Short Communication

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Postextrasystolic Contractility Normally Decays in Alternans in Canine *In Situ* Heart

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Abstract: We have reported that the postextrasystolic (PES) potentiation of left ventricular (LV) contractility usually decays in alternans at heart rates above 80–100 beats/min in the canine excised, cross-circulated heart. We examined whether the PES contractility would also decay in alternans even in the canine *in situ* heart presumably more physiological than the excised heart. In anesthetized, ventilated, and open-chest mongrel dogs, we measured LV pressure and volume with a micromanometer and a conductance catheter cannulated into the LV and obtained LV end-systolic maximum elastance (E_{max}) as the reasonably load-independent contractility index. We inserted an extrasystole followed by a compensatory pause into steady-state regular beats at heart rates above 90 beats/min and analyzed the PES decay pattern of E_{max}. We found that E_{max} potentiated in the first PES beat decayed in alternans within 5–6 PES beats. This indicates that PES contractility also decays in alternans in the normal canine in situ heart. [The Japanese Journal of Physiology 53: 313–318, 2003]

Key words: arrhythmia, compensatory pause, pressure–volume loop, E_{max}, Ca recirculation.

We have reported that left ventricular (LV) contractility in terms of end-systolic maximum elastance (E_{max}, end-systolic pressure/volume ratio) always decays in alternans within 5–6 postextrasystolic (PES) beats in the canine excised, cross-circulated heart [1, 2]. We have confirmed that this holds consistently under widely changed end-diastolic volume, heart rate above 80–100 beats/min, and temperature (33–38°C) as well as under intracoronary infusions of Ca^{2+}, catecholamines, pentobarbital, and ryanodine, and under global postischemic stunning in the canine excised, cross-circulated heart [1–10].

We therefore doubted the general view that PES contractility potentiation would decay exponentially or monotonically in normal hearts under physiological conditions [11–13] but would decay in alternans in abnormal hearts or under unphysiological conditions [14–17]. However, whether the PES contractility usually decays in alternans or exponentially in the canine *in situ* heart, which is more physiological than the excised, cross-circulated one, has not yet been documented. This question should be solved because the alternans and exponential decay patterns of the PES contractility require different methods to obtain the intramyocardial Ca^{2+} recirculation fraction for assessing myocardial Ca^{2+} handling [3, 11, 18].

Therefore in the present study, we examined whether the PES contractility decayed in alternans even in the normal open-chest canine in situ heart. We measured LV pressure (P) and volume (V) to calculate LV end-systolic maximum elastance (E_{max}) as a reasonably load-independent contractility index [1–3, 8, 9, 19]. The resultant E_{max} data show evidently that the PES E_{max} consistently decayed in alternans even in the normal canine LV *in situ*.

Methods

All procedures in this study conformed to the animal care guidelines of our institutions, the Japanese Physiological Society, and the US National Institute of

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Health. We anesthetized 7 mongrel dogs (7.8±1.4 kg, mean±SD; range: 5.9–9.5 kg) with pentobarbital sodium (25 mg/kg, I.V.) after premedication with ketamine hydrochloride (50 mg/kg, I.M.) and thoracotomized them midsternally under artificial ventilation. We cannulated a 3 F catheter-tip micromanometer (Aisin Seiki, Kariya, Japan) and a 7 F eight-electrode conductance catheter (Webster Laboratories, Baldwin Park, CA, USA) via apical stabs into the LV.

The method for measuring LV V by means of the conductance catheter has been described in detail elsewhere [20, 21]. Briefly, the method is based on measuring the electrical conductance of each of the five consecutive segments of blood in the LV cavity. To measure LV conductance volume, we used a custom-made conditioner-processor (SI Medicotech Co., Japan). Total LV conductance volume was calculated from the five conductances after calibrating the conductivity of blood (α) that was measured in the sampling cuvette. A parallel conductance of the LV, which is mainly due to the current through the LV wall but not to intra-LV blood volume, was determined by the standard method using an intraatrial saline infusion [20, 21]. The equivalent volume to the parallel conductance (V_p) was subtracted from total LV conductance volume to obtain LV V which represents total intra-LV blood volume. LV unstressed volume (V_o) was then determined by extrapolating the end-systolic P–V relationship drawn through the end-systolic P–V points of multiple P–V loops obtained during a transient aortic occlusion.

We paced the left atrium by electrical stimuli to avoid any spontaneous fluctuation of heart rate. The pacing rate was set at 163±36 beats/min (range: 90–200 beats/min) slightly above the spontaneous sinus rates in the respective hearts. These pacing rates were higher on average than the sinus rates (60–120 beats/min) in conscious dogs, but still much lower than 250–300 beats/min that could cause sustained alternans in the normal excised, cross-circulated canine hearts [22]. The anesthesia per se did not suppress canine cardiac conditions to the extent that the sustained PES alternans could occur even at the present pacing rate [7, 23].

We produced an extrasystole by left atrial stimulation at an arbitrary timing between two consecutive steady-state regular beats. Each extrasystole produced a compensatory pause and the PES beats at the pacing rate. We repeated this procedure at 1–2 min intervals to obtain two or three extrasystolic cases in each heart. The reason for only 2–3 cases per heart was that this extrasystole protocol was inserted within a relatively short waiting time before the main protocol for other studies by using the same LV micromanometer and conductance catheter.

All LV P and V signals were sampled at 3 ms intervals and digitally stored on a computer. We calculated LV time-varying elastance $E(t)$ as $P(t)/[V(t)-V_o]$ and obtained its end-systolic maximum value (E_{max}) [19]. E_{max} is accepted as the reasonably load-independent index of LV contractility among the available indexes [1–3, 8, 9, 19]. We analyzed E_{max} of the regular beat before extrasystole, the extrasystole, and the first through sixth PES beats (PES1–6). We also obtained dP/dt of these beats by differentiating LV $P(t)$, using a 3-point moving average of $P(t)$ data to eliminate high-frequency noises.

To analyze the alternans magnitude and decay pattern of E_{max} during PES beats, we normalized the raw E_{max} values relative to their respective regular-beat values in the 18 individual cases of the seven hearts. We first analyzed the differences of the normalized E_{max} values at the respective beats from unity by paired t-test at a significance level of $p=0.05$ [24]. We then analyzed the normalized E_{max} values by the repeated measures analysis of variance (ANOVA) and examined the significance of their variations by F test with a significance level of $p=0.05$ [24]. We finally performed multiple comparison of the beat-to-beat changes in the normalized E_{max} values by Bonferroni t-test with a corrected significance level of $p=0.0018=0.05/28$ for a total of 28 beat-to-beat comparisons [24]. Peak LV P and max $\pm dP/dt$ values were also analyzed in the same way. We used StatView 5.0 in these analyses.

Results

On average in the seven hearts, the regular beat interval maintained by left atrial pacing was 330±37 ms (range: 298–667 ms); the extrasystolic beat interval was 252±27 (203–392) ms; the first PES beat interval was 408±78 (331–954) ms with a compensatory pause, which was 78±45 (31–151) ms longer than the regular beat interval. Stroke volume of the regular beat was 3.5±1.5 (2.1–6.9) ml; cardiac output 551±137 (448–725) ml/min; V_p 13.3±4.1 (9.1–17.2) ml; V_o 5.0±2.1 (0.6–10.5) ml. Peak LV P of the regular beats was 95±19 (81–133) mmHg; their E_{max} was 19.9±6.2 (12.2–30.3) mmHg/ml; their max dP/dt was 1974±391 (1,450–2,520) mmHg/s.

Figure 1 shows a representative example of the E_{max} alternans decay during the PES beats in one LV. Figure 1A shows a representative P–V loops of the last regular beat (R), the extrasystole (ES), and the first through sixth PES beats (PES1–6). The P–V loop of ES was the shortest and narrowest. The P–V loop of

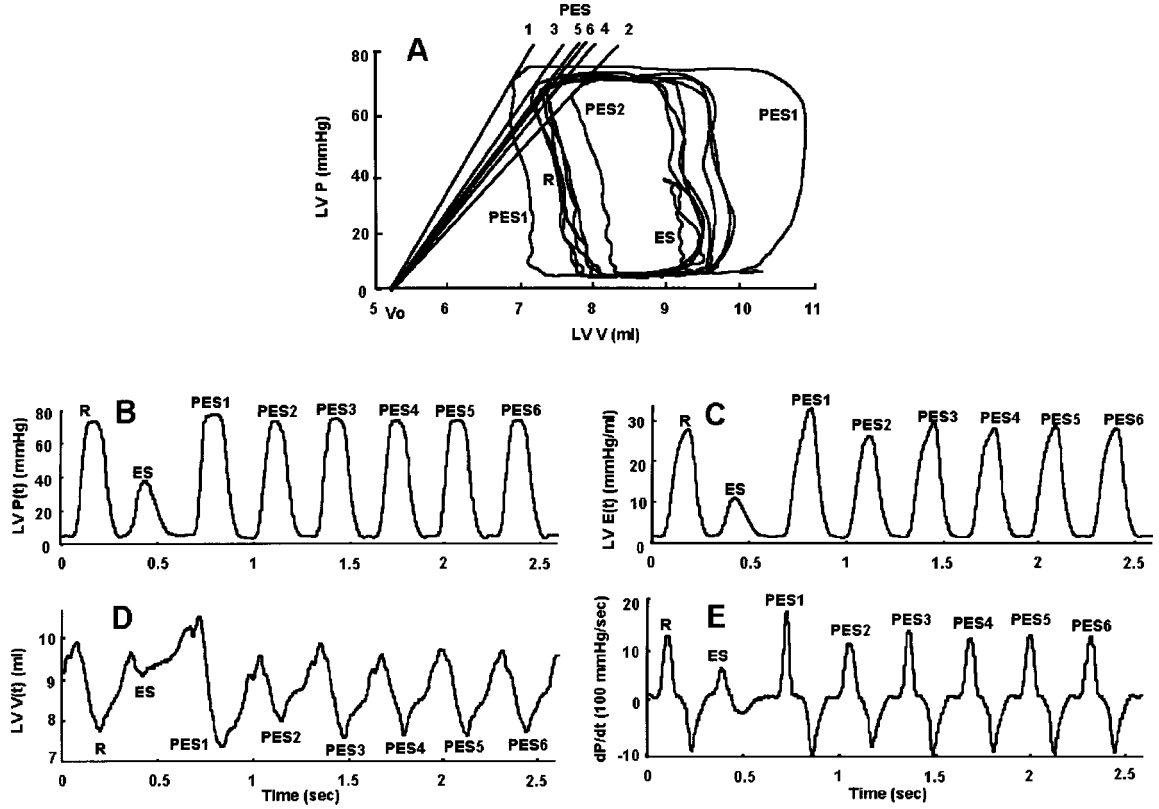

Fig. 1. Alternans decay of postexstrasystolically potentiated contractility (E_{max}) of the *in situ* ejecting left ventricle (LV) of an anesthetized open-chest dog. A shows a representative LV pressure–volume (P–V) loops of the last regular beat (R), the extrasystole (ES), and the first through sixth postextrasystolic beats (PES1–6). LV V, LV volume after subtraction of parallel conductance; V_o, predetermined LV volume at which peak LV P was zero. **B**, **C**, **D**, and **E** show the LV $P(t)$, $E(t)$ whose peak is a contractility index E_{max}, $V(t)$, and dP/dt, i.e., time-derivative of $P(t)$, curves, respectively, of the same beats as shown in A. $E(t)=P(t)/[V(t)-V_o]$.

PES1 was the tallest and widest. The P–V loop of PES2 however became slightly narrower than that of R. The P–V loop of PES3 was again wider than that of PES2 and R. The P–V loops of PES4–6 gradually converged to that of R. As a whole, the end-systolic points of the LV P–V loops transiently alternated horizontally instead of vertically within PES1–6 beats.

Figure 1B–E show the LV $P(t)$, $E(t)$, $V(t)$, and dP/dt curves, respectively, of the same beats shown in Fig. 1A. Peak LV P values of PES1–3 and the widths around the peaks of these LV $P(t)$ curves slightly alternated (Fig. 1B). The E_{max} as the peak of the LV $E(t)$ curve obviously decayed in alternans over PES1–4 (Fig. 1C). The end-diastolic and end-systolic LV V values as well as stroke volume also alternated over PES1–4 (Fig. 1D). Simultaneously, max $\pm$dP/dt also decayed in alternans over PES1–4 (Fig. 1E). All LV $P(t)$, $E(t)$, $V(t)$, and dP/dt curves of PES5–6 virtually returned to those of R.

We observed similar alternans decays of E_{max} in all 18 cases of the 7 hearts, but not exponential or monotonic decay of the PES E_{max}. As for the PES changes in peak LV P, 5 hearts showed similar but weaker alternans decays and two hearts showed monotonic decays. End-systolic and end-diastolic LV V values showed either obvious or weak alternans decays. Max $+$dP/dt showed more or less alternans decays, but max $-$dP/dt showed little or no alternans decays.

Figure 2 shows the relative changes in E_{max} and peak LV P of the last regular beat (R), the extrasystole (ES), and the first through sixth PES beats (PES1–6) normalized in regard to the respective R data in the seven hearts. Figure 2A and C show their changes in the individual cases. E_{max} alternans was always obvious over PES1–4. However, peak LV P alternans was not. In 4 cases in 2 hearts, peak LV P of PES1 neither returned to nor exceeded the R level and gradually recovered over PES2–6.

Figure 2B and D show means$\pm$SD of E_{max} and peak LV P at the respective beats shown in Fig. 2A and C. On average, both E_{max} and peak LV P decreased obviously in ES and increased in PES1 as expected. These ES and PES1 values of both E_{max} and peak LV P were significantly different from their R levels.

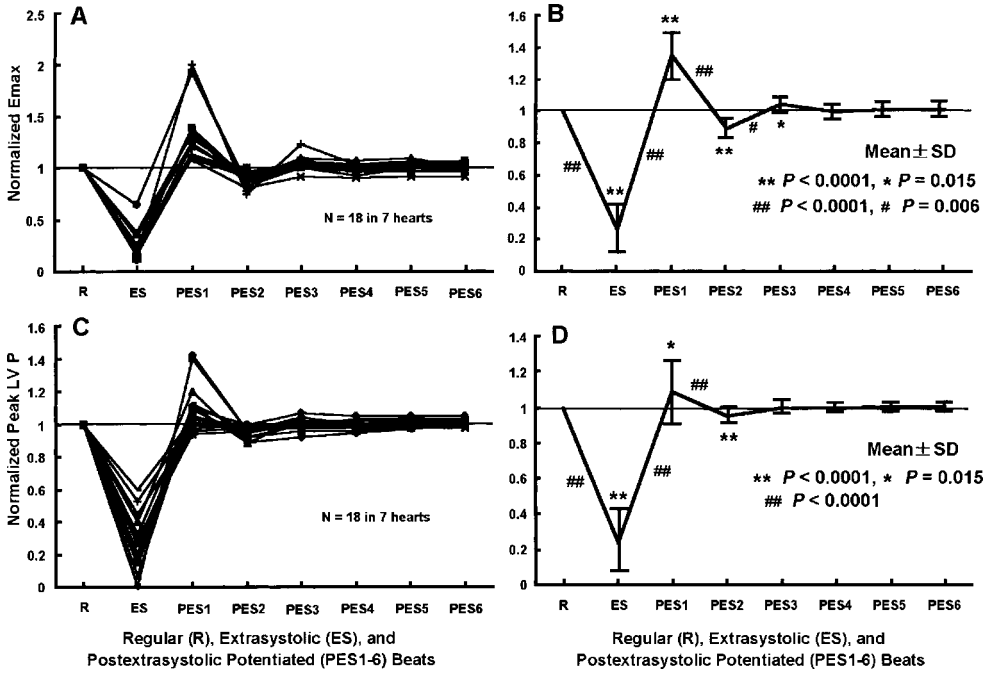

Fig. 2. Graphs showing plots of individual data of normalized E_{max} and peak LV P in a total of 18 cases of seven hearts (A and C) and their mean±SD (B and D) of the last regular beat (R), the extrasystole (ES), and the first through sixth postextrasystolic potentiated beats (PES1–6) relative to that of the regular beat (R). In B and D, the asterisks indicate significant differences of the data from the regular beat level (unity line) by paired *t*-test (* $p<0.015$, ** $p<0.0001$). The sharp signs ($^{\#}$) indicate the significant differences of the data between two consecutive beats by ANOVA and Bonferroni test ($p<0.0018$ after Bonferroni correction; $^{\#}p<0.006$, $^{\#\#}p<0.0001$). No marks indicate insignificant differences with $p>0.05$.

In Fig. 2B, after the E_{max} potentiation in PES1, E_{max} decreased in PES2 and increased again in PES3 across the R level. These E_{max} values were significantly different from the R level by paired *t*-test. ANOVA and Bonferroni test showed that the decrease in E_{max} in PES2 and its increase in PES3 were significant. E_{max} virtually returned to the R level in PES4. Thus, E_{max} decayed in alternans within PES1–4.

In Fig. 2D, after the potentiation on average of peak LV P in PES1, peak LV P decreased in PES2 below the R level. Peak LV P value of PES2 was significantly different from the R level by paired *t*-test. ANOVA and Bonferroni test showed that the decrease in peak LV P in PES2 was significant. Peak LV P virtually returned to the R level in PES3. Thus peak LV P decayed in alternans within PES1–3.

Although not shown, max $+dP/dt$ on average showed statistically significant alternans within PES1–3 in a manner similar to peak LV P. However, neither end-systolic nor end-diastolic LV V showed significant alternans decay on average.

Discussion

The present results show evidently that the LV PES contractility in terms of Emax decays consistently in alternans even in the normal open-chest canine *in situ* heart in the same way as in the excised, cross-circulated canine heart. This contradicts the general view that the PES contractility alternans represents more or less abnormal hearts or unphysiological cardiac conditions [14–16].

We produced the extrasystole under the regular atrial pacing so that the first extrasystole was always followed by a compensatory pause in the present study. We chose this type of extrasystole because both the contractile potentiation in the first PES beat and the magnitudes of the contractility alternans components in PES1–6 were greater with the compensatory pause than without it [9]. However, we doubt that the compensatory pause eliminated the exponential decay of postextrasystolic potentiation because the exponential contractility decay did not occur even without a compensatory pause in the excised canine heart [9]. The present results combined with these previous results indicate the generality of the alternans decay of PES contractility in the canine heart under not only variously unphysiological but also reasonably physiological conditions.

The alternans E_{max} decay always disappeared in PES4–6 and never continued as sustained alternans in our present study as well as in our previous studies [1–6, 8–10, 25–27]. The present pacing rates were

much lower than the pacing rates (250–300 beats/min) that caused sustained alternans in excised, cross-circulated canine hearts [22]. Besides, we have already found that the PES contractility alternans decay consistently exists within the heart rate range of 100–150 beats/min produced by para-Hisian pacing after atrioventricular block in the excised, cross-circulated normal canine hearts under physiological conditions [9].

Compared to the obvious E_{max} alternans during PES beats, peak LV P alternated much less in the ejecting LV in contrast to the isovolumic LV where LV P is proportional to E_{max} at a fixed LV volume. This might be one reason that the LV contractility alternans decay during PES beats has been overlooked in normal ejecting hearts under physiological conditions. From the present results, we speculate that the PES contractility alternans decay would exist more frequently even in normal hearts than generally considered. This possibility warrants further investigation of the PES contractility alternans decay not only in canine hearts, but also in human ones.

Although max $+dP/dt$ alternated in a similar manner to peak LV P, we are less interested in the changes in peak LV P and max $+dP/dt$. These variables are load-dependent and their changes cannot directly reflect the changes in LV contractility when LV preload or afterload, or both, change in ejecting hearts in situ as in the present study.

When PES contractility decays exponentially, we can calculate the intramyocardial Ca^{2+} recirculation fraction (RF) by Morad and Goldman's method [11]. A greater RF indicates a more economical Ca^{2+} handling because of the twice-greater Ca^{2+} : ATP stoichiometry of the sarcoplasmic reticulum Ca^{2+} pump than the sarcolemmal Na^+/Ca^{2+} exchanger coupled with the Na^+/K^+ pump [3, 8, 11]. By combining RF with myocardial O_2 consumption ($\dot{V}O_2$) for excitation-contraction coupling, one can further assess total Ca^{2+} handling [3, 8]. However, if one dares to apply this method to the PES alternans decay, RF will be seriously underestimated even if the decay appears almost exponential [28].

We have already modified Morad and Goldman's method for the PES alternans decay. Our method is to extract the exponential component by peeling off the oscillatory decay component from the alternans E_{max} decay during PES beats [3, 8]. We have so far successfully obtained RF from the alternans E_{max} decay and assessed the total Ca^{2+} handling in canine excised, cross-circulated beating hearts [3–6, 8, 10, 26]. The present study suggests the feasibility of this Ca^{2+} handling analysis method to canine *in situ* hearts.

One may concern the relatively high heart rate, low peak LV P, high E_{max}, low stroke volume, and their large variations in steady-state regular beats among the hearts in the present study. We would suspect that these were due to the decreased cardiac output after thoracotomy under anesthesia and the resultant enhancement of the sympathetic tone via the baroreflex. These cardiac variables suggest that the *in situ* hearts we studied were not fully physiological, though much more physiological than the excised, cross-circulated heart preparation [1–10]. However, we needed the normalized E_{max} changes relative to the regular beat level in the present study. Therefore, the present findings (Fig. 2) were not affected by the relatively large variations of cardiac variables.

We conclude that the alternans contractility decay consistently occurs during PES beats even in the normal open-chest canine *in situ* ejecting heart and does not necessarily indicate abnormal cardiac conditions. A similar study remains to be done to test the full generality of the PES alternans decay of LV contractility in the entirely normal, closed-chest canine *in situ* hearts under not only anesthetic but also conscious conditions.

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