Alternans Decay of Postextrasystolic Potentiation in Human Left Ventricle

Masaki TANABE, Katsuya ONISHI*, Kaoru DOHI, Masaaki ITO,
Takeshi NAKANO, and Hiroyuki SUGA†

First Department of Internal Medicine and * Department of Laboratory Medicine,
Mie University School of Medicine, Tsu, 514–8507 Japan; and

† National Cardiovascular Center Research Institute, Suita, 565–8565 Osaka, Japan

Abstract: An organ-level assessment of the total Ca^{2+} handled in the excitation-contraction coupling in a beating heart has been accomplished in canine left ventricles (LVs). This approach combines the intramyocardial Ca^{2+} recirculation fraction (RF) with the cardiac O_2 consumption for the excitation-contraction coupling. The RF has conventionally been obtained from the exponential decay of the postextrasystolic (PES) potentiation of myocardial contractility. However, in canine LVs, the PES contractility in terms of E_{max} (end-systolic pressure–volume ratio) has been shown to decay generally in alternans under both physiological and pathological conditions. Nevertheless, the RF can be obtained from the exponential decay component in the PES E_{max} alternans decay. We expected that the same Ca^{2+} assessment could be applied to

the human heart. As the first step, we investigated whether the PES E_{max} would decay in alternans or exponentially in patient LVs. We retrospectively analyzed 13 patient cases that had stable regular beats unexpectedly interrupted by a spontaneous extrasystole followed by a PES compensatory pause during their diagnostic examination. These patients had either mitral regurgitation, old myocardial infarction, or dilated cardiomyopathy. Their LV E_{max} decayed consistently in alternans within the first several PES beats. These E_{max} alternans decays resemble those reported in canine LVs. This finding suggests for the first time the applicability of the same organ-level RF assessment method developed for canine hearts to human hearts. [The Japanese Journal of Physiology 54: 87–91, 2004]

Key words: arrhythmia, E_{max} , calcium, recirculation fraction.

One of the present authors, H. Suga, and his group have developed an integrative analysis method to assess the total amount of myocardial Ca^{2+} handled in the excitation-contraction coupling in beating canine hearts [1–6]. This method requires that the intramyocardial Ca^{2+} recirculation fraction (RF) and the left ventricular (LV) O_2 consumption for the excitation-contraction coupling both be measured in a beating heart [1–6]. The RF has conventionally been calculated from the exponential decay rate of the postextrasystolic (PES) potentiated E_{max} [7, 8]. However, against general expectations [7, 8], Suga's group has found that the LV PES E_{max} generally decays in alter-

nans in canine hearts under both physiological and pathological conditions [1–6, 9]. Nevertheless, they succeeded in extracting an exponential decay component from the PES E_{max} alternans decay by peeling off the oscillatory component. They obtained the RF from the exponential decay component and then the total amount of Ca^{2+} handled in the excitation-contraction coupling [1–6].

We expected that the same approach successfully applied to the beating canine heart would also be applicable to the human heart. We first investigated in patient LVs whether the PES E_{max} would decay in alternans or exponentially. Although the PES potentia-

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Correspondence should be addressed to: Hiroyuki Suga, National Cardiovascular Center Research Institute, 5–7–1 Fujishirodai, Suita, 565–8565 Japan. Tel: +81–6–6833–5012, Fax: +81–6–6833–1421, E-mail: hsuga@ri.ncvc.go.jp

tion in patients with failing hearts is known to appear often as a transient pulsus alternans in systemic arterial pressure [8, 10], the PES $E_{\max}$ alternans remained to be analyzed in the human LV.

We therefore reviewed LV pressure and conductance–volume data in 130 patients with mitral regurgitation (MR), old myocardial infarctions, or dilated cardiomyopathy (DCM). We found only 13 cases that had stable regular beats interrupted by a spontaneous extrasystole followed by a PES compensatory pause. In these cases, $E_{\max}$ decayed consistently in alternans within the first several PES beats. The $E_{\max}$ alternans decay occurred even when the peak LV pressure did not show alternans. These $E_{\max}$ alternans decays resemble those observed in canine LVs [1–6]. The present finding would provide a novel clinical approach to evaluate the intramyocardial Ca^{2+} recirculation fraction in the human heart.

Methods

We reviewed 130 patients who underwent a diagnostic heart catheterization plus LV volumetry with a conductance catheter at the Mie University Hospital. After providing signed informed consents, they were cannulated with a 6F single-field conductance catheter (Webster Laboratories, Baldwin Park, CA, USA) into the LV via the femoral artery. The catheter lumen had a 2F micromanometer (Millar Instruments, Inc., Houston, TX). The conductance signal was converted to LV volume (V) with a Sigma 5 processor (Leycom, Zoetermeer, The Netherlands) [11].

The conductance volumetry has been described in detail elsewhere [11, 12]. Briefly, in the LV pressure–volume (P – V) study of each patient, we calibrated a conductance-to-LVV conversion by using a thermodilution-derived stroke volume. A calibration offset (i.e., parallel conductance) was corrected at the end diastole by matching the conductance signal with LVV measured by biplane ventriculography. The LV P and V signals were sampled at 3 ms intervals.

We found a spontaneous ventricular extrasystole (ES) in 35 cases and no ES in the other 95. Of the 35 cases, only 13 had stable regular beats interrupted by a single spontaneous ES followed by a PES compensatory pause. These 13 had either right atrial pacing (9 cases), right ventricular pacing (3 cases), or no pacing (1 case). Peak LVP and end-systolic LVV of these 13 cases showed obvious PES alternans within the first several PES beats. Of these 13 cases, 4 patients had no signs or symptoms of heart failure, and 9 had heart failure (3 patients in NYHA class I, 3 in class II, and 3 in class III). Of these 9 patients, 4 had been previously admitted to a hospital because of pulmonary

edema. Plasma BNP (brain natriuretic peptide) levels of the 13 cases ranged from 18 to 618 pg/ml with mean $\pm$ SD of 124 ± 177 pg/ml. Two NYHA III patients, one NYHA II patient, and one NYHA I patient had BNP > 100 pg/ml.

The other 22 of the 35 cases with ES had either slightly irregular beat intervals or no compensatory pause because of no pacing. We did not analyze these 22 cases because the beat intervals around the ES would have critically affected the decay pattern of the PES potentiation [9].

$E_{\max}$ is an LV contractility index practically independent of LV preload and afterload [6, 13]. We therefore used $E_{\max}$ to quantify the contractility of the human in situ ejecting LV where arrhythmias disturb not only its contractility, but also preload and afterload. Since the volume intercept (V_0) of the LV end-systolic P – V relation had not been determined in the present patients, we had to assume V_0 to be zero. We calculated the instantaneous LV P/V ratio as the instantaneous elastance E (LVE) and identified its maximum value as $E_{\max}$ in each contraction. Therefore the present $E_{\max}$ is not exactly the same as the original $E_{\max}$ that has been recognized as a reasonably load-independent index of LV contractility [6, 13]. However, we confirmed that changes in V_0 from 0 to 15–20 ml did not qualitatively affect the alternans decay, though they quantitatively affected its magnitude.

To analyze the relative changes in $E_{\max}$ of these pre-ES regular beats, ES, and first through sixth PES (PES1–6) beats, we normalized their $E_{\max}$ values relative to the averaged $E_{\max}$ value of the six pre-ES regular beats in each of the 13 cases. Peak LVPs were similarly normalized.

We first analyzed the differences of the normalized $E_{\max}$ values of the 13 cases at the respective beats from the regular beat level by a paired t -test at a significance level of $p=0.05$. We then analyzed these normalized $E_{\max}$ values among the cases by using an analysis of variance (ANOVA) with a significance level of $p=0.05$. We finally performed multiple comparisons of the beat-to-beat changes in the normalized $E_{\max}$ values by a Bonferroni post hoc test with a corrected significance level of $p=0.0018=0.05/28$. The peak LVPs were also analyzed in the same way. We used the StatView 5.0 program in all these statistical analyses.

Results

In the 13 cases we analyzed, the regular beat interval was 638 ± 204 (mean $\pm$ SD) ms at a pacing rate of 101 ± 25 beats/min. The ES beat interval was 405 ± 162 ms or $64 \pm 24\%$ of the regular beat interval.

Fig. 1. Alternans decay of postextrasystolically potentiated $E_{\max}$ of the left ventricle (LV) with mitral regurgitation (NYHA III, BNP540 pg/ml). A shows LV pressure-volume (P - V) loops of the last stable regular beat, extrasystole (ES), 1st PES (PES1) beat, and 2nd-6th PES beats. **B-E** show their LVP, LVE (LV P/V ratio, see METHODS), LVV, and dP/dt curves.

The first PES beat interval was 870 ± 327 ms or $136 \pm 24\%$ of the regular beat interval. The peak LVP of the regular beat was 112 ± 19 mmHg. The $E_{\max}$ was 1.7 ± 1.2 mmHg/ml, and the max dP/dt was $1,820 \pm 640$ mmHg/s. The ejection fraction was 0.56 ± 0.11 , ranging from 0.31 (DCM) to 0.71 (two MRs). These $E_{\max}$ and EF data indicate that the 13 cases had normal to moderately failing hearts.

Figure 1 shows a representative case of the PES $E_{\max}$ alternans decay. Figure 1A shows the P - V loops of the last regular beat, ES, and the PES1-6 beats. The ES P - V loop was the shortest and narrowest, and the PES1 P - V loop was the tallest and widest. Thereafter, the P - V loop quickly returned to regular beats within the first several beats from alternans.

Figure 1B-E show the LVP, LVE, LVV, and dP/dt curves of the same beats shown in Fig. 1A. The peak LVPs of PES1-3 beats varied slightly (Fig. 1B). $E_{\max}$ during PES beats (Fig. 1C, representing the peak of the LVE curve) also decayed in alternans, but it decayed neither exponentially nor monotonically. The end-systolic LVV and the stroke volume alternated during the PES beats (Fig. 1D). However, the end-diastolic volume and max $\pm dP/dt$ did not (Fig. 1D and E).

We observed similar $E_{\max}$ alternans decays in all the other 12 cases. But the peak LVP and max $\pm dP/dt$ in

PES1 beat were not always potentiated, and the peak LVPs did not always decay in the alternans. The end-systolic and end-diastolic LVVs did not always alternate in the PES beats.

Figure 2 shows the relative changes in $E_{\max}$ and peak LVP in the six pre-ES regular beats (R6-1), the ES beats, and PES1-6 beats. Their magnitudes were normalized relative to the average R level (barred R labeled between R1 and ES in Fig. 2) of the six pre-ES beats. Figure 2A and C show changes in the individual cases. $E_{\max}$ alternans decay was obvious in PES1-4 beats in all 13 cases. However, the peak LVP alternans decay was not always observed.

Figure 2B and D show the mean $\pm$ SD of $E_{\max}$ and peak LVP at the respective beats. Both $E_{\max}$ and peak LVP decreased in ES beats and increased in PES1 beats. In Fig. 2B, after the $E_{\max}$ potentiation in PES1 beat, the $E_{\max}$ in PES2-3 beats alternated significantly across the R level. $E_{\max}$ values in PES4-6 beats were not significantly different from the R level. Thus $E_{\max}$ significantly decayed in alternans within PES1-3 beats.

In Fig. 2D, the peak LVP was significantly potentiated in PES1 beat, and it was significantly decreased below the R level in PES2 beat. The peak LVP in PES3 beat was not significantly different from the R level. Thus the peak LVP decayed in alternans within

Fig. 2. Individual data of the normalized $E_{\max}$ and peak LVP in 13 human hearts (A and C) and their mean $\pm$ SD (B and D) of the last six regular beats (R1–6), their average to which all values were normalized (barred R), extrasys-

tole (ES), and 1st–6th PES-potentiated (PES1–6) beats. Asterisks indicate paired *t*-test significance levels. Sharp signs indicate Bonferroni test significance levels.

the first two PES beats. Neither the $\pm \max dP/dt$ nor the end-diastolic and end-systolic LVVs significantly alternated after the PES1 beat.

Discussion

These show that the LV PES $E_{\max}$ consistently decayed in alternans within the first several PES beats in the studied human patient hearts. This $E_{\max}$ alternans occurred after the stable regular beats were interrupted by a single spontaneous ES beat followed by a PES compensatory pause. Although the PES alternans decays of the systemic arterial pressure and peak LVP have been occasionally observed clinically, to the best of our knowledge the present study is the first one reporting on the LV PES $E_{\max}$ alternans in human hearts. This study thus demonstrates that human hearts share the same type of PES $E_{\max}$ alternans decay as those observed in canine hearts either *ex vivo* isovolumic [1–6] or *in situ* ejecting [14]. Although we did not observe an exponential or monotonic decay of PES $E_{\max}$ in the studied patient hearts with a spontaneous ES during the diagnostic examination, the present study does not exclude the possibility of the exponential

decay of the PES $E_{\max}$ in human hearts.

Compared to the obvious $E_{\max}$ alternans during the PES beats, peak LVP varied much less in the present study. This difference between $E_{\max}$ and LVP, however, existed in the previous study on canine *in situ* ejecting hearts [14]. These results contrast to the proportional PES alternans decays of both $E_{\max}$ and LVP in canine isovolumic LVs at a given LVV [1–6]. The different behavior of LVP from $E_{\max}$ derives naturally from the $E_{\max}$ dependently variable preload and stroke volume in *in situ* ejecting LVs (Iribe *et al.*, including Suga: manuscript submitted).

From these results, we speculate that the PES contractility alternans decay may occur more frequently in human hearts than was generally expected [10]. We would therefore consider that the PES $E_{\max}$ alternans decay could be used to evaluate the RF in human hearts, as it is in canine hearts. This consideration warrants further confirmation of the PES contractility alternans decay in normal and diseased human hearts. When such studies are prospectively performed in human hearts, V_0 should be determined to obtain the quantitatively reliable PES $E_{\max}$ alternans decay.

The PES $E_{\max}$ alternans should be measured as accurately as possible, especially when the RF is calculated from the exponential decay component contained in the $E_{\max}$ alternans decay [1–6]. Suga's previous group has recently shown that the RF is greatly miscalculated by the magnitude of the oscillatory component in the $E_{\max}$ alternans decay [15].

We conclude that the postextrasystolically potentiated left ventricular contractility decays in alternans within the first several postextrasystolic beats in human patient hearts. This $E_{\max}$ alternans decay will occur even when the peak left ventricular pressure does not show alternans. This finding suggests for the first time the applicability of the same organ-level assessment method of the intramyocardial Ca^{2+} recirculation fraction developed for canine hearts to human hearts. This applicability may lead to a novel clinical approach to evaluate the myocardial Ca^{2+} handling in the human heart.

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