coronary blood was washed out with Tyrode’s solution with 2 mM $Ca^{2+}$ buffered by N-2-hydroxyethyl-piperazine-N-2-ethanesulfonic acid (HEPES) at constant pressure for 5 minutes. The solution was changed to HEPES-buffered Tyrode’s solution containing 2 mM $Ca^{2+}$ and 20 mM 2,3-butanedione monoxime (BDM) after the heart beat was stabilized. Once the contraction stopped completely, the
heart was removed from the Langendorff apparatus. A thin papillary muscle was dissected out from the rabbit right ventricular (RV) and mouse LV walls.

After both ends of the isolated muscle were tied with silk threads, the muscle was mounted horizontally in an experimental chamber, immersed in a bath, and continuously perfused with Tyrode’s solution. One end of the muscle was connected to the fixed hook and the other end was attached to the arm of a tension transducer (BG-10, Kulite Semiconductor Products, Leonia, NJ; compliance 2.5 μm/g, unloaded resonant frequency 0.6 kHz). A pair of black platinum electrodes was placed parallel to the muscle, which was regularly stimulated by a single square pulse of 5 ms duration at 0.5 Hz; the strength of the stimulation was 1.5 times the threshold. The muscle was slowly stretched and adjusted to the length at which the developed tension reached a maximum (Lmax).

**Tyrode’s solution:** Tyrode’s solution buffered with HEPES was used in all experiments, including muscle dissection. The composition of the solution (in mM) was as follows: NaCl, 136.9; KCl, 5.4; MgCl₂, 0.5; NaHPO₄, 0.33; HEPES, 5; and glucose 5. The pH was adjusted to 7.40 ± 0.05 with NaOH at 24°C, and the solution was equilibrated with 100% O₂. The temperature of the solution was continuously monitored with a thermocouple and maintained at 30 ± 0.5°C.

**Tension curve:** Tension was measured using a storage oscilloscope (7TO7A, NEC San-ei, Tokyo). The tension signals were sampled at 1-ms intervals and digitized with an A/D converter. All tension data were stored on a computer (PC-9801, NEC, Tokyo) for later analysis. The isometric tension curve was measured from the time before starting twitch stimulation to the time when the tension returned to the resting tension level, ie, close to zero mN/mm². The first order time derivative of tension (dF/dt) was obtained by differentiating the sampled data after digital smoothening using an 11-point, nonweighted moving average of digitized tension signals. The original isometric tension curve was divided into distinct phases with boundaries set at dF/dtmax, the peak tension, dF/dt_min, and the resting tension to evaluate four temporal phases of the curve, as shown in Figure 1. Phase I was defined as the period from the beginning of twitch stimulation to the point corresponding to dF/dtmax, Phase II as the period from the point corresponding to dF/dtmax to the point corresponding to the peak tension, Phase III as the period from the point corresponding to the peak tension to the point corresponding to dF/dt_min, and Phase IV, ie, the conventional relaxation phase of the isometric tension curve, as the period from the point corresponding to dF/dt_min to the point corresponding to the resting tension. The rising phase of the curve was defined as the period from the beginning of twitch stimulation to the point corresponding to the peak tension, and the falling phase was defined as the period from the point corresponding to the peak tension to the point corresponding to the resting tension.
Half-logistic (h-L) and mono-exponential (m-E) function equations: The h-L function (Eq. 1) was used to fit the original isometric tension curves during Phases I and III using the least squares method in DeltaGraph 4.0 (DeltaPoint, Monterey, CA). Similarly, a second h-L function (Eq. 2) was used to fit the curves for Phases II and IV.

\[ F(t) = \frac{2F_A}{1 + \exp[-(t-t_C)/F_{T_L}]} + F_B \]  
(Eq. 1)

\[ F(t) = 2F_A/\{1 + \exp[(t-t_C)/F_{T_e}]\} + F_B \]  
(Eq. 2)

where \( t \) is the time, \( F_A \) is the h-L amplitude constant, \( F_{T_L} \) is the h-L time constant, \( F_B \) is the h-L nonzero asymptote, and \( t_C \) is a constant. The \( F_{T_L} \) values during Phases I and III correspond to the time for the curves to increase and decrease from \( F(F_{T_L}) = \{2F_A/(1 + e) + F_B\} \) to \( F(t_C) = \{F_A + F_B\} \), respectively, and the \( F_{T_L} \) values during Phases II and IV correspond to the time for the curves to increase and decrease from \( F(t_C) = \{F_A + F_B\} \) to \( F(F_{T_L}) = \{2F_A/(1 + e) + F_B\} \), respectively. \( F(F_{T_L}) \) is \( 2/(1 + e) \) (~0.54) of \( F_A \). The \( t_C \) values during Phases I and II represent the time at \( dF/dt_{\text{max}} \), and the \( t_C \) values during Phases III and IV represent the time at \( dF/dt_{\text{min}} \). The h-L curves given by Eqs. 1 and 2 increase or decrease monotonically, but not in a sigmoid manner.

An m-E function (Eq. 3) was also used to fit the original isometric tension curves during Phases I and III, and a second m-E function (Eq. 4) was used for curve-fitting of Phases II and IV.

\[ F(t) = F_0 \exp[(t-t_C)/F_{T_E}] + F_\infty \]  
(Eq. 3)

\[ F(t) = F_0 \exp[-(t-t_C)/F_{T_E}] + F_\infty \]  
(Eq. 4)

where \( t \) is the time, \( F_0 \) is the m-E amplitude constant, \( F_{T_E} \) is the m-E time constant, and \( F_\infty \) is the m-E nonzero asymptote, and \( t_C \) is a constant. The \( F_{T_E} \) values during Phases I and III correspond to the time for the curves to increase and decrease from \( F(F_{T_E}) = \{F_0/e + F_\infty\} \) to \( F(t_C) = \{F_0 + F_\infty\} \), respectively, and the \( F_{T_E} \) values during Phases II and IV correspond to the time for the curves to increase and decrease from \( F(t_C) = \{F_0 + F_\infty\} \) to \( F(F_{T_E}) = \{F_0/e + F_\infty\} \), respectively. \( F(F_{T_E}) \) is \( 1/e \) (~0.37) of \( F_0 \). The \( t_C \) value during Phases I and II represents the time at \( dF/dt_{\text{max}} \), and the \( t_C \) value during Phases III and IV represents the time at \( dF/dt_{\text{min}} \). The m-E curves given by Eqs. 3 and 4 increase or decrease monotonically.

It should be noted that the h-L functions (Eqs. 1 and 2) have the same number of coefficients as the m-E functions (Eqs. 3 and 4) and that \( F_A, F_{T_L}, \) and \( F_B \) in Eqs. 1 and 2 are conceptually similar to \( F_0, F_{T_E}, \) and \( F_\infty \) in Eqs. 3 and 4, respectively.

Statistical analysis: Goodness of fit was evaluated by comparing the correlation coefficient (\( r \)) and residual mean squares (RMS) for the h-L and m-E curve-fitting models. A paired Student’s \( t \) test was applied to Fisher’s Z transformation:

\[ Z = 1/2[\ln(1 + r) - \ln(1 - r)] \]  
(30)

Residual values were calculated as the observed
isometric tension curve value minus the best-fit h-L or m-E value at each sampling data point. RMS was calculated as the residual sum of squares divided by the residual degrees of freedom, which indicates the number of data points analyzed minus the number of parameters in the function. The h-L and m-E RMS values were compared using the Wilcoxon signed-rank test. The $F_{\text{h-L}}$, $F_{\text{m-E}}$, h-L Z, m-E Z, h-L RMS, and m-E RMS values were compared among the four phases by one-way analysis of variance (ANOVA). When one-way ANOVA was significant (F-test, $P < 0.05$), multiple comparisons were performed using the post hoc Scheffe’s test. Analyses were performed using Statcel (OMS, Saitama, Japan) and StatView 5.0 (SAS Institute Inc, Cary, NC, USA) software. Values are expressed as the mean ± standard deviation (SD) unless otherwise noted. A $P$ value of $< 0.05$ was considered to indicate statistical significance.

**Results**

**Tension characterization:** The diameters of the isolated muscle specimens in the 7 rabbits and 15 mice were $0.73 \pm 0.13$ and $0.63 \pm 0.11$ mm, respectively. The muscle lengths in rabbit and mouse were $3.30 \pm 0.77$ and $2.01 \pm 0.43$ mm, respectively. The observed isometric tension curve data in rabbit and mouse are summarized in the Table.

**Half-logistic (h-L) and mono-exponential (m-E) parameters:** Representative h-L and m-E curve-fits for the observed isometric tension curves during Phases I, II, III, and IV in a rabbit muscle are shown in Figure 2, and the residuals calculated from the observed values during Phases I, II, III, and IV minus the best-fit h-L and m-E curves are shown in Figure 3. The time durations of Phases I, II, III, and IV were $172.9 \pm 23.0$, $129.9 \pm 16.1$, $134.9 \pm 18.7$, and $461.4 \pm 36.8$ ms, respectively, in rabbit, and $82.8 \pm 4.9$, $58.9 \pm 7.8$, $45.6 \pm 8.3$, and $300.8 \pm 18.3$ ms, respectively, in mouse.

### Table. Characteristics of Isometric Tension Curves in Isolated Rabbit RV and Mouse LV Papillary Muscles

<table>
<thead>
<tr>
<th></th>
<th>Rabbit</th>
<th>Mouse</th>
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<tbody>
<tr>
<td>Tension at $dF/dt_{\text{max}}$ (mN/mm²)</td>
<td>7.8 ± 1.5</td>
<td>2.8 ± 2.0</td>
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<tr>
<td>Peak tension (mN/mm²)</td>
<td>15.6 ± 2.6</td>
<td>8.3 ± 6.1</td>
</tr>
<tr>
<td>Tension at $dF/dt_{\text{min}}$ (mN/mm²)</td>
<td>9.0 ± 1.1</td>
<td>5.6 ± 4.0</td>
</tr>
<tr>
<td>Time to $dF/dt_{\text{max}}$ (ms)</td>
<td>172.9 ± 23.0</td>
<td>82.8 ± 4.9</td>
</tr>
<tr>
<td>Time to peak tension (ms)</td>
<td>302.7 ± 33.4</td>
<td>141.7 ± 10.8</td>
</tr>
<tr>
<td>Time to $dF/dt_{\text{min}}$ (ms)</td>
<td>437.6 ± 36.8</td>
<td>187.3 ± 18.6</td>
</tr>
<tr>
<td>$dF/dt_{\text{max}}$ (mN/mm²/s)</td>
<td>100.1 ± 32.3</td>
<td>140.6 ± 89.3</td>
</tr>
<tr>
<td>$dF/dt_{\text{min}}$ (mN/mm²/s)</td>
<td>-70.5 ± 13.6</td>
<td>-79.8 ± 52.0</td>
</tr>
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</table>

Mean ± SD in 7 isolated rabbit RV and 15 isolated mouse LV papillary muscles. $dF/dt_{\text{max}}$ indicates maximum of the first order time derivative of tension and $dF/dt_{\text{min}}$ minimum of the first order time derivative of tension.
Figure 1. Four phases of the isometric tension curve. The isometric tension curve is divided into four phases with boundaries set at the maximum of the first order time derivative of tension ($dF/dt_{\text{max}}$), the peak tension, the minimum of the first order time derivative of tension ($dF/dt_{\text{min}}$), and the resting tension. Phase I: period from the beginning of twitch stimulation to the point corresponding to $dF/dt_{\text{max}}$. Phase II: period from the point corresponding to $dF/dt_{\text{min}}$ to the point corresponding to the peak tension. Phase III: period from the point corresponding to the peak tension to the point corresponding to $dF/dt_{\text{min}}$. Phase IV: period from the point corresponding to $dF/dt_{\text{min}}$ to the point corresponding to the resting tension.

Figure 2. Representative half-logistic (h-L) and mono-exponential (m-E) curve fits for four phases of isometric tension curve in an isolated rabbit RV papillary muscle. A, B, C, and D: Representative h-L curve fits for the observed isometric tension curves during Phases I, II, III, and IV, respectively. E, F, G, and H: Representative m-E curve fits for Phases I, II, III, and IV in A, B, C, and D, respectively. Thin dotted lines indicate observed isometric tension curve; thick dashed lines, best-fit h-L or m-E curve; $F_{\text{t}}$, h-L time constant; $F_{\text{te}}$, m-E time constant; $r$, correlation coefficient; and Z, Z transformation of $r$. 
Figure 3. Residuals of representative half-logistic (h-L) and mono-exponential (m-E) curve fits for four phases of isometric tension curve in an isolated rabbit RV papillary muscle. A, B, C, and D: Residuals calculated from the observed isometric tension curves during Phases I, II, III, and IV minus the best-fit h-L curves (Figure 2), respectively. E, F, G, and H: Residuals calculated from the observed data for Phases I, II, III, and IV minus the best-fit m-E curves (Figure 2), respectively. RMS indicates residual mean squares.

Figure 4. Half-logistic (h-L) and mono-exponential (m-E) time constants for four phases of isometric tension curves in isolated rabbit RV and mouse LV papillary muscles. Mean ± SD in 7 isolated rabbit RV and 15 isolated mouse LV papillary muscles. A: h-L (black squares: $F_{\tau_L}$) and m-E time constants (white circles: $F_{\tau_E}$) for isometric tension curves during Phases I, II, III, and IV in rabbit. B: $F_{\tau_L}$ (black squares) and $F_{\tau_E}$ (white circles) for Phases I, II, III, and IV in mouse. †: $P < 0.05$, ††: $P < 0.001$ versus Phase I; ‡: $P < 0.05$, ‡‡: $P < 0.001$ versus Phase II; ¶: $P < 0.05$, ¶¶: $P < 0.001$ versus Phase III. §
respectively, in mouse.

The h-L and m-E time constant (F\(\tau\)_L and F\(\tau\)_E) values for the four phases are shown in Figure 4. In rabbit, the F\(\tau\)_L and F\(\tau\)_E values for Phase I were smaller than those for Phase IV. In mouse, the F\(\tau\)_L and F\(\tau\)_E values for Phase I were the smallest among the four phases, and the F\(\tau\)_L value for Phase IV was the largest among the four phases. The h-L and m-E amplitude constant (F\(A\) and F\(b\)) and nonzero asymptote (F\(\infty\) and F\(_\infty\)) values for the four phases are shown in Figure 5. The F\(A\) and F\(_0\) values and the F\(b\) and F\(_\infty\) values seemed to be similar.

**Figure 5.** Half-logistic (h-L) and mono-exponential (m-E) amplitude constants and nonzero asymptotes for four phases of isometric tension curves in isolated rabbit RV and mouse LV papillary muscles. Mean ± SD in 7 isolated rabbit RV and 15 isolated mouse LV papillary muscles. A: h-L (black bars: F\(A\)) and m-E amplitude constants (white bars: F\(_0\)) for isometric tension curves during Phases I, II, III, and IV in rabbit. B: F\(A\) (black bars) and F\(_0\) (white bars) for Phases I, II, III, and IV in mouse. C: h-L (black bars: F\(b\)) and m-E nonzero asymptotes (white bars: F\(_\infty\)) for Phases I, II, III, and IV in rabbit. D: F\(b\) (black bars) and F\(_\infty\) (white bars) for Phases I, II, III, and IV in mouse.
Goodness of half-logistic (h-L) and mono-exponential (m-E) fits: The mean h-L $r$ values for Phases I, II, III, and IV were 0.9958, 0.9996, 0.9995, and 0.9999, respectively, in rabbit, and 0.9950, 0.9996, 0.9994, and 0.9996, respectively, in mouse; and the mean m-E $r$-values for Phases I, II, III, and IV were 0.9915, 0.9984, 0.9985, and 0.9978, respectively, in rabbit, and 0.9984, 0.9986, 0.9984, and 0.9971, respectively, in mouse. Z transformation of the h-L $r$-values for each of the four phases gave values that were higher than for the corresponding Z transformation of the m-E $r$-values in both rabbit and mouse, as shown in Figure 6.
In rabbit, the h-L and m-E Z-values for Phase I were the lowest among the four phases ($P < 0.001$), the h-L Z-value for Phase IV was the highest among the four phases ($P < 0.05$), and the m-E Z-value for Phase IV was higher than those for Phases I and III ($P < 0.05$). In mouse, the h-L and m-E Z-values for Phase I were the lowest among the four phases ($P < 0.001$), the h-L Z-value for Phase IV was higher than those for Phases I and III ($P < 0.05$), and the m-E Z-value for Phase IV was the highest among the four phases ($P < 0.001$). The h-L RMS values for the four phases were smaller than the m-E RMS values in both rabbit and mouse, as shown in Figure 6. In rabbit, the h-L and m-E RMS values for Phase I were the largest among the four phases ($P < 0.001$).

**DISCUSSION**

The current results demonstrate that h-L functions provide better fits than m-E functions for the two partial rising and two partial falling phases of the isometric tension curves in both isolated rabbit and mouse papillary muscles. The h-L functions provide a quantitative characterization of the amplitudes and time courses of the four phases.

**Ca\(^{2+}\) handling in the four phases:** Myocardial contraction and relaxation are continuous time phenomena that are regulated by intracellular Ca\(^{2+}\) level.\(^{32}\) We recently showed that h-L functions provide a better fit of intracellular Ca\(^{2+}\) declines from any starting point, compared to conventional m-E functions.\(^{33}\) During a cardiac cycle, the contraction process causes Ca\(^{2+}\) inflow into the cytoplasm via L-type Ca\(^{2+}\) channel, Ca\(^{2+}\)-induced Ca\(^{2+}\) release from the sarcoplasmic reticulum (SR), and Ca\(^{2+}\) binding to troponin C,\(^{34-38}\) whereas the relaxation process involves Ca\(^{2+}\) dissociation from troponin C, Ca\(^{2+}\) sequestration into the SR, and Ca\(^{2+}\) removal from the cytoplasm to the extracellular space via the Na\(^+\)/Ca\(^{2+}\) exchanger. In our previous study, $P_k$ for Phase I was the smallest among the four phases.\(^{6}\) Our current results show that $F_k$ during Phase I was also the smallest among the four phases and $F_k$ during Phase IV in mouse was the largest among the four phases (Figure 4). However, $F_k$ has a similar value during Phases II and Phase III. These results show that there are different time constants for Phase I and Phase II in the rising phase, and for Phase III and Phase IV in the falling phase, but that the time constant does not differ between Phase II and Phase III of the isovolumic LV pressure curve and the isometric tension curve. Brutsaert, et al have suggested that the relaxation phase should include the muscular contraction process physiologically.\(^{39}\) We speculate that the tension waveform in Phase I is mainly related to the contraction process; that is, the rapid increase in intracellular Ca\(^{2+}\) concentration due to Ca\(^{2+}\) inflow into the cytoplasm, Ca\(^{2+}\)-induced Ca\(^{2+}\) release from the SR, Ca\(^{2+}\) binding to troponin C,
and cross-bridge association. Conversely, the tension waveform in Phase IV is mainly related to the relaxation process; that is, the decrease in intracellular Ca\(^{2+}\) concentration due to Ca\(^{2+}\) dissociation from troponin C and Ca\(^{2+}\) removal from the cytoplasm, and cross-bridge dissociation. The tension waveforms in Phases II and III are probably related to both the contraction and relaxation processes. Therefore, FT\(_{L}\) for Phase I and FT\(_{L}\) for Phase IV may be useful as pure inotropic and lusitropic indices, respectively.

The aim of curve-fitting is to obtain a time constant during each phase. We speculate that the time constant during the rising phase represents the required time to increase the intracellular Ca\(^{2+}\) concentration, bind Ca\(^{2+}\) to troponin C, and allow cross-bridge association. Conversely, the time constant during the falling phase represents the required time to decrease in the intracellular Ca\(^{2+}\) concentration, release Ca\(^{2+}\) from troponin C, and allow cross-bridge dissociation.

For example, application of the h-L function (Eq. 1) to Phase III in rabbit gives F\(_A\), F\(_L\), and F\(_B\) values of -7.8 mN/mm\(^2\), 52 ms, and, 16.4 mN/mm\(^2\), respectively. F\(_A\) is a negative value because F\(_B\) is larger than F\(_A\).

**Half-logistic (h-L) and mono-exponential (m-E) fits:** m-E functions have been used for modelling maturity indices for skeletal muscle mass and as indices of tension development rates in cardiac and skeletal muscle. Moreover, mathematical models based on m-E equations are typically used to evaluate relaxation tension; however, the m-E model does not match the acquired waveform precisely. In our previous study, the goodness of the h-L fit for the isometric relaxation tension curve from dF/dt\(_{\text{min}}\) to the resting tension, corresponding to Phase IV, was found to exceed the goodness of m-E fit under any length and extracellular Ca\(^{2+}\) conditions at any endpoint. Moreover, h-L functions have been used widely to fit the isovolumic LV pressure decrease from dP/dt\(_{\text{min}}\) in animal experiments, and h-L functions also provide a better fit to the isovolumic LV pressure decrease in clinical dilated cardiomyopathy and hypertrophic cardiomyopathy. Furthermore, the superiority of the h-L approach compared to the m-E approach holds for the isovolumic relaxation LV pressure curve at any LV volume and any temperature. In our previous study, the superiority of the h-L approach also held for the four phases of the isovolumic LV pressure curve at any LV volume. In the present study, we evaluated the four phases of the isometric tension curve in the myocardium and found that h-L functions provided superior representation of these phases compared to m-E functions (Figure 6). The h-L curve-fitting appears to minimize systemic bias and provides a more reliable assessment during each phase. In contrast, m-E curve-fitting may result in over- or underestimation of time constants under various physiological, pharmacological, and pathological conditions.

In our previous work, the average h-L r-values for Phase I of the isovolu-
mic LV pressure curves were between 0.9990 and 0.9992, and the average h-L r-values for Phases II, III, and IV were between 0.9996 and 0.9998; therefore, the average h-L r-value for Phase I was the lowest among the four phases. In the present study, the goodness of h-L fit for Phase I of the isometric tension curve was also the worst among the four phases (Figure 6); thus, the residuals during the period of rapidly rising tension were larger (Figure 3).

In our previous study, PT_L did not change with LV preloading in any of the four phases, whereas PE_E is overestimated with decreasing temperature and underestimated with decreasing temperature in Phase IV. In the present study, FT_L was shown to be a reliable index for estimation of changes in the four phases. Therefore, our results indicate that PT_L and FT_L are more accurate and useful inotropic and lusitropic indices than PE_E and FE_E, respectively.

Although the FA and F_0 values, and FB and F_∞ values seemed to be similar (Figure 5), the goodness of h-L fit for each phase was superior to the m-E fit (Figure 6); therefore, FA and FB, more reliably show the amplitude and asymptote, respectively, of the four phases of the isometric tension curves. In our previous study, the absolute PA and PB values for the isovolumic LV pressure curves during the four phases increased with an increase in LV volume. This finding indicates that PA and PB during isovolumic LV contraction and relaxation are dependent on LV preload. Therefore, FA and FB could be useful parameters to represent the amplitudes and asymptotes of the four phases under different preloads.

Both h-L and m-E functions characterize a convex or concave curve, because they were divided with a boundary at the inflection points of the rising and falling curves, ie, dF/dt_max and dF/dt_min, and the peak tension and the resting tension. Therefore, the slopes of both functions increase or decrease monophonically. If the four partial phases have inflection points in the rising and falling curves, the goodness of both h-L and m-E fits deteriorates over the inflection point.

Clinical application: Our contention is that myocardial isomeric partial tension and cardiac isovolumic partial LV pressure are best characterized by h-L curve-fitting. We consider that the h-L approach also applies for evaluation of the isovolumic contraction phase from closing of the mitral valve to opening of the aortic valve and the isovolumic relaxation phase from closing of the aortic valve to opening of the mitral valve in working hearts where the entire LV pressure curve is physiological, but not always isovolumic, during the cardiac cycle. Furthermore, our model might be useful to establish a link between nonphysiological and physiological situations and evaluate inotropism and lusitropism in vivo.

Limitations: Although the h-L curve-fits appear to be superior to the m-E curve-
fits, both approaches might be improved by considering horizontal components of the tension curve. Phases I and IV include a clear horizontal component. Phases II and III do not seem to include such a component. However, between Phases II and III, there is a point where dP/dt becomes zero, i.e., the isometric tension curve becomes horizontal. Artificial horizontal lines might be needed in these phases, which may further improve h-L curve-fitting compared to the m-E model.

In addition, we divided the isometric tension curve into the four phases and curve-fitted using the h-L and m-E models with just three indices and coefficients (the time constants, amplitude constants, and nonzero asymptotes), the fewest parameters that can be used to represent a nonlinear curve. The advantages and disadvantages of the models might be compared with respect to the evaluation of F_L and F_E for the different intervals during each phase. Both the residuals of the h-L and m-E fits did not seem to represent random error, as shown in Figure 3, but we intend to develop h-L and m-E functions with an additional parameter or a new function to fit the four phases more accurately. If we divide the whole sequence into multiple phases and perform a piece-wise curve-fit using different equations with more parameters, we should expect that this approach would yield a better approximation.

The h-L functions show the amplitudes and time courses accurately for the four phases of the isometric tension curves in normal papillary muscles at 100% L_max and extracellular Ca^{2+} 2 mM at 30°C. The F_A, F_L, and F_B values would alter with changes in muscular conditions or environment such as L_max, extracellular Ca^{2+} level, and temperature. Further examination of this concept under different physiological, pharmacological, and pathological situations is needed for interpretation of myocardial Ca^{2+} handling.

Finally, the study is limited to two animal species, and an investigation in other species is needed to understand species differences.

**Conclusion**

The h-L functions can be used to fit the two partial rising and two partial falling phases of isometric tension curves in the isolated rabbit RV and mouse LV papillary muscles more accurately than the m-E functions. This finding broadens the concept that the h-L function characterizes quantitatively the amplitudes and time courses of the four sequential phases. The F_L values for Phases I and IV could be accurate and useful indices of inotropism and lusitropism, and this approach might provide a way to detect subtle changes in cardiac myocardial performance in different animals and could yield significant insight into the contraction and relaxation mechanisms of normal and diseased hearts.
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