Postextrasystolic contractile decay always contains exponential and alternans components in canine heart

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We have reported that the postextrasystolic (PES) potentiation (PESP), after an extrasystole (ES) and a compensatory pause (CP), decays in alternans over several beats in canine hearts (3, 8, 10, 14, 15, 20, 21, 25). We confirmed that the PESP decay, including transient mechanical alternans after other types of arrhythmia, has generally been recognized as a sign of abnormal cardiac conditions such as ischemia, hypothermia, and so forth (7, 19, 29, 31). By contrast, we have found that existence and absence of a CP consistently determine the decay patterns of the PESP even in canine normoxic blood-perfused, normothermic hearts (3, 8, 10, 14, 15, 20, 21, 25).

We then found that the alternans PESP decay pattern could reasonably be described by the sum of an exponential decay component and a sinusoidal decay component (8, 10, 14, 15, 20, 21, 25). Therefore, the generality of the equation and the reliability of the alternative RF determination method by widely changing the ES coupling interval (ESI), CP, and heart rate in the canine excised, cross-circulated left ventricle. We found that all PESP decays consisted of the sum of an exponential and a sinusoidal decay component of variable magnitudes whether a CP existed or not. Their decay constants as well as the calculated RF were independent of the ESI and CP. This confirmed the utility of our alternative RF determination method regardless of the ESI, CP, and heart rate. Direct experimental evidence of Ca2+ dynamics supportive of this alternative method, however, remains to be obtained.

Cardiac contractility; extrasystole; mechanical potentiation; mechanical alternans; transient alternans
formed para-Hisian pacing by precisely programmed stimuli. We first confirmed that the PESP consistently decayed in transient alternans with a CP, regardless of RI or ESI. We also found that the PESP, even without a CP, had a small but obvious transient alternans component, which is contrary to the general belief (16, 17, 28). Thus all the transient alternans PESP proved to consist of an exponential and a sinusoidal decay component, although their magnitudes considerably varied depending on the RI, ESI, and CP. Beat constants $\tau_s$ and $\tau_a$ and RF values calculated from both PESPs with and without a CP were respectively comparable regardless of ESI but decreased as RI increased. However, their products, $\tau_s \cdot RI$ and $\tau_a \cdot RI$, were independent of RI. These results provided firm evidence supportive of the generality of the equation and the reliability of the alternative RF calculation method that we have recently developed (8, 10, 14, 15, 20, 21, 25).

METHODS

Surgical preparation. All the experiments were conducted in conformity with the “Guiding Principles for Research Involving Animals and Human Beings” endorsed by the American Physiological Society. The heart preparation we used has been described in detail elsewhere (4, 12, 13, 18, 20–27).

Briefly, two mongrel dogs were anesthetized with ketamine hydrochloride (50 mg im) and pentobarbital sodium (25 mg/kg iv) for each experiment. Arterial and venous cross-circulation tubes were cannulated into the common carotid arteries and the external jugular vein of the support dog. The coronary circulation was never interrupted during the surgery. A complete atrioventricular block was made by either formaldehyde injection or electrical ablation. Para-Hisian pacing was performed with a bipolar electrode.

A thin latex balloon (unstretched volume of 50 ml) fitted in the left ventricle (LV) was filled with water and connected to our custom-made volume servo pump (4, 12, 13, 18, 20–27). The servo pump enabled us to accurately measure and precisely control LV volume (LVV). LV pressure (LVP) was measured with a miniature pressure gauge (P-7, Konigsberg) placed within the apical end of the balloon. Temperature of the blood and the heart was kept constant at 37°C with heaters.

LV epicardial electrocardiogram (ECG) was recorded with a pair of screw-in electrodes. Monophasic action potential (MAP) was also recorded with an epicardial electrode pressed on the LV anterolateral surface in four of the seven hearts. LVP, LVV, ECG, and MAP signals were digitized at 2-ms intervals with an A/D converter (Lab-NB, National Instruments), displayed on a computer, and stored on a hard disk (Power Macintosh 7100/80; Apple Computers, Cupertino, CA).

Pacing protocol. Figure 1, A and B, shows the two different pacing patterns. The pacing pattern consisted of 10 or more stimuli at RIs of 400, 500, or 600 ms in a priming period. One extrasystolic stimulus at a variable coupling interval (ESI > 300 ms) was then inserted. The first PES stimulus at a PES beat interval (PESI 1) was given either with a CP (Fig. 1A) or without the CP (Fig. 1B); both were followed by the same RI for 10 or more PES beats. The three RIs correspond to heart rates of 150, 120, and 100 beats/min, respectively. Thus the pacing pattern in Fig. 1B differed from that in Fig. 1A only in the PESI 1, which was equal to the RI with no CP.

These stimuli were produced by a stimulator controlled with a Power Macintosh computer (Apple Japan, Tokyo, Japan) installed with LabVIEW 3.1 (National Instruments). The ESI was increased from 300–320 to 400–600 ms (=RI) at 10-ms intervals every 20 beats, which was enough for the PESP to disappear completely and for the peak isovolumic pressure to return to the preES level.

Data analyses. To evaluate the beat-to-beat changes in LV contractility during each PESP decay, we used the maximum LV elastance ($E_{\text{max}}$) as an index of ventricular contractility (22–24). $E_{\text{max}}$ was calculated for the first through sixth PES beats (PES 1–6) as the ratio of peak LVP to the corrected LVV (22–24). We obtained the corrected LVV by subtracting from LVV the unstressed $V_0$, which we identified as the LVV by which peak isovolumic LVP was zero (22–24). We normalized the $E_{\text{max}}$ values relative to the $E_{\text{max}}$ of the preceding regular beat (mean $E_{\text{max}}$ of the 3 stable beats). Because LVV was a fixed constant (9.5–20.5 ml) in each experiment, the changes in $E_{\text{max}}$ were proportional to those in isovolumic LVP at a fixed LVV. Mean ± SD of $E_{\text{max}}$ of regular beats was

![Figure 1](http://alpha.heart.physiology.org/)
8.54 ± 3.04 mmHg/ml, or 3.75 ± 0.77 mmHg · ml⁻¹ · 100 g LV wt⁻¹, at RI of 600 ms, indicating usual LV contractility.

We examined whether the normalized $E_{\text{max}}$ values ($nE_{\text{max}}$) during each PESP decay could be fitted by the following equation, which we had proposed and used in the recent retrospective studies (8, 10, 14, 20, 21, 25):

$$nE_{\text{max}} = a \cdot \exp\left[\frac{-i}{\tau_a}\right] + b \cdot \exp\left[\frac{-i}{\tau_b}\right] \cos(\pi(i-1)) + 1 \quad (1)$$

where $i$ is the ordinal number of the PES beat ($i = 1–6$), $a$ is the normalized magnitude (dimensionless) of the exponential term in the PES 1, and $b$ is the normalized magnitude (dimensionless) of the other exponential term multiplying the unity-amplitude cosine term in the PES 1. Denominators $\tau_a$ and $\tau_b$ are the beat constants of the first and second exponential terms, respectively, expressed in beat number but not in time unit (16). We calculated RF as $\exp(-1/\tau_1)$ (8, 10, 14, 20, 21, 25). This equation was developed by Morad and Goldman (16) and has been proven useful by other investigators (17, 28). Neither $a$, $b$, nor $\tau_a$ is related to the RF determination.

The first term is a monoexponential function that has conventionally been used for the monotonic PESP decay (16, 17, 28). This term has been related to the Ca²⁺ influx exceeding the Ca²⁺ influx during the PESP to recover Ca²⁺ homeostasis in regular beats (16, 17). The second term could be related to the delay of the Ca²⁺ releasability via the sarcoplasmic reticulum (SR) (1, 2). We suspect that this sinusoidal term is partly related to the potentiation and restitution mechanisms (15, 30, 33).

We used LabVIEW 3.1 for the curve fitting by the Levenberg-Marquart method on a Power Macintosh computer. The goodness of the curve fitting was evaluated by the correlation coefficient ($r$).

The duration of the MAP (action potential duration; APD) was obtained by determining the duration at 90% repolarization of the full amplitude of the MAP in all the regular beats, ES beats, and PES 1–6.

Statistics. The data were presented as means ± SD. Differences in $a$, $b$, $\tau_a$, and $\tau_b$ were analyzed by two-way repeated measures ANOVA. Significance of their multiple comparisons was tested by the Student-Newman-Keuls method on StatView 5.0. We considered $P < 0.05$ to indicate statistical significance.

RESULTS

Decay patterns. Figure 1A shows a representative transient alternans PESP decay following an ESI of 324 ms and a CP (476 ms; PES 1 = RI − ESI) at an RI of 400 ms. Peak LVP of the PES 1 was greater than that of the regular beat. However, the PES 2 was considerably weaker than not only the PES 1 but also the regular beat. The PES 3 was moderately stronger than not only the PES 2 but also the regular beat. PES 4–6 gradually returned to the regular beat level in small alternans. All other PESP cases following different RIs and ESIs with CPs in this heart as well as in all the other hearts decayed in transient alternans similar to those in Fig. 1A. This transient alternans PESP resembled the PESP decay pattern that we consistently observed in our retrospective studies (3, 8, 10, 14, 20, 21, 25).

Figure 1B shows a representative transient alternans PESP decay following the same ESI of 324 ms as in Fig. 1A but without the CP (400 ms; PESI 1 = RI) at the same RI of 400 ms. Whether the PES 1 had a CP or not was the single difference of the pacing stimuli between Fig. 1A and Fig. 1B. In Fig. 1B, all of PES 1–5 were stronger than the regular beat in contrast to those in Fig. 1A. However, Fig. 1B did not resemble the conventional monotonic PESP decay pattern (11, 16, 17, 28), in that the PES 2 was obviously smaller than the PES 3 in a similar manner as in Fig. 1A. Namely, Fig. 1B seemed to have a small alternans component. All the other PESP cases following different RIs and ESIs without CPs in this heart as well as in all the other hearts decayed in transient alternans similar to those in Fig. 1B. Thus, against the expectation obtained in our respective studies (3, 8, 10, 14, 20, 21, 25), the PESP decayed neither exponentially nor monotonically, even without CP.

Figure 2A is a three-dimensional (3-D) graph relating $nE_{\text{max}}$ of the PES 1-6 against ESIs with CP in one heart. The ESI was varied from 310 to 500 ms in 10-ms steps, and the RI was fixed at 500 ms. All the cases showed transient alternans PESP decays over the PES 1–6 regardless of ESI. The shorter the ESI, the greater the transient alternans.

Figure 2B is a side view of Fig. 2A from the left side as indicated by the eye and arrow. This clearly shows the $nE_{\text{max}}$−ESI relations of the PESP with CP. PES 1, 3, and 5 were stronger than the regular beat at any ESI above the RI (500 ms), indicating that PES 1, 3, and 5 were potentiated. However, PES 2 and 4 at any ESI above the RI were weaker than the regular beat, although the PES 2 was much weaker than the PES 4. The PES 6 returned to the regular beat level at any ESI. The same decay pattern was observed at any RI with a CP in all the hearts.

Figure 2C is a 3-D graph relating $nE_{\text{max}}$ of PES 1–6 against ESIs without CP in the same heart as in Fig. 2A. The ESI was varied from 310 to 500 ms in 10-ms steps, and the RI was also fixed at 500 ms. All the cases also showed the transient alternans PESP decay over PES 1–6. The shorter the ESI, the greater the transient alternans. The PES 1 without CP was slightly weaker than that with CP (Fig. 2A) at any ESI, but the PES 2 without CP was stronger than that with CP.

Figure 2D is a side view of Fig. 2C. This shows the $nE_{\text{max}}$−ESI relations of the PESP without CP. In contrast to Fig. 2B, PES 1–6 were stronger than the regular beat at any ESI. However, the PES 2 was always weaker than the PES 3, causing the alternans decay. The same decay pattern was observed at any RI without CP in all the hearts. We never observed the conventional exponential or monotonic PESP decay at any RIs and ESIs regardless of CP.

Curve fitting. Figure 3 shows a representative set of the best-fit Eq. 1 curves (solid line) together with their exponential decay component (dashed line) and exponential term (dotted line) of the sinusoidal decay component in one heart. RI was varied from 600 to 500 and 400 ms from left to right with CP (Fig. 3, A–C) and without CP (Fig. 3, D–F) at an ESI of 300 ms. The solid
Alternating curves best fit the data points with \( r > 0.999 \).

In Fig. 3, A–C, the \( y \)-intercept of the first exponential term (i.e., amplitude constant \( a \) in Eq. 1) was always much smaller than the \( y \)-intercept of the second exponential term (i.e., amplitude constant \( b \) in Eq. 1). However, \( a \) and \( b \) reversed their relative magnitudes in Fig. 3, D–F. Thus the PESP decay always had an exponential decay component (first term of Eq. 1) and a sinusoidal decay component (second term of Eq. 1) regardless of CP in this heart. The same results were obtained at any RIs and ESIs regardless of CP in all the hearts.

Figure 4 plots \( a \), \( b \), \( \tau_e \), and \( \tau_s \) as a function of ESI at RIs of 600, 500, and 400 ms, both with (Fig. 4, A–C) and without CP (Fig. 4, D–F) in one heart. In Fig. 4, A–C, amplitude constant \( a \) was much smaller than \( b \) at any RIs and ESIs. In Fig. 4, D–F, amplitude constant \( a \) was comparable with \( b \) at any RIs and ESIs. Both \( a \) and \( b \) decreased as the ESI increased in all the panels. Mean \( a \)-to-\( b \) ratio over the entire range of ESI without CP was significantly greater (\( P < 0.01 \)) than that with CP at any RI, as summarized in Table 1. In other words, the amplitude of the exponential decay component was significantly greater in the PESP decays without CP than with CP.

Figure 4 also shows that \( \tau_e \) and \( \tau_s \) were largely independent of ESI at any RI, regardless of CP. Percent coefficients of variation (CVs; \( CV = SD/mean \)) of \( \tau_e \) and \( \tau_s \) were 4.5 and 7.2 in Fig. 4A, 3.7 and 2.8 in Fig. 4B, 7.9 and 3.1 in Fig. 4C, 4.6 and 6.9 in Fig. 4D, 3.7 and 7.3 in Fig. 4E, and 3.7 and 1.4 in Fig. 4F. These CV values were practically small, indicating the reasonable independence of \( \tau_e \) and \( \tau_s \) from ESI. Plots of \( \tau_e \) are lacking above an intermediate ESI at which the convergence of the curve fitting became poor. The poor fitting occurred when parameter \( a \) decreased below a certain level (\( \leq 0.094 \pm 0.055 \) with CP and \( \leq 0.113 \pm 0.058 \) without CP) at longer ESIs. This poor fitting seemed likely attributable to the decreasing signal-to-noise ratio of the decreasing \( nE_{\text{max}} \) values of PES 1–6 with increasing ESI, as discussed elsewhere (8). At the longer ESIs, where \( \tau_e \) was not obtainable, the first exponential term with \( a \) and \( \tau_e \) was neglected, and the second term with \( b \) and \( \tau_s \) was fit to the data (8, 10, 14, 15, 20, 21, 25). For this reason, a reliable \( \tau_s \) value continued to be obtained for increasing ESI, even after a reliable \( \tau_e \) was no longer obtained, as shown in Fig. 4.
Within the ESI ranges with reliable \( \tau_e \) and \( \tau_s \), \( \tau_s \) was always two to three times greater than \( \tau_e \). Similar results were obtained in all the other hearts.

Table 2 lists mean ± SD values of \( \tau_e \) and \( \tau_s \) in the number of beats (i.e., beat constants) as well as their products with RI in seconds (i.e., time constants) at all ESIs in all the hearts. Both \( \tau_e \) and \( \tau_s \) significantly decreased with increasing RI, regardless of CP. However, no difference existed in either \( \tau_e \) or \( \tau_s \) between those with and without CP. Mean ± SD values of CVs of \( \tau_e \) and \( \tau_s \) are also listed. Their mean values were only 10 ± 6% for \( \tau_e \) and 8 ± 6% for \( \tau_s \) with CP and 10 ± 3% for \( \tau_e \) and 7 ± 3% for \( \tau_s \) without CP, indicating the reasonable independence of \( \tau_e \) and \( \tau_s \) from ESI regardless of CP.

Table 2 also lists \( \tau_e \cdot \text{RI} \) and \( \tau_s \cdot \text{RI} \). In contrast to \( \tau_e \) and \( \tau_s \), \( \tau_e \cdot \text{RI} \) and \( \tau_s \cdot \text{RI} \) were not significantly changed with RI regardless of CP. Neither \( \tau_e \) nor \( \tau_s \) (and neither \( \tau_e \cdot \text{RI} \) nor \( \tau_s \cdot \text{RI} \) ) was significantly different between those with and without CP.

Table 2 lists RF \( =\exp(-1/\tau_s) \). There was no significant difference in RF, with or without CP, at any RI. RF had a greater SD with CP than without CP at any RI. RF significantly decreased with increasing RI without CP, but similar decreases in RF with increasing RI were not significant with CP.

MAP duration. No MAP tracing showed electrical alternans during the PESP at any RIs and ESIs, regardless of CP in any of the hearts. Figure 5 shows two representative examples (mean ± SD) of ADP at 90% duration (APD90) of the MAPs over the PESPs with (Fig. 5A) and without (Fig. 5B) CP in one heart. Figure 5A averaged eight cases, with an RI of 600 ms and a varied ESI between 300 and 500 ms with CP. Figure 5B averaged 21 cases, with an RI of 600 ms and a varied ESI between 300 and 500 ms without CP. APD90 of only the ES was significantly shorter than the APD90 values of the three preceding regular beats (R 1–3) and PES 1–6. The SD of the ES APD90 was greater than the SDs of the PES 1–6, because the APD90 of ES de-
creased as ESI decreased ($r = 0.850$ in Fig. 5A and $0.950$ in Fig. 5B; both $P < 0.001$). Similar results were obtained in all the other RI (500 and 400 ms) cases in this heart as well as in the other hearts.

**DISCUSSION**

The present study revealed for the first time that the PESP, regardless of whether the PESI 1 has a CP, always decayed in transient alternans consisting of an exponential decay component and an exponentially decaying sinusoidal component. This observation was made in canine blood-perfused normally functioning hearts under physiological perfusion conditions. This heart preparation is the same type that we have been using consistently over many years with expertise (4, 12, 13, 17, 20, 22, 23, 26). The present finding evidently supports the utility of our recently developed method of RF (internal Ca$^{2+}$-RF) determination (3, 8, 10, 14, 15, 20, 21, 25), as discussed below.

Both exponential and sinusoidal components decayed over $PES 1–6$ at heart rates of 100, 120, and 150 beats/min. This consistent observation of the alternans PESP decay seems to refute the conventional belief that the PESP normally decays exponentially but in alternans only under abnormal contractile conditions (e.g., ischemia, hypothermia) (7, 11, 16, 31).

Against both the conventional, generally held belief (11, 16, 27, 31) and our expectation from our previous studies (3, 8, 10, 14, 15, 20, 21, 25), we did not observe a representative case of exponential or monotonic PESP decay in the present study at all. This intriguing result could be related to the obvious difference in the PESP without CP between the present controlled cases (Figs. 1–3) and the previous spontaneous cases. In other words, the ES always originated from the same para-Hisian pacing site as the constant pacing in the controlled PESPs in the present study. In contrast, the ES not followed by a CP was exclusively of supraventricular origin in the spontaneous PESPs under no constant atrial pacing in our previous studies (3, 8, 10, 14, 15, 20, 21, 25). However, we cannot yet conclude that this pacing difference has caused the difference of the PESP decay pattern between the present controlled PESP experiment and our previous spontaneous PESP experiments.

The exponential PESP decay has been accounted for by myocardial Ca$^{2+}$-handling models consisting of the

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**Table 1. Comparison of amplitude ratio a/b of PESP with and without a CP**

<table>
<thead>
<tr>
<th>RI, ms</th>
<th>With CP (dimensionless)</th>
<th>Without CP (dimensionless)</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>0.14 ± 0.18</td>
<td>2.55 ± 2.06*</td>
</tr>
<tr>
<td>500</td>
<td>0.11 ± 0.07</td>
<td>1.68 ± 1.13*</td>
</tr>
<tr>
<td>400</td>
<td>0.11 ± 0.05</td>
<td>1.87 ± 2.11*</td>
</tr>
</tbody>
</table>

Values are means ± SD, obtained from mean $a/b$ values from all different extrasystolic coupling intervals (ESIs) in 7 hearts. ESI was varied from 300 to regular beat interval (RI) at intervals of 10 ms. $a/b$, amplitude ratio of first and second exponential terms in Eq. 1 (see METHODS); here, $a$ is amplitude of first monoexponential term, and $b$ is amplitude of exponential term multiplying unity-amplitude sinusoidal term. CP, compensatory pause in first postextrasystolic beat interval. *Significant difference ($P < 0.01$) from with-CP values.
internal Ca\(^{2+}\) uptake store, the Ca\(^{2+}\) release store, and the Ca\(^{2+}\) moving path within the SR plus the transsarcolemmal Ca\(^{2+}\) influx and efflux paths (16, 17, 28, 32). In addition, there is proportionality, although not linear, between sarcoplasmic-bound Ca\(^{2+}\) and peak force (5, 9). On these bases, the exponential nature of the conventional monotonic PESP decay has been accounted for by a gradual beat-by-beat recovery of the Ca\(^{2+}\) influx-efflux balance (or Ca\(^{2+}\) homeostasis) from the once augmented sarcoplasmic Ca\(^{2+}\) before the PES I (16, 17, 32).

This recovery of the transient Ca\(^{2+}\) influx-efflux imbalance has been modeled by Morad and Goldman (16). This model is the basis of the concept of myocardial internal Ca\(^{2+}\) RF, to be obtained by \(\exp(-1/\text{beat constant})\) (16). We have shown the utility of this Ca\(^{2+}\)-handling model in combination with our mechanoenergetic (\(E_{\text{max}}\)-PVA-\(\dot{V}O_2\)) framework. The present findings of the dependence of \(\tau_e\) on RI and the independence of \(\tau_e\) and \(\tau_s\) from RI indicate that the restoration of the Ca\(^{2+}\) homeostasis is a function of time during PESP rather than the beat number of PES I–6.

The absence of electrical alternans seems to negate the possibility that the alternans decay component of the PESP is primarily derived from alternating Ca\(^{2+}\) influx (31). It rather supports the notion that the alternans component is derived from the Ca\(^{2+}\)-handling mechanism that is inherent in the SR. In fact, Adler et al. (1, 2) proposed Ca\(^{2+}\)-handling models that could simulate transient mechanical alternans without assuming alternating Ca\(^{2+}\) influx. Our recent simulation has shown that the transient alternans component of the PESP could be partly derived from the postextrasystolic potentiated restitution (15). Because the restitution and potentiation primarily manifest the beat interval-dependent Ca\(^{2+}\)-handing properties of the SR (33), we would consider that the exponentially decaying cosine term in Eq. 1 also primarily manifests the SR characteristics.

In our retrospective studies (3, 8, 10, 14, 15, 20, 21, 25), we have found that \(\tau_e\) and hence RF changed sensitively with cardiac contractile conditions. Therefore, the present study reinforces our integrative approach to the study of myocardial Ca\(^{2+}\) handling at the beating whole heart level. Although \(\tau_s\) seems to characterize the alternans decay and hence the SR Ca\(^{2+}\)-handling properties, we have found that \(\tau_s\) was insensitive to the cardiac contractile conditions (3, 8, 10, 14, 15, 20, 21, 25). However, our unpublished studies show that \(\tau_s\) sensitively changes with myocardial temperature and 2,3-butanedione monoxime treatment. Therefore, we believe that simultaneous determination of both \(\tau_e\) and \(\tau_s\) would help elucidate myocardial total Ca\(^{2+}\) handling in a beating heart.

### Table 2. Comparison of beat constants, CVs, time constants, and RFs of PESP decays with and without CP

<table>
<thead>
<tr>
<th></th>
<th>600-ms RI</th>
<th>500-ms RI</th>
<th>400-ms RI</th>
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<tbody>
<tr>
<td></td>
<td>With CP</td>
<td>Without CP</td>
<td>With CP</td>
</tr>
<tr>
<td>(\tau_e), beats</td>
<td>1.37 ± 0.45*</td>
<td>1.25 ± 0.19</td>
<td>1.46 ± 0.40*</td>
</tr>
<tr>
<td>CV, %</td>
<td>13.0 ± 6.7</td>
<td>7.0 ± 1.6</td>
<td>8.7 ± 4.0</td>
</tr>
<tr>
<td>(\tau_e), beats</td>
<td>0.64 ± 0.07†</td>
<td>0.76 ± 0.11†</td>
<td>0.85 ± 0.09†</td>
</tr>
<tr>
<td>CV, %</td>
<td>11.7 ± 8.2</td>
<td>8.3 ± 0.3</td>
<td>6.7 ± 2.9</td>
</tr>
<tr>
<td>(\tau_s) RI, ms</td>
<td>819 ± 269</td>
<td>751 ± 115</td>
<td>730 ± 199</td>
</tr>
<tr>
<td>(\tau_s) RI, ms</td>
<td>383 ± 44*</td>
<td>457 ± 67</td>
<td>424 ± 43</td>
</tr>
<tr>
<td>RF</td>
<td>0.455 ± 0.173</td>
<td>0.446 ± 0.053†</td>
<td>0.487 ± 0.122</td>
</tr>
</tbody>
</table>

Values are means ± SD, obtained from mean values from all different ESIs in 7 hearts. \(\tau_e\), beat constant of monoexponential term of Eq. 1 (see METHODS); \(\tau_s\), beat constant of exponential term multiplying unity-amplitude sinusoidal term of Eq. 1; \(\tau_s\) RI, time constant of exponential term multiplying sinusoidal term; RF, internal Ca\(^{2+}\) recirculation fraction that was calculated from \(\tau_e\) as RF = \(\exp(-1/\tau_e)\). *Significant difference (\(P < 0.05\)) from RI = 400 ms. †Significant difference (\(P < 0.01\)) from RI = 400 ms.
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There are some limitations in this study. Eq. 1 is a practically reasonable, phenomenologically integrative equation to describe the PESP but not a physiologically ideal, constitutive one. Direct experimental evidence of Ca\(^{2+}\) dynamics supportive of Eq. 1 remains to be obtained. Nevertheless, both the exponential term and the product of the exponential and cosine terms in Eq. 1 are popular in analogy to describe any decay at a constant rate and any sinusoidal oscillation decaying at another constant rate, respectively. This analogy is theoretically allowable, although the PESP data are discrete but not continuous. We do not intend to imply in Eq. 1 that myocardial Ca\(^{2+}\) handling contains any continuously exponential and sinusoidal mechanisms. These terms only characterize myocardial Ca\(^{2+}\)-handling mechanisms related to the peak isovolumic pressure development at a given ventricular volume, i.e., contractility or \(E_{\text{max}}\). Taking advantage of this, we have succeeded in characterizing total Ca\(^{2+}\) handling in our canine heart model (8, 10, 14, 15, 20, 21, 25).

In conclusion, we have discovered that in our model, the PESP always decays in transient alternans consisting of an exponential decay component and an exponentially decaying sinusoidal component, regardless of the extrasystolic and postESIs and heart rate. These novel findings validate the reliability of our method of RF determination recently developed (20). This validation reinforces the utility of our combination of RF with cardiac mechnoenergetics in the \(E_{\text{max}}\)-PVA-V\(\text{O}_2\) framework for better understanding of myocardial total Ca\(^{2+}\) handling in a beating whole heart (3, 8, 10, 14, 15, 21, 25).

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