Ventricular contractility in atrial fibrillation is predictable by mechanical restitution and potentiation

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Suzuki, Shunsuke, Junichi Araki, Terumasa Morita, Satoshi Mohri, Takeshi Mikane, Hiroki Yamaguchi, Shunji Sano, Tohru Ohe, Masahisa Hirakawa, and Hiroyuki Suga. Ventricular contractility in atrial fibrillation is predictable by mechanical restitution and potentiation. Am. J. Physiol. 275 (Heart Circ. Physiol., 44): H1513–H1519, 1998.—We recently found that contractility (Emax) of an individual irregularly arrhythmic beat in electrically induced atrial fibrillation (AF) is reasonably predictable from the ratio of the preceding beat interval (RR1) to the beat interval immediately preceding RR1 (RR2) in the canine left ventricle. Moreover, the monotonically increasing relation between Emax and the RR1-to-RR2 ratio (RR1/RR2) passed through or by the mean arrhythmic beat Emax as well as the regular beat Emax at RR1/RR2 = 1. We hypothesized that this Emax-RR1/RR2 relation during irregular arrhythmia could be attributed to the basic characteristics of the mechanical restitution and potentiation. To test this, we adopted a known comprehensive equation describing the force restitution and potentiation as a function of two preceding beat intervals and simulated contractilities of irregular arrhythmic beats with randomized beat intervals on a computer. The simulated Emax-RR1/RR2 relation reasonably resembled the one that we recently observed experimentally, supporting our hypothesis. We therefore conclude that the primary mechanism underlying the varying contractilities of irregular beats in AF is mechanical restitution and potentiation.

irregular rhythm; arrhythmia; interval-force relation; contractility; calcium

Atrial fibrillation (AF) has recently attracted more interest in cardiology and cardiac surgery (4). AF produces ventricular irregular (absolute) arrhythmia and decreases cardiac output (3, 11). The decreased cardiac output seems to be partly caused by decreased ventricular end-diastolic volume (11). However, the contribution of depressed ventricular contractilities to the decreased cardiac output remains to be fully elucidated (5–8, 26). Recently, we found that the average contractility (Emax; end-systolic pressure-volume ratio, which is a load-independent index of contractility, see METHODS) of individual arrhythmic beats in AF was comparable to the Emax of regular beats at the average arrhythmic heart rate in the canine left ventricle (LV) (26). Moreover, the Emax of each arrhythmic beat was reasonably predictable from the ratio (RR1/RR2) of the preceding beat interval (RR1) to the beat interval immediately preceding RR1 (RR2) (26). However, this interesting finding has not yet been accounted for by the restitution and potentiation phenomena of myocardial contractility (6–8).

We hypothesized that the experimentally observed Emax-RR1/RR2 relation would be a manifestation of the basic characteristics of the mechanical restitution and potentiation phenomena. In fact, we found that Emax was positively correlated with RR1 and negatively correlated with RR2 (26). Although similar correlations have been documented (6–8), no previous studies had been done with a load-independent index of contractility such as Emax (26). The Emax-RR1/RR2 relation reminded us of the mechanical restitution and potentiation mechanisms as functions of the premature and postextrasystolic beat intervals (27).

We therefore investigated whether the mechanical restitution and potentiation curves could account for the experimentally observed Emax-RR1/RR2 relation of irregularly arrhythmic beats. We performed a computer simulation using the comprehensive equation that Yue et al. (27) established to describe the mechanical restitution and potentiation curves. The irregular arrhythmia was simulated by randomized beat intervals. We obtained results that reasonably simulated the Emax-RR1/RR2 relation during absolute arrhythmia (26), supporting our hypothesis.

METHODS

We used the following equation in the simulation

\[ nE_{\text{max}} = |G \cdot \exp \left[-\frac{(RR2 - t_2)}{\tau}\right] + H \cdot \left[1 - \exp \left[-\frac{(RR1 - t_1)}{\tau}\right]\right] \]  

(1)

where nEmax is normalized contractility (dimensionless) of an irregularly arrhythmic beat of interest immediately after two consecutive beat intervals, RR1 (in s) and RR2 (in s), as schematically shown in Fig. 1A. Here, Emax of the arrhythmic beat (marked by arrow in Fig. 1A) was normalized to Emax of the regular beat at the average arrhythmic beat rate. G is an amplitude constant (dimensionless); H is a plateau level constant (dimensionless); t1 and t2 are refractory periods (in s) of the restitution and potentiation, respectively; and \( \tau \) is a time constant (in s) common to both restitution and potentiation. Essentially the same equation as Eq. 1 had been proposed by Yue et al. (27) as a model of postextrasystolic potentiation (PESP) in the canine LV. They intended to describe the potentiated contractility of the first postextrasystolic beat (PES1) following the extrasystole (ES) produced artificially.

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after a stable series of regular beats, as shown in Fig. 1A: irregular arrhythmia during experimentally produced atrial fibrillation in excised cross-circulated canine hearts. Atrium was continuously stimulated by 20-Hz alternative current. LVP, left ventricular peak isovolumic pressure; ECG, left ventricular epicardial bipolar electrocardiogram; E\(_{\text{max}}\), contractility index of a beat of interest, obtained as peak isovolumic pressure divided by isovolumic volume minus unstressed volume (V\(_0\)). V\(_0\) was obtained in regular beats by decreasing ventricular volume until peak isovolumic pressure became zero. RR\(_1\), preceding beat interval; RR\(_2\), beat interval immediately preceding RR\(_1\); RR\(_3\)–6, beat intervals preceding RR\(_2\). B: postextrasystolic potentiation of the first postextrasystolic beat (PES1) following an extrasystole (ES). PES1, first postextrasystolic beat interval, which is equivalent to RR\(_1\) as viewed from PES1; ESI, extrasystolic beat interval, which is equivalent to RR\(_2\) as viewed from PES1; RI, regular beat intervals.

A

![Diagram](http://image.com)

B

![Diagram](http://image.com)

**Fig. 1.** Experimentally observed curves and definitions of variables. A: irregular arrhythmia during experimentally produced atrial fibrillation in excised cross-circulated canine hearts. Atrium was continuously stimulated by 20-Hz alternative current. LVP, left ventricular peak isovolumic pressure; ECG, left ventricular epicardial bipolar electrocardiogram; E\(_{\text{max}}\), contractility index of a beat of interest, obtained as peak isovolumic pressure divided by isovolumic volume minus unstressed volume (V\(_0\)). V\(_0\) was obtained in regular beats by decreasing ventricular volume until peak isovolumic pressure became zero. RR\(_1\), preceding beat interval; RR\(_2\), beat interval immediately preceding RR\(_1\); RR\(_3\)–6, beat intervals preceding RR\(_2\).

**RESULTS**

Figure 3 shows simulation results of a representative set of changes in RR\(_1\) and RR\(_1\)/RR\(_2\) as a function of beat number (Fig. 3A and B, respectively) and the correlogram between RR\(_1\) and RR\(_2\) (Fig. 3C) over 100 consecutive arrhythmic beats. Although RR\(_2\) changes are not shown, they were essentially the same as the RR\(_1\) changes except that the beat number was lagged by one; any RR\(_1\) was RR\(_2\) in the next beat by definition. The changes in RR\(_1\) and RR\(_2\) were irregular by mathematical randomization, as seen by the lack of significant correlation in the correlogram, which is called a Lorenz plot (Refs. 10, 12; Fig. 3C). As the result, RR\(_1\)/RR\(_2\) changed widely and randomly. We judged this arrhythmia to have reasonably simulated the irregular arrhythmia in our previous experimental AF (26), although correlation between RR\(_1\) and RR\(_2\) may not always be nil in reality (10, 12). However, this difference would not have influenced the consequent results (see DISCUSSION).

In Fig. 3, the range of RR\(_1\) or RR\(_2\) was 0.3–0.9 s with a mean of 0.6 s. Similar results were obtained for other ranges including 0.3–0.5 s (mean 0.4 s) and 0.4–2.3 s (mean 1.35 s) as described in Fig. 7. Figure 4 shows simulation results using the same RR\(_1\) and RR\(_2\) data shown in Fig. 3. The correlogram between nE\(_{\text{max}}\) of the irregular arrhythmic beats and their RR\(_1\) (Fig. 4A) shows a positive and significant correlation with a correlation coefficient (r) of 0.469 (P < 0.05). The correlogram between nE\(_{\text{max}}\) of the irregular arrhythmic beats and their RR\(_2\) (Fig. 4B) shows a negative and significant correlation, with r = −0.657 (P < 0.05). Figure 4C shows the sequential changes in nE\(_{\text{max}}\) over this series of 100 irregular arrhythmic beats. These contractility changes were random in a similar manner to RR\(_1\), RR\(_2\), or RR\(_1\)/RR\(_2\) shown in Fig. 3, A and B.
Despite these random changes, the correlogram between the normalized contractilities of these arrhythmic beats and their RR1/RR2 (Fig. 4D) showed a significant positive correlation (r = 0.955, P < 0.001). Moreover, the data points at or near RR1/RR2 = 1 fell on or close to unity nE max, as we reported recently in canine LV (26).

Figure 5 illustrates the potentiation curve, G · \exp[−(RR2 − t_1/\tau)] + H, as a function of RR2; the restitution curve, 1 − \exp[−(RR1 − t_2/\tau)], as a function of RR1; and their product as a function of RR1 = RR2 (hence RR1/RR2 = 1). This product is the PESP as a function of RR1 = RR2. G, H, t_1, t_2, and \tau for these simulated curves were the same as those used for the standard case shown in Figs. 3 and 4. RR1 and RR2 changed between 0.3 and 0.9 s around a mean of 0.6 s. When RR1 = RR2 = 0.6 s, there was no restitution and potentiation and hence nE max after RR1 = RR2 = 0.6 s was unity as shown by the horizontal line at the height of unity nE max. The solid curve shows nE max of an arrhythmic beat as a function of RR1 = RR2. It passed through the unity level at RR1 = RR2 = 0.6 s. It increased as RR1 = RR2 increased from 0.2 to 0.4 s and rolled off thereafter at or very close to the unity level. This indicates that normalized contractilities of arrhythmic beats were equal or close to unity at any RR1 = RR2 over its wide range between 0.4 and at least 1.2 s. We confirmed the generality of this characteristic as described below.

Figure 6 shows six graphs, similar to Fig. 5, with different G values ranging from 0.5 to 3 at intervals of 0.5. While G increased from 0.5 to 1.5 (Fig. 6, A–C), the nE max curve of arrhythmic beats increased to unity with increasing RR1 = RR2 from 0.2 to 0.6 s. While G further increased from 2 to 3 (Fig. 6, D–F), the nE max curve more steeply increased to unity although the curve slightly overshot with increasing RR1 = RR2 from 0.2 to 0.6 s and then gradually decayed below unity. Taken together, nE max of arrhythmic beats was always equal or very close to unity as long as the values for RR1 = RR2 moved between 0.3 and 0.9 s over the wide range of G. The representative G = 1.7, which was obtained physiologically (27) and hence used in our
The present results have shown that Eq. 1 can reasonably well simulate our previous observation in experimental AF (26). This indicates that the underlying mechanism of the reasonably linear relation between $nE_{\text{max}}$ and RR1/RR2 that we observed experimentally (26) would primarily be a manifestation of the well-known mechanical restitution and potentiation or more generally the interval-force relation (2, 25, 27). Moreover, the results have also shown that the beat intervals (RR3–6) preceding RR1 and RR2 little affect $E_{\text{max}}$ of an arrhythmic beat of interest in AF.

The present simulation has also shown that, at any range and mean values of arrhythmic beat intervals, their mean $nE_{\text{max}}$ virtually coincides with the unity $nE_{\text{max}}$ of regular beats whose RI is equal to mean RR1 (= mean RR2). This is interesting because we simply fixed G at 1.7 and H at 1.0 in the standard cases of simulation where RI was fixed at 0.6 s (Figs. 3–6). These G and H values were taken from the report in which RI was kept at 0.46 s (27). Although we changed G widely (Fig. 6), $nE_{\text{max}}$ not only at the given RI of 0.6 s but also at other RR1 (= RR2) values fell on or very close to the unity $nE_{\text{max}}$.

It should be noted that the heavy solid curves in Figs. 5, 6, and 7, A–C, are a function of RR1 and RR2 in a specific condition such as RR1 = RR2 but are not a function of arbitrarily changing RR1 and RR2. The plotted data points in Fig. 7, D–F, indicate that $nE_{\text{max}}$ varies from unity when RR1 and RR2 change independently of each other and hence RR-to-RR2 ratio deviates from unity. Figure 7, D–F, also indicates that scattering of $nE_{\text{max}}$ at a given RR1/RR2 decreases with narrowing of the range of RR1 and RR2. Because the average R-R was ~0.35 s and the range of the R-R was 0.25–0.60 s in our previous experiments (26), Fig. 7F seems closest to reality. Whether and how closely Fig. 7, D and E, simulates reality remain to be experimentally studied.

The high correlation between $nE_{\text{max}}$ and RR1/RR2 (26) is outstanding among documented correlations between a variety of cardiodynamic and beat interval variables, which are generally low whether significant or insignificant (4, 6–8, 13, 14). This most unique $nE_{\text{max}}$-RR1/RR2 relation is now found to be a manifestation of the mechanical restitution and potentiation that
Fig. 6. Normalized contractility and its components as a function of beat interval (RR1, RR2) for different values of $G$ in potentiation term of equation. $G$ was increased from 0.5 (A) to 1.0, 1.5, 2, 2.5, and 3.0 (B–F). Each panel draws restitution and potentiation curves as functions of RR1 and RR2, respectively, and their product curve as a function of $RR1 = RR2$ (in s) (hence $RR1/RR2 = 1$). $H = 1; t_1 = t_2 = 0.2 \text{s}; \tau = 0.18 \text{s}$.

Fig. 7. Correlograms between normalized contractility of arrhythmic beat and RR1/RR2 (A, C, and E) and normalized contractility and its components as a function of RR1 and RR2 (B, D, and F) for different working ranges of RR1 and RR2. RR1 was given by $0.3 + 0.2 \text{RR}(i)$ in A and B, $0.3 + 0.9 \text{RR}(i)$ in C and D, and $0.3 + 0.2 \text{RR}(i)$ in E and F. B, D, and F show restitution and potentiation curves as functions of RR1 and RR2, respectively, and their product curve as a function of $RR1 = RR2$ (hence $RR1/RR2 = 1$).
are known to be the basic characteristics of myocardial contraction (13, 27).

An interesting use of Eq. 1 would be a simulation of LV pump performance in AF in the cardiovascular system model (19, 20). Such a simulation would facilitate better understanding of the factors (range and mean of arrhythmic heart rate, changes in venous return, end-diastolic volume, afterload pressure, etc.) that have been suspected to be responsible for decreased cardiac output in AF (3, 11).

Equation 1 was based on physiological experiments on normal canine hearts (27). Qualitatively the same mechanical restitution and potentiation phenomena have been obtained in human hearts (6–8, 13, 14). Therefore, we expect that essentially the same results as the present simulation would occur in human hearts.

However, we do not know yet whether the same results as the present simulation would occur even in pathological hearts. The generality of the $E_{\text{max}}$ RR1/RR2 relation remains to be studied in patients.

We only assumed $E_{\text{max}}$ to be a function of RR1 and RR2. Therefore, we could simulate isovolumetric contractions. However, we already know that $E_{\text{max}}$ is slightly affected by ejecting activation and deactivation (16, 21–23). This mechanism may partly underlie the scattering of the $E_{\text{max}}$-RR1/RR2 relation in ejecting contractions (26). In this respect, the generality of the $E_{\text{max}}$-RR1/RR2 relation also remains to be studied in patients.

Although we attribute the contractility-RR1/RR2 relation to the mechanical restitution and potentiation, we do not discuss any deeper intracellular mechanism here (25, 27). This aspect is beyond the scope of the present simulation.

A limitation of the present result may exist in its application to irregular beats in diseased hearts, in which intraventricular conduction pathway is abnormal. For such an application, one should first study empirically whether the relatively unique relation found in our previous study (26) exists between $E_{\text{max}}$ and RR1/RR2. One should also confirm the results observed by Yue et al. (27) in the normal canine heart model, on which Eq. 1 is based, in such diseased hearts.

We conclude that the relatively unique contractility-RR1/RR2 relation that we recently discovered (26) could be reasonably well simulated mathematically by a combination of the known mechanical restitution and potentiation. This strongly suggests that these basic myocardial contractile properties are primarily responsible for the beat-to-beat changes in LV contractility of irregular arrhythmic beats in AF.

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