Pressure-Interval Relationship Characterizes Left Ventricular Irregular Beat Contractilities and Their Mean Level during Atrial Fibrillation

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Abstract: How left ventricular (LV) contractility relates to irregular RR intervals during atrial fibrillation (AF) is still unclear. We investigated the relationship between the LV contractility ($E_{\max}$) of individual beats and their preceding RR intervals during AF in isovolumic contractions in excised cross-circulated canine hearts, and additionally in ejecting contractions in situ canine hearts. Atrial high-frequency electrical stimulation induced AF. We recorded a LV electrocardiogram, volume and pressure, and calculated the $E_{\max}$ of every arrhythmic beat. Multiple linear regression analysis between $E_{\max}$ and the six preceding RR intervals of all arrhythmic beats during 1 min AF

showed the preceding RR interval (RR1) and the pre-preceding interval (RR2) to be the predominant predictors of $E_{\max}$. The $E_{\max}$ -RR1/RR2 scattergram was closely fitted by a linear regression line. We found $E_{\max}$ at RR1/RR2=1 on the regression line to be virtually identical with both mean $E_{\max}$ during AF and stable $E_{\max}$ obtained during regular atrial pacing at the same intervals as the mean RR interval during AF. These results newly indicate that the pressure-interval relationship predominantly characterizes LV irregular beat contractilities and their mean level during AF. [Japanese Journal of Physiology, 47, 101–110, 1997]

Key words: force-interval relationship, mechanical restitution, mechanical potentiation, arrhythmia, $E_{\max}$

Atrial fibrillation (AF) is a common cardiac arrhythmia [1]. The main determinants of its cardiodynamic manifestation are the irregular RR intervals and the resultant interbeat changes in ventricular contractility as well as ventricular filling and ejection pressures. To evaluate the arrhythmic changes in ventricular contractility, the intrinsic myocardial force-interval (i.e., contractility versus RR interval) relationship has been used to account for the arrhythmic variations of the left ventricular (LV) contraction during AF [2–5].

However, LV contractilities of arrhythmic beats during AF have not been characterized by an index of contractility independent of the simultaneous changes in preload and afterload. We believed that the pressure-interval relationship could be a key to characterize the LV contractilities of arrhythmic beats during

AF.

The aim of this study was to clarify how irregular RR intervals affect the LV contractilities of individual arrhythmic contractions on the basis of the pressure-interval relationship. To this end, we used an index of contractility end-systolic LV maximal elastance ($E_{\max}$) which is relatively load- and heart rate-independent under steady-state conditions within their physiological ranges [6–10]. We mainly explored the relationship between beat-to-beat variations of LV $E_{\max}$ and RR intervals of isovolumic contractions to avoid any influence (ejecting activation and deactivation) on the $E_{\max}$ of the beat-to-beat variations of ventricular filling and ejection during electrically induced AF in excised cross-circulated canine hearts [6]. We additionally studied the same relationship of ejecting contractions

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in *in situ* canine hearts where $E_{\max}$ could be slightly influenced by the simultaneous beat-to-beat variations of ventricular filling and ejection during AF. We obtained the results indicating that the pressure-interval relationship, particularly the interval ratio of the preceding two beats, predominantly characterizes LV irregular beat contractilities and their mean level during AF.

METHODS

Surgical preparation of excised cross-circulated hearts for isovolumic contractions.

Experiments were performed in six excised cross-circulated canine heart preparations of the same type that we have been using in other studies [11–14]. The surgical procedures are described in detail elsewhere [15]. Briefly, two mongrel dogs (6–25 kg) were anesthetized with pentobarbital sodium (25 mg/kg, *i.v.*) after premedication with ketamine hydrochloride (7 mg/kg, *i.m.*). Blood was heparinized (1,000 units/kg) in both dogs. The common carotid arteries and external jugular vein were cannulated in the larger dog (support dog) for cross circulation of the excised heart preparation. The chest of the smaller dog (heart donor dog) was opened midsternally under artificial ventilation. The arterial and venous cross-circulation tubes from the support dog were cannulated into the left subclavian artery and the right ventricle (RV) via the right atrial appendage, respectively. The heart-lung section was isolated from systemic and pulmonary circulation by ligation of the descending aorta, inferior vena cava, azygos vein, superior vena cava, brachiocephalic artery, and pulmonary hili in this order. Cross circulation was started and the supported beating heart was excised with no interruption of coronary circulation.

A thin latex balloon (unstressed volume ~50 ml) mounted on a rigid connector (14 mm, internal diameter) was placed in the LV and the connector was secured at the mitral annulus. A miniature pressure gauge (model P-7, Konigsberg Instruments, Inc., Pasadena, CA, USA) was placed inside the apical end of the balloon to measure LV pressure (P). The balloon was connected to our custom-made volume servo pump, which controlled and measured LV volume (V) [9]. An LV epicardial electrocardiogram (ECG) was recorded to measure the RR intervals.

Electrical stimulation at 20 Hz by two electrodes on the left atrial appendage induced and maintained AF. The temperature of the heart was monitored and maintained constant near 36°C throughout the experiment with heaters placed on the coronary arterial perfusion

tube and under the box containing the heart. The systemic arterial blood pressure of the support dog served as the coronary perfusion pressure of the excised heart. Systemic hypotension under cross circulation was prevented with intravenous indomethacin (5 mg per dog) as usual [14, 16]. When the mean perfusion pressure decreased to below 80 mmHg, we restored it by slowly transfusing whole blood reserved from the heart donor dog or by infusing dextran solution as needed. The arterial pH, P_{O_2} , and P_{CO_2} of the support dog were repeatedly measured and maintained within their physiological ranges using supplemental oxygen and intravenous sodium bicarbonate.

Surgical preparation of *in situ* hearts for ejecting contractions.

Six mongrel dogs (6–12 kg) were anesthetized with pentobarbital sodium (25 mg/kg, *i.v.*) after premedication with ketamine hydrochloride (50 mg/kg, *i.m.*) and intubated in each experiment. Anesthesia was maintained by fentanyl (100 µg/h per dog, *i.v.*). The dogs were thoracotomized midsternally. A 3F catheter-tip micro-manometer (Aisin Seiki, Kariya, Japan) was inserted into the LV from the apex to measure LVP. A 7F eight-electrode conductance catheter (Webster Laboratories, Baldwin Park, CA, USA) was introduced into the LV through an apical stab and placed along the ventricular long axis to measure LVV. The method for measuring LVV by means of the conductance catheter was described previously [17, 18]. Briefly, the method is based on measuring the time-varying electrical conductances $G(t)$ of the five segments of blood in the LV cavity. The LV total blood volume was calculated from the segmental conductances after calibrating blood conductivity, which was measured in a sampling cuvette. To measure the conductances and to convert them to LVV, a custom-made conditioner-processor (SI Medicotech Co., Ltd., Japan) was used. Two stimulating electrodes were placed on the left atrial appendage to induce AF. The parallel conductance (G_p) (i.e., the conductance of the LV wall tissues and surroundings), which partially conducts the driving current, overestimated intraventricular $G(t)$. G_p was obtained by the hypertonic saline dilution method, and a constant offset volume (V_c) was calculated from the G_p [17]. The absolute LV volume was obtained by subtracting V_c from the conductance volume.

Experimental protocols. We first produced AF for 1 min to obtain the mean RR interval during AF (mean AF RR) and recorded the LV ECG, LVP, and LVV simultaneously. After stopping the 20 Hz atrial stimulation, we electrically paced the left atrium at the same regular intervals as the mean AF RR and

recorded the LV ECG, LVP, and LVV to obtain the $E_{\max}$ of stable contractions ($sE_{\max}$). Finally, we again produced AF and recorded the LV ECG, LVP, and LVV to obtain the $E_{\max}$ of every arrhythmic contraction during AF (Fig. 1). This sequence was common to both isovolumic and ejecting studies.

Isovolumic protocol for the excised hearts: In the 6 excised cross-circulated canine hearts, we first determined V_0 as the LVV at which peak isovolumic LVP was zero and then chose a constant mid-range end-diastolic LVV so that the peak isovolumic LVP was about 80–100 mmHg. After recording AF for 1 min to determine the mean AF RR, we obtained the $sE_{\max}$ at the mean AF RR. Then, we obtained the $E_{\max}$ of all isovolumic contractions and RR intervals for 1 min during AF and calculated the mean $E_{\max}$ ($mE_{\max}$) as explained in more detail below, in the sections on contractility index ($E_{\max}$) and RR interval.

Ejecting protocol for the in situ hearts: In the 6 open-chest canine hearts, we determined $sE_{\max}$ and V_0 by gradual aortic occlusion over several regular beats [18] under regular atrial pacing at the mean AF RR. Then, we obtained the $E_{\max}$ of all individual beats and RR intervals for 1 min during AF and calculated the $mE_{\max}$, as explained below.

Contractility index ($E_{\max}$).

$E_{\max}$ of isovolumic contractions in the excised hearts: LV contractility was assessed by end-systolic elastance, $E_{\max}$ [7, 8]. $E_{\max}$ has been generally recognized to be a ventricular contractility index relatively load- and heart rate-independent under steady-state conditions [6]. Since we studied the $E_{\max}$ of isovolumic beats at a given LV volume, the obtained $E_{\max}$ values reliably reflect LV contractilities independent of preload and ejection. We connected the predetermined V_0 (since V_0 is considered almost constant throughout each acute experiment, as shown in our previous paper [13]) and the peak LVP of each isovolumic contraction at the preset constant LVV and identified its slope as the $E_{\max}$ of this contraction (Fig. 2a). The same calculation was repeated for all individual contractions during AF as well as regular contractions before AF.

$E_{\max}$ of ejecting contractions in the in situ hearts: We recorded instantaneous LVP and conductance catheter LVV during gradual occlusion of the ascending aorta over several regular beats [18] under atrial pacing at the mean AF RR. The end-systolic P - V relation (ESPVR) line was obtained by simple linear regression analysis of the end-systolic P - V data points identified as the left-upper corners of the P - V loops obtained by aortic occlusion. This ESPVR line was characterized by its slope, $sE_{\max}$ and its extrapolated

Fig. 1. Original recordings during electrically induced atrial fibrillation in one isovolumically contracting canine left ventricle. Signals (from top down) are LV pressure, LV volume (constant), and LV electrocardiogram (ECG). We defined the preceding interval immediately before any beat of interest (arrow) as RR1, the pre-preceding interval as RR2, and the third to sixth preceding intervals as RR3, RR4, RR5, and RR6.

V -intercept, V_0 [18]. During AF, we determined $E_{\max}$ as the slope of the line connecting the already obtained V_0 (since V_0 is considered almost constant throughout each acute experiment, as shown in our previous paper [16]) and the left-upper corner of the P - V loop of each ejecting contraction (Fig. 2b).

After each isovolumic or ejecting experiment, the LV, septum and RV free wall were weighed. The LV and RV weights were 47.5 ± 9.9 and 21.3 ± 6.6 g (6 hearts) in the isovolumic experiments, and 46.5 ± 15.1 and 15.7 ± 5.5 g (6 hearts) in the ejecting experiments. Using these LV weights, the $E_{\max}$, (in $\text{mmHg} \cdot \text{ml}^{-1}$) was normalized for 100 g LV and expressed in $\text{mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g LV}$.

RR interval. Figure 1 shows a representative set of original recordings of consecutive irregular arrhythmic isovolumic contractions during AF in one heart. We defined the RR interval first preceding any contraction of interest (arrow) as RR1, the RR interval second preceding or pre-preceding as RR2 and the RR interval third to sixth preceding as RR3 through RR6.

Statistics. Data were presented as mean $\pm$ SD. We evaluated correlations between the $E_{\max}$ and a combination of preceding RR1–6 by multiple regression analysis. We compared $mE_{\max}$, $sE_{\max}$, and the predicted $E_{\max}$ at $\text{RR1/RR2}=1$ by repeated measurement analysis of variance and Bonferroni's t -test.

Mathematical analysis: We attempted to find a mathematical function to fit the scattergram of

Fig. 2. Representative drawings of the left ventricular (LV) pressure-volume trajectory of three consecutive contractions (from 1 through 3) in isovolumic (a) and ejecting (b) contractions in canine hearts during electrically induced atrial fibrillation (AF). a: V_0 was determined as the LV volume at which the peak isovolumic LV pressure was zero. The E_{max} during AF was identified as the slope of the solid line connecting the predetermined V_0 and the peak

LV pressure of each isovolumic contraction at the constant LV volume. b: V_0 is the volume-axis intercept of the end-systolic pressure-volume relation obtained (though the relation is not shown) during gradual aortic occlusion under regular atrial pacing at the same intervals as the mean RR during AF. The E_{max} during AF was identified as the slope of the solid line connecting the predetermined V_0 and the left upper corner of each pressure-volume loop.

E_{max}/mE_{max} against RR1/RR2. We describe in RESULTS why we chose RR1/RR2 to correlate with E_{max}/mE_{max} . We chose linear regression analysis because neither exponential nor logistic fitting was significantly better than linear fitting (see DISCUSSION). We evaluated how well the regression line fit the E_{max}/mE_{max} -RR1/RR2 scattergram by the correlation coefficient between them.

RESULTS

Isovolumic contractions during AF in excised hearts

Figure 3a shows a representative E_{max} -RR1 scattergram of a heart (No. 6). Although there was a tendency for E_{max} to increase with RR1, the scatter was large and there was only a loose positive correlation (linear correlation coefficient $r=0.696$, $p<0.001$, $n=142$ beats for 1 min). Figure 3b shows a representative E_{max} -RR2 scattergram for the same heart as in Fig. 3a. Although there was a tendency for E_{max} to decrease

Fig. 3. The scattergrams of beat-to-beat contractility (E_{max}) against preceding RR interval (RR1) (a) and pre-preceding RR interval (RR2) (b) during the same irregular arrhythmic isovolumic contractions in one heart (No. 6).

Table 1. Multiple regression analysis between $E_{\max}$ and six previous RR intervals.

	Partial regression coefficient (b)	Standard error (SE)	t-value (b/SE)	Standard partial regression coefficient (b×SD)
RR1	0.0905	0.0025	36.93*	0.869
RR2	-0.0570	0.0025	-23.10*	-0.547
RR3	0.0032	0.0025	1.31	0.031
RR4	-0.0230	0.0025	-9.33*	-0.221
RR5	-0.0051	0.0024	-2.08	-0.049
RR6	-0.0007	0.0024	-0.27	-0.006

RR1, preceding RR interval; RR2, pre-preceding RR interval; RR3, the third preceding RR interval; RR4, the fourth preceding RR interval; RR5, the fifth preceding RR interval; RR6, the sixth preceding RR interval (see Fig. 1). SD, standard deviation; * $p < 0.01$; multiple correlation coefficient=0.958; F -value=353. Each t -value, which is given by dividing the partial regression coefficient by its standard error, represents importance of each RR interval. $n=181$ beats in an isovolumically contracting heart (No. 2).

Table 2. Comparison of t -value[†] by multiple regression analysis between $E_{\max}$ and six previous RR intervals in six isovolumic hearts.

	Heart					
	1	2	3	4	5	6
RR1	43.65*	36.93*	18.63*	24.36*	29.45*	20.59*
RR2	-31.52*	-23.10*	-17.12*	-20.62*	-23.21*	-18.20*
RR3	0.28	1.31	-0.99	0.44	-0.74	-2.17
RR4	-6.98*	-9.33*	-3.36*	-7.01*	-3.33*	-3.09*
RR5	-2.57	-2.08	-2.07	-0.11	-1.45	0.48
RR6	-3.65*	-0.27	-2.18	-1.28	-1.18	-1.02

RR1, preceding RR interval; RR2, pre-preceding RR interval; RR3, the third preceding RR interval; RR4, the fourth preceding RR interval; RR5, the fifth preceding RR interval; RR6, the sixth preceding RR interval. In every case the obtained F -value with the multiple regression equation was greater than that for $p < 0.001$. * $p < 0.01$; [†] partial regression coefficient/standard error of partial regression coefficient.

with RR2, the scatter was large and there was only a loose negative correlation ($r = -0.615$, $p < 0.001$, $n = 142$ beats for approximately 1 min). Therefore, $E_{\max}$ was not uniquely determined by either RR1 or RR2 alone. The other hearts showed similar results. Therefore, we performed multiple regression analysis.

Table 1 shows a representative result of a multiple regression analysis of contribution of RR1–6 to the $E_{\max}$ of one heart (No. 2). We used RR1–6 since post-extrasystolic potentiation has been reported to affect the six subsequent beats [19]. Our data show that RR1 had the highest correlation with $E_{\max}$ and that RR2 also correlated highly with $E_{\max}$, though less than RR1, as indicated by the large t -values. Although RR4 also showed statistically significant correlation with $E_{\max}$, its absolute t -value was much smaller than those of RR1 and RR2. RR3, RR5, and RR6 did not significantly correlate with $E_{\max}$. This result shows that only RR1 and RR2 play a major role in determining $E_{\max}$. For the 5 other hearts, we also analyzed the contribution of the six previous RR intervals to $E_{\max}$.

Table 2 summarizes the t -values in all 6 hearts. The absolute t -values of RR1 and RR2 were always much greater than those of the other RR intervals. These results indicate that RR1 and RR2 predominantly contributed to the $E_{\max}$ of all 6 hearts. Therefore, we attempted to express $E_{\max}$ by the ratio of RR1 to RR2 (RR1/RR2). We obtained a hint of this method from previous reports [2, 5], as discussed in the $E_{\max}$ and RR1/RR2 section of DISCUSSION.

Figure 4 shows a representative $E_{\max}$ (left axis)-RR1/RR2 scattergram for one heart (No. 6). The $E_{\max}$ is distributed widely between 2.52 and 9.03 mmHg · ml⁻¹ · 100 g LV. This graph shows a positive linear correlation between LV $E_{\max}$ and RR1/RR2. This correlation ($r = 0.921$) was remarkably higher than those in Fig. 3a and b.

We then normalized the $E_{\max}$ of every arrhythmic contraction by dividing it by the $E_{\max}$ during AF. Linear regression analysis was performed to fit the normalized scattergram. Figure 4 shows the $E_{\max}/E_{\max}$ (right axis)-RR1/RR2 scattergram. $E_{\max}/E_{\max}$ is dis-

tributed widely between 0.46 and 1.64 (dimensionless), where $mE_{\max}$ is $5.50 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g LV}$. The other hearts showed similar results. The mean

Fig. 4. A scattergram of $E_{\max}$ (left axis) and $E_{\max}/mE_{\max}$ (right axis) against the RR1/RR2 of isovolumic contractions during AF for the same heart (No. 6) as shown in Fig. 3. The regression line was $E_{\max} = 5.39 \times (\text{RR1/RR2}) - 0.064$. $E_{\max}/mE_{\max}$ is $E_{\max}$ normalized by the mean $E_{\max}$ ($mE_{\max}$) during AF ($5.50 \pm 1.51 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g LV}$). The same regression line corresponded to $E_{\max}/mE_{\max} = 0.98 \times (\text{RR1/RR2}) - 0.012$. Dotted lines indicate the unity lines of $E_{\max}/mE_{\max}$ and RR1/RR2.

correlation coefficient between the regression line and the $E_{\max}/mE_{\max}$ -RR1/RR2 scattergram was 0.927 ± 0.017 for the 6 hearts ($p < 0.05$) (Table 3). Therefore, the normalized regression line fit the data reasonably well. The slope (A) and y intercept (B) values of the regression line obtained from the isovolumic contractions ($n = 195 \pm 45$ beats) in each of the 6 hearts are listed in Table 3. Slope A did not vary much among individual hearts, meaning little dispersion of normalized $E_{\max}$ as a function of RR1/RR2.

We found that the regression line passed through a point near $E_{\max}/mE_{\max} = 1$ (0.961 ± 0.014 , $n = 6$ hearts) at RR1/RR2 = 1. Therefore, $E_{\max}$ at RR1/RR2 = 1 was expected to equal $mE_{\max}$. We then compared the $E_{\max}$ predicted at RR1/RR2 = 1 on the regression line with both $mE_{\max}$ during AF and $sE_{\max}$ observed at the mean AF RR. Table 4 shows no significant differences among the average $mE_{\max}$ observed during AF ($8.82 \pm 6.57 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g LV}$), average $sE_{\max}$ ($8.02 \pm 6.33 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g LV}$) observed at mean AF RR (154 ± 27 beats/min) ($n = 6$ hearts) and average predicted $E_{\max}$ at RR1/RR2 = 1 ($8.53 \pm 6.41 \text{ mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g LV}$). Although RR1/RR2 was distributed around unity, both RR1 and RR2 at unity RR1/RR2 were usually shorter than the mean AF RR in all hearts except one.

Table 3. Parameters (A and B) of the linear regression line in six isovolumic hearts.

	Heart						Mean $\pm$ SD
	1	2	3	4	5	6	
A	1.42	1.54	0.94	1.33	1.11	0.98	1.22 ± 0.25
B	-0.44	-0.57	0.02	-0.38	-0.17	-0.01	0.26 ± 0.24
r	0.939	0.933	0.899	0.920	0.948	0.921	0.927 ± 0.017

A , slope of the regression line. B , y intercept. A and B values are dimensionless. r , correlation coefficient. $n = 163$ –251 beats from each heart. SD, standard deviation.

Table 4. Comparison among $mE_{\max}$, $sE_{\max}$, and the predicted $E_{\max}$ at RR1/RR2 = 1 in six isovolumic hearts.

	Hearts						Average
	1	2	3	4	5	6	
$mE_{\max}$	15.6 ± 3.8	18.8 ± 7.1	4.81 ± 1.43	4.22 ± 1.78	4.04 ± 1.60	5.50 ± 1.51	8.82 ± 6.57
$sE_{\max}$	11.8 ± 0.2	19.3 ± 0.2	4.22 ± 0.06	4.00 ± 0.06	3.75 ± 0.07	5.00 ± 0.10	8.20 ± 6.33
$E_{\max}$ at RR1/RR2 = 1	15.3	18.1	4.63	4.01	3.80	5.33	8.53 ± 6.41
$E_{\max}/mE_{\max}$ at RR1/RR2 = 1	0.982	0.962	0.963	0.945	0.941	0.969	0.961 ± 0.014

$mE_{\max}$, $sE_{\max}$, and average are mean $\pm$ standard deviation. $mE_{\max}$, mean $E_{\max}$ during atrial fibrillation (AF); $sE_{\max}$, stable $E_{\max}$ under constant atrial pacing at mean RR during AF; $E_{\max}$ at RR1/RR2 = 1, the predicted $E_{\max}$ value at RR1/RR2 = 1 on the regression line; $E_{\max}/mE_{\max}$ at RR1/RR2 = 1, the predicted $E_{\max}/mE_{\max}$ value at RR1/RR2 = 1 on the regression line. These data were compared by repeated measures analysis of variance and Bonferroni's t -test. No significant difference was found among hearts and their average values. The unit of $mE_{\max}$, $sE_{\max}$, and $E_{\max}$ at RR1/RR2 = 1 is $\text{mmHg} \cdot \text{ml}^{-1} \cdot 100 \text{ g LV}$. $E_{\max}/mE_{\max}$ at RR1/RR2 = 1 is dimensionless.

Ejecting contractions during AF in in situ hearts

Figure 5 shows a representative $E_{\max}/mE_{\max}$ -RR1/RR2 scattergram for ejecting contractions in one heart. This scattergram is more dispersed than any of the isovolumic scattergrams. The average correlation coefficient between the regression line and the data was 0.801 ± 0.048 ($p < 0.05$) ($n = 6$ hearts). Although the average correlation coefficient was much worse than any isovolumic coefficient, the average $E_{\max}/mE_{\max}$

Fig. 5. A representative scattergram of $E_{\max}/mE_{\max}$ against RR1/RR2 during AF in one in situ ejecting canine heart. The $mE_{\max}$ during AF was 11.3 ± 6.4 mmHg $\cdot$ ml $^{-1}$ $\cdot$ 100 g LV. The data are more dispersed than those of the isovolumic contractions shown in Fig. 4. Dotted lines indicate the unity lines of $E_{\max}/mE_{\max}$ and RR1/RR2.

value during AF experimentally observed at $0.95 < \text{RR1/RR2} < 1.05$ was 1.003 ± 0.061 (Table 5). This value was close to that of the isovolumic contractions (0.978 ± 0.025 , Table 5).

Three of the 6 ejecting hearts could be paced at the mean AF RR (170 ± 17 beats/min). The average $sE_{\max}$ at the mean AF RR and $mE_{\max}$ during AF were 12.26 ± 2.55 and 10.52 ± 1.17 mmHg $\cdot$ ml $^{-1}$ $\cdot$ 100 g LV, respectively. There were no significant differences between these values.

However, the remaining three hearts could not be paced without pulsus alternans at as high as their mean tachycardiac AF RR (255 ± 41 beats/min). Consequently, atrial pacing was performed at 170 ± 17 beats/min so as not to cause pulsus alternans. The average $sE_{\max}$ and average $mE_{\max}$ during AF were 14.42 ± 0.86 and 8.74 ± 2.35 mmHg $\cdot$ ml $^{-1}$ $\cdot$ 100 g LV, respectively. The $mE_{\max}$ was smaller than the average $sE_{\max}$ at the regular pacing rate of 35–116 beats/min, less than the mean tachycardiac AF RR.

DISCUSSION

Contractility index. Atrial dysfunction and ventricular filling disturbance during AF deteriorate cardiac function [2–5]. However, little is known how the LV contractility per se of arrhythmic beats during AF contributes to ventricular pump dysfunction. One reason for this seems to be the inadequate assessment

Table 5. $E_{\max}/mE_{\max}$ during AF at $0.95 < \text{RR1/RR2} < 1.05$.

Hearts		$E_{\max}/mE_{\max}$ at $0.95 < \text{RR1/RR2} < 1.05$	n/total	(%)
Isovolumic	1	0.964 ± 0.079	85/251	33.8
	2	0.970 ± 0.135	87/186	46.8
	3	1.019 ± 0.210	85/251	33.9
	4	0.961 ± 0.105	26/184	15.2
	5	0.956 ± 0.108	87/186	46.8
	6	0.999 ± 0.099	85/251	33.9
Average		0.978 ± 0.025		35.1 ± 11.6
Ejecting	1	1.073 ± 0.375	28/163	17.2
	2	1.047 ± 0.424	32/167	19.2
	3	0.969 ± 0.336	77/225	34.2
	4	0.949 ± 0.257	55/154	35.7
	5	1.051 ± 0.439	31/189	16.4
	6	0.930 ± 0.381	36/199	18.1
Average		1.003 ± 0.061		23.5 ± 9.0

$mE_{\max}$, mean $E_{\max}$ during atrial fibrillation (AF); $E_{\max}/mE_{\max}$ at $0.95 < \text{RR1/RR2} < 1.05$, experimentally obtained $E_{\max}/mE_{\max}$ value at $0.95 < \text{RR1/RR2} < 1.05$. $E_{\max}/mE_{\max}$ values are mean $\pm$ standard deviation (SD) in individual hearts. Average values are mean $\pm$ SD of the mean values of $E_{\max}/mE_{\max}$ in the 6 hearts. n/total , number of beats distributed at $0.95 < \text{RR1/RR2} < 1.05$ in a total number of beats during AF. %, percent value of n beats in the total beats. Average % values are mean $\pm$ SD of the percent values in the 6 hearts.

of LV contractilities of individual beats during AF. Many indexes such as LV dp/dt max [4], ejection fraction [5, 20], mean rate of circumferential fiber shortening [5] and stroke distance [2] have been used for assessing LV contractilities during AF. However, these contractility indexes are known to change with the simultaneous changes in preload and afterload [6].

We used $E_{\max}$ for the first time for evaluating LV contractility during AF [7, 8]. $E_{\max}$ has been confirmed to be relatively independent of preload, afterload, and heart rate under steady-state conditions within their physiological ranges [6–10]. Particularly, $E_{\max}$ in isovolumic contractions at a constant LV volume is free from any preload and stroke volume changes which change in in situ ejecting contractions.

$E_{\max}$ and six previous RR intervals. The present multiple regression analysis has indicated that RR1 was the most important predictor of $E_{\max}$ in view of the positive correlation coefficient between them, and that RR2 was the second most important predictor of $E_{\max}$ in view of the negative correlation coefficient between them. This indicates that a longer RR1 after a shorter RR2 yields greater contractility. The analysis has also shown that earlier RR intervals (RR3–6) did not contribute much to $E_{\max}$. All these results support the concept that mechanical restitution and potentiation [21] (i.e., greater postextrasystolic contractility after a more premature and weaker extrasystolic contractility than regular beat contractility) play important roles in the beat-to-beat variations of LV contractility during AF.

$E_{\max}$ and RR1/RR2. Although RR1 and RR2 are the most important factors to determine $E_{\max}$, we assumed that RR1 always affects $E_{\max}$ under the reciprocal influence of RR2, and hence we normalized RR1 by RR2 (RR1/RR2). Postextrasystolic contractility (force) has been shown to be an increasing function (restitution) of the interval between extrasystolic and postextrasystolic stimuli (equivalent to our RR1 as shown in Fig. 1) [21]. This relation has been shown to be a decreasing function (potentiation) of the interval between the extrasystolic and immediately preceding steady-state stimuli (equivalent to our RR2 shown in Fig. 1) [21]. These results also suggest that postextrasystolic contractility is an increasing function of RR1/RR2. Therefore, we believe it reasonable to choose RR1/RR2 to correlate with $E_{\max}$ during AF. Although previous investigators had used RR1/RR2 or its reciprocal to correlate with cardiac performance indexes (ejection fraction, pulse pressure) [2, 5], these indexes are known to be relatively load-dependent as discussed above. We are therefore the first researchers to correlate RR1/RR2 with $E_{\max}$ as a relatively load-

independent contractility index during AF, and found a reasonably good correlation between them.

Linear $E_{\max}/_mE_{\max}$ -RR1/RR2 relation of isovolumic contractions in excised cross-circulated hearts. We have found that the scattergram of $E_{\max}$ against RR1/RR2 is much less dispersed than the already documented scattergram of LV performance indexes against either RR1, RR2, or RR1/RR2 during AF [2–5]. Previous investigators have described the LV contractilities of arrhythmic beats during AF as a function of their irregular beat intervals using relatively load-dependent indexes of contractility [2–5]. The mechanical restitution and potentiation that play important roles in the beat-to-beat variations of LV contractility have been well fitted by a monoexponential curve [21]. We first tried a similar monoexponential fitting. The average correlation coefficient was 0.937 ± 0.015 . This value was not significantly different from that by linear regression analysis. We therefore contend that the relation between LV arrhythmic beat contractilities and RR1/RR2 during AF could be practically expressed by a regression line. The small variation of the slope of the regression lines among the hearts (Table 3) indicates that the pressure-interval relationship was reasonably normalized.

The present results indicate $E_{\max}$ at RR1/RR2=1 on the regression line to be nearly equal to both $_mE_{\max}$ during AF and $_sE_{\max}$ during regular atrial pacing at the mean AF RR. This suggests that the irregular rhythm itself does not affect the mean level of LV contractility during AF in isovolumic hearts. Furthermore, this suggests that the mean intracellular calcium level during AF is not affected by the beat-to-beat variations of intracellular calcium concentrations caused by mechanical potentiation and restitution [21].

$E_{\max}/_mE_{\max}$ -RR1/RR2 relation of ejecting contractions in in situ hearts. The $_sE_{\max}$ obtained in the ejecting hearts that could be paced at the same rate as the mean AF RR were nearly equal to $_mE_{\max}$, although the $E_{\max}/_mE_{\max}$ -RR1/RR2 scattergram of the ejecting hearts was more dispersed than that of the isovolumically contracting hearts. Furthermore, the average $E_{\max}/_mE_{\max}$ value during AF experimentally observed at $0.95 < \text{RR1/RR2} < 1.05$ was virtually in unity (Table 5). This means that, as in isovolumic contractions, $_mE_{\max}$ was nearly equal to $E_{\max}$ at RR1/RR2=1 even in ejecting contractions.

In the hearts with tachycardiac AF, we were unable to pace the atrium at a regular rate as high as their mean AF RR without eliciting pulsus alternans. In these hearts, $_mE_{\max}$ was smaller than the $_sE_{\max}$ obtained at the regular pacing rate considerably slower than the mean tachycardiac AF RR. This could be a manifesta-

tion of the inverse force-frequency relationship (negative staircase phenomenon) [22], namely, a lower contractility at a higher heart rate, opposite the Bowditch phenomenon, above the physiological heart rate range.

Limitation. We investigated the beat-to-beat variations of LV contractility during electrically induced AF mainly in the isovolumically contracting LV of excised cross-circulated hearts. We chose a constant mid-range end-diastolic LVV so that the peak isovolumic LVP was about 80–100 mmHg. This volume load was intermediate and appropriate to study the changes in $E_{\max}$ during AF. The changes in $E_{\max}$ were within $\pm 60\%$ around ${}_mE_{\max}$ in isovolumic contractions. Within this range of $E_{\max}$, no problems seem to exist in using $E_{\max}$ as a contractility index during AF. In in situ ejecting contractions, the normalized $E_{\max}$ -RR1/RR2 scattergram of ejecting contractions was more dispersed than the isovolumic scattergram. This dispersion may have been derived from the methodological differences in volume measurement, reflex interference and/or other unknown mechanisms. However, this study has shown that we can apply the same normalized $E_{\max}$ -RR1/RR2 scattergram to the ejecting heart to obtain the predicted $E_{\max}$ at RR1/RR2=1 from a sufficient number of beats. Therefore, application of the method established herein for acute and electrically induced AF to in situ pathological AF is encouraged.

Conclusion. We found that beat-to-beat changes in left ventricular (LV) contractility, in terms of $E_{\max}$ during atrial fibrillation (AF), correlate reasonably well with the ratio (RR1/RR2) of the preceding RR interval (RR1) to the pre-preceding RR interval (RR2). We also found a linear correlation between RR1/RR2 and the $E_{\max}$ of each beat normalized to the mean level of contractility (${}_mE_{\max}$) during AF. The ${}_mE_{\max}$ and predicted $E_{\max}$ at RR1/RR2=1 on the regression line were nearly equal to the stable $E_{\max}$ (${}_sE_{\max}$) at a regular atrial pacing equal to the mean RR during AF. These results have given us a physiologically sound background for all of the ${}_mE_{\max}$ during AF, $E_{\max}$ predicted at RR1/RR2 during AF, and ${}_sE_{\max}$ at a regular heart rate as good indicators of the LV contractility during and without AF, at least in normal canine hearts. Therefore, this study indicates that the pressure-interval relationship predominantly characterizes LV irregular beat contractilities and their mean level during AF.

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