Slow rate during AF improves ventricular performance by reducing sensitivity to cycle length irregularity

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The major aim of this study was to assess the role of the cycle length irregularity on ventricular performance during AF by studying the relationships between several hemodynamic parameters: maximal LV (LVmax) power, the minimum of the first derivative of LV pressure (dP/dtmin), and the time constant of isovolumic pressure decay (τ) and the ratio RRp/RRpp during various underlying average ventricular rates. We applied nonlinear estimation methods to determine the LV performance-interval relationships.

METHODS

The study was approved by the Institutional Animal Research Committee and is in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Terminology. The ventricular cycle length (VCL) is the time interval between two consecutive ventricular depolarizations. It can be measured between the QRS complexes of the surface ECG or by the use of electrical signals recorded directly from the ventricles. In this study, an individual VCL was determined as the R-R interval between two consecutive ventricular depolarizations. In this study, an individual VCL was determined as the R-R interval between two consecutive ventricular depolarizations. In this study, an individual VCL was determined as the R-R interval between two consecutive ventricular depolarizations.

During regular rhythm there is a simple relationship between the constant VCL and the heart rate (HR), namely, HR (beats/min) = 60,000/VCL (ms). However, because the VCL changes from beat to beat (especially during AF), only an average HR can be determined based on the average VCL of a large number of beats. According to the above equation, a prolongation of the average VCL is equivalent to a slowing of the average HR. In the following text, we will quantify the changes in the HR by using the parameter (average) VCL.
Accordingly, its irregularity will be measured as a ratio of two consecutive R-R cycle lengths (see subsequent text).

**Surgical preparation.** The study procedures have been previously described (29, 32). The study was performed using 10 healthy open-chest dogs. Briefly, anesthesia was maintained with 1–2% isoflurane, with monitoring of volume status, arterial blood gases, and body temperature. Subcutaneous needle electrodes obtained a standard ECG. Custom-made quadripolar Ag-AgCl plate electrodes were sutured to the high right atrium and right ventricular apex for recording local electrical activity. Similar bipolar plate electrodes were sutured to two epicardial fat pads that contain para-sympathetic (vagal) neural pathways selectively innervating the sinus node and the AV node (23). A Millar catheter was inserted through the left carotid artery and advanced into the left ventricle for pressure measurements. A flowmeter probe (model 16A/20A, HT 207, Transonic Systems; Ithaca, NY) was placed around the ascending aorta. All signals were amplified, displayed, and stored on a dedicated recording system (CardioLab, GE Marquette Medical Systems).

**Study protocol.** After the recording of the hemodynamics at normal sinus rhythm, AF was induced by rapid right atrial pacing (20 Hz, 1 ms) and was further maintained by subthreshold stimulation (20 Hz, 50 μs) of the sinus node fat pad located near the right upper pulmonary vein-atrial junction (23). In several cases, AF was maintained simply by continuing the rapid right atrial pacing.

The following four steps were then performed in each experiment. In step 1, after the hemodynamics stabilized for a minimum of 15 min, data were recorded during “fast” AF. The term fast is used to stress that this was the step with the fastest ventricular rate (or the shortest VCL) in each animal, which was observed before any modifications of the rate were attempted.

In steps 2–4, while the atria continued to fibrillate, three longer average VCLs were achieved by graded AV nodal vagal stimulation. For quantitative purposes, these VCLs were expressed as a percentage from the spontaneous sinus cycle length (SCL) in each animal. Because the average VCL observed during fast AF was only 58 ± 5% of SCL, the three longer VCL were chosen as 75%, 100%, and 125% of the SCL (29).

The computer-controlled vagal stimulation consisted of brief bursts of current impulses synchronized with the ECG (Fig. 1) and was applied onto the fat pad located at the left atrium-inferior vena cava junction (23). This epicardial structure contains vagal pathways to the AV node and its activation produces selective dromotropic effects and a slowing of the rapid right atrial pacing. The brief artefacts seen after each ECG complex are produced by the selective atrioventricular (AV) node fat pad vagal stimulation. ECG, surface electrocardiogram; RVE, right ventricular endomyocardium; LVP, LV pressure; AoF, aortic flow.

Fig. 1. The hemodynamic measurements for each individual ventricular beat [e.g., current left ventricular (LV) response] were correlated with the durations of two ventricular cycle lengths (VCL). RRp is the R-R duration of the preceding VCL, whereas RRpp is the R-R duration of the prepreceding VCL. These intervals were measured between the upstrokes of the electrograms recorded from the right ventricular apex. The brief artefacts seen after each ECG complex are produced by the selective atrioventricular (AV) node fat pad vagal stimulation. ECG, surface electrocardiogram; RVE, right ventricular electrogram; LVP, LV pressure; AoF, aortic flow.

peak LV pressure and expressed in watts (2). Second, peak relaxation was characterized by dP/dtmin. Finally, the time course of relaxation was characterized by τ. It was calculated by fitting the pressure-time data (from the point of dP/dtmin to LV pressure 5 mmHg higher than next LV end-diastolic pressure) to the equation (24)

\[
P(t) = (P_0 - P_b) \times e^{-\frac{t}{\tau}} + P_b
\]

where \(P_0\) is the pressure decay asymptote, \(P_b\) is the pressure at dP/dtmin, and \(t\) is a time at \(P(t)\) referenced to time of dP/dtmin occurrence. An interval of >25 ms was considered necessary to calculate \(\tau\).

We measured the duration of each VCL electronically by using the electrograms recorded at the right ventricular apex, as the time interval R-R (in ms) between the upstrokes (maximum first derivative) of two consecutive responses. The VCL irregularity was expressed as a ratio of two consecutive R-R intervals. As shown in Fig. 1, for each ventricular beat (e.g., current LV response in Fig. 1) two characteristic cycle lengths were determined. RRp is the cycle length immediately preceding the analyzed beat. RRpp is the prepreceding one. The ratio RRp/RRpp was used in subsequent calculations related to the analyzed beat (see below).

The parameter RRp/RRpp has been previously used to estimate the average values of hemodynamic parameters during AF. However, only linear regressions have been considered (26, 27). In the present study, the relationship between \(LV_{\text{max}}\) power or \((dP/dt_{\text{min}})\) and RRp/RRpp was modeled by the following nonlinear equation

\[
LV_{\text{power}} = -dP/dt_{\text{max}} = R_{\text{max}} \times \left[1 - e^{(RRp/RRpp-min - RRp/RRpp)} \times C\right]
\]

where \(R_{\text{max}}\) is a maximum response (plateau of the relationship), RRpp/RRpp-min is minimum RRpp/RRpp at which aortic flow could still be observed, and \(C\) is the curvature of the relationship.

Similarly, the relationship between \(\tau\) and RRp/RRpp was fitted to the equation

\[
\text{AJP-Heart Circ Physiol} \bullet \text{VOL} 283 \bullet \text{DECEMBER} 2002 \bullet \text{www.ajpheart.org}
\]
\[ \tau = (\tau_{\text{max}} - \tau_{\text{min}}) \times e^{\frac{\text{RRp}/\text{RRpp min} - \text{RRp}/\text{RRpp}_{\text{VC}}}{\text{RRp}/\text{RRpp}_{\text{VC}}}} + \tau_{\text{min}} \quad (2) \]

where \( \tau_{\text{max}} \) is maximum \( \tau \), \( \tau_{\text{min}} \) is minimum \( \tau \) (plateau of the relationship), and \( \text{RRp}/\text{RRpp}_{\text{min}} \) is the minimum \( \text{RRp}/\text{RRpp} \) at which \( \tau \) could be determined.

**Comparison of LV max power and contractility index \( E_{\text{max}} \).** Because LV max power is preload dependent (11) and therefore is not an optimal contractility index, we compared it to the theoretical normalized maximal elastance \( (E_{\text{max}}) \) the slope of LV end-systolic pressure volume relationships to evaluate how close the two indexes were correlated in the framework of the present experimental model. We used the equation derived by Yue et al. (31) that has been previously validated in a numerical simulation of contractility in AF (26) and calculated the normalized \( E_{\text{max}} \) from actual \( \text{RRp} \) and \( \text{RRpp} \) intervals in six randomly picked data sets. The normalized \( E_{\text{max}} \) was then compared by linear regression to the LV max power measured in the same data sets.

We also determined the relationship between the normalized \( E_{\text{max}} \) and \( \text{RRp}/\text{RRpp} \) during fast AF and when the VCL was prolonged to 125% SCL.

**Statistical analysis.** Data are represented as means \( \pm \) SD. The presence of nonlinear components in LV performance – \( \text{RRp}/\text{RRpp} \) relationships was confirmed in six randomly chosen data sets. For this purpose, after initial simple linear regression analysis, a fourth-order polynomial equation was fitted to the residuals.

The impact of VCL prolongation on the parameters in Eqs. 1 and 2 (i.e., C, plateau, and \( \text{RRp}/\text{RRpp}_{\text{min}} \)) was tested by one-way repeated-measures ANOVA, followed by Huynh-Feldt correction or with Friedman ANOVA if a strong violation of sphericity or variance homogeneity assumptions was observed.

The \( C \) of the three hemodynamic parameters (\( \text{LVmax} \) power, \( \text{dP/dt}_{\text{min}} \), and \( \tau \)) was compared by two-way repeated-measures ANOVA, followed by contrast analysis. A \( P \) value of \(<0.05 \) was considered significant.

**RESULTS**

**Comparison of theoretical normalized \( E_{\text{max}} \) and \( \text{LVmax} \) power.** The coefficients of correlation between the normalized \( E_{\text{max}} \) and the \( \text{LVmax} \) power in six evaluated data sets ranged from 0.86 to 0.92 (\( P < 0.0001 \) for all). However, as shown in Fig. 2, the \( \text{LVmax} \) power underestimated the normalized \( E_{\text{max}} \) when \( E_{\text{max}} \) values were <0.75.

As shown in Fig. 3, the relationship between the theoretical normalized \( E_{\text{max}} \) and \( \text{RRp}/\text{RRpp} \), the ratio calculated from R-R intervals in a representative experiment. Data obtained during fast atrial fibrillation (AF) are shown with solid circles and fitted with a red trace. Data obtained during prolongation of the average VCL to 125% of the normal sinus cycle length (SCL) are shown with open triangles and fitted with a blue trace.

**Global characterization of LV performance parameters during AF at various average VCL.** The parameters characterizing the ventricular rate and its variance in the studied animals are shown in Table 1. The average VCL during fast AF (285 \( \pm \) 54 ms) was 58% of the intrinsic SCL (489 \( \pm \) 81 ms). During vagal-induced slowing, average VCL was prolonged to 371 \( \pm \) 62 ms (75% SCL), 486 \( \pm \) 81 ms (100% SCL), and 601 \( \pm \) 91 ms (125% SCL), respectively. In an average animal, the standard deviation of both the VCL and the ratio \( \text{RRp}/\text{RRpp} \) showed a tendency to increase during vagal nerve stimulation.

To illustrate the impact of VCL prolongation on LV performance, in Fig. 4 the measured values for each of the hemodynamic parameters in a typical animal are presented in the scatterogram format of Lorenz (or Poincaré) plots (1, 10, 16). Briefly, each point in the Lorenz plot has as an \( x \)-coordinate the “current beat” value of a parameter and as a \( y \)-coordinate the “preceding beat” value of same parameter. The Lorenz plots permit an easy and fast evaluation of tendencies, as well as some quantification of the properties of distribution. Thus it can be seen that prolongation of the average VCL (from fast AF to 125% SCL) produced

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**Fig. 2.** Relationship between the theoretical normalized maximal elastance \( (E_{\text{max}}) \) and the maximal LV power \( (\text{LVmax} \text{ power}) \) in a representative experiment. The linear regression line indicates a close correlation \( (r = 0.91, P < 0.0001) \).

**Fig. 3.** Relationship between the theoretical normalized \( E_{\text{max}} \) and \( \text{RRp}/\text{RRpp} \), the ratio calculated from R-R intervals in a representative experiment. Data obtained during fast atrial fibrillation (AF) are shown with solid circles and fitted with a red trace. Data obtained during prolongation of the average VCL to 125% of the normal sinus cycle length (SCL) are shown with open triangles and fitted with a blue trace.
uniformed changes in all studied parameters. First, the original “clouds” present during fast AF (Fig. 4, left) were transformed into progressively more tightly packed groups, indicating less variable LV$_{\text{max}}$ power, dP/d$t_{\text{min}}$, and $\tau$. Quantitatively, this resulted in a smaller scattering index $S$ for longer VCL (8). Second, the scatterogram mean (red dots) indicated that with longer VCL there was an increase in LV$_{\text{max}}$ power and dP/d$t_{\text{min}}$, whereas $\tau$ decreased. For example, the proportion of the beats with LV$_{\text{max}}$ power $< 1$ dropped from 50.4% (during fast AF) to 5.3% (at VCL = 125% SCL).

Nonlinear relationship between LV performance parameters and RR$_{p}$/RR$_{pp}$ at various average VCL. The above scatterograms do not permit quantification of the role of the cycle length irregularity. For that purpose, we determined the nonlinear relationships between LV performance parameters (LV$_{\text{max}}$ power, dP/d$t_{\text{min}}$, and $\tau$) and RR$_{p}$/RR$_{pp}$. Figure 5 illustrates the results obtained in one representative experiment. The regression lines for each level of VCL are shown along with the raw data points. Figure 5, E, J, and O, contain the four superimposed regression lines for each parameter, respectively.

As shown in Fig. 5, A–E, for the LV$_{\text{max}}$ power, during VCL prolongation the plateau, the RR$_{p}$/RR$_{pp}$min, and $C$ progressively decreased ($P < 0.0001$ for all three parameters). The combined result of these changes was an increasing value of LV$_{\text{max}}$ power at RR$_{p}$/RR$_{pp}$ = 1, shown with the prolongation of VCL (Table 2, $P < 0.0001$).

Similarly, as shown in Fig. 5, F–J, for the parameter dP/d$t_{\text{min}}$, during VCL prolongation the plateau, the RR$_{p}$/RR$_{pp}$min, and $C$ progressively decreased ($P < 0.04$ for all three parameters). Again, this resulted in a

### Table 1. Characteristics of ventricular time intervals

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Mean VCL, ms</th>
<th>Mean SD of VCL, ms</th>
<th>Mean RR$<em>{p}$/RR$</em>{pp}$</th>
<th>Mean SD of RR$<em>{p}$/RR$</em>{pp}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous sinus rate</td>
<td>489</td>
<td>2</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Fast AF</td>
<td>285</td>
<td>50</td>
<td>1.02</td>
<td>0.21</td>
</tr>
<tr>
<td>AF with VCL, 75% SCL</td>
<td>371</td>
<td>80</td>
<td>1.04</td>
<td>0.30</td>
</tr>
<tr>
<td>AF with VCL, 100% SCL</td>
<td>486</td>
<td>112</td>
<td>1.06</td>
<td>0.39</td>
</tr>
<tr>
<td>AF with VCL, 125% SCL</td>
<td>601</td>
<td>120</td>
<td>1.07</td>
<td>0.38</td>
</tr>
</tbody>
</table>

The mean of 500 ventricular cycle lengths (VCL) and their standard deviations were measured in 10 animals. AF, atrial fibrillation; RR$_{p}$/RR$_{pp}$, ratio of preceding and prepreceding R-R intervals; SCL, spontaneous cycle length. The characteristics were observed during spontaneous sinus rate, fast AF, and AF with vagally induced prolongation of the average VCL to 75%, 100%, and 125% of the SCL. Irregularity was defined by the ratio of two consecutive intervals of RR$_{p}$/RR$_{pp}$, and the mean and SD of 500 RR$_{p}$/RR$_{pp}$ was measured in each animal.
larger absolute value of $dP/dt_{\min}$ at $RR_p/RR_{pp} = 1$ with longer VCL (Table 3, $P < 0.0001$).

Finally, as shown in Fig. 5, $K-O$, for $\tau$, during VCL prolongation the plateau and the C did not change (Table 4, $P = 0.08$ and 0.1, respectively). However, $\tau$ at $RR_p/RR_{pp} = 1$ still decreased, i.e., the relaxation improved (Table 4, $P < 0.0001$). This was due to a leftward shift of $\tau - RR_p/RR_{pp}$ relations at longer VCL (Fig. 5O).

There was a highly significant difference in $C$ between the three LV performance parameters ($P < 0.0001$). In particular, the $C$ for $LV_{max}$ power was larger than for $dP/dt_{\min}$ and $\tau$ ($P = 0.003$ for both vs. LV maximal power).

### Table 2. Parameters characterizing nonlinear relationship $LV_{max}$ power $- RR_p/RR_{pp}$ during AF

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Plateau, W</th>
<th>Minimum $RR_p/RR_{pp}$</th>
<th>Curvature $C$</th>
<th>$LV_{max}$ Power, W at $RR_p/RR_{pp} = 1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast AF</td>
<td>22,909 ± 29,905*</td>
<td>0.78 ± 0.09*</td>
<td>3.308 ± 4398*</td>
<td>1.5 ± 0.6*</td>
</tr>
<tr>
<td>AF with VCL, 75% SCL</td>
<td>15.3 ± 10.2*</td>
<td>0.65 ± 0.09*</td>
<td>2.21 ± 1.87*</td>
<td>2.3 ± 0.9*</td>
</tr>
<tr>
<td>AF with VCL, 100% SCL</td>
<td>7.2 ± 2.9*</td>
<td>0.50 ± 0.11*</td>
<td>1.01 ± 0.57*</td>
<td>2.9 ± 1.1*</td>
</tr>
<tr>
<td>AF with VCL, 125% SCL</td>
<td>5.0 ± 1.8*</td>
<td>0.42 ± 0.11*</td>
<td>0.63 ± 0.31*</td>
<td>3.0 ± 0.9*</td>
</tr>
</tbody>
</table>

Values are means ± SD. LV, left ventricular. Parameters characterize the nonlinear relationship $LV_{max}$ power $- RR_p/RR_{pp}$ during fast AF and during AF with the three prolonged average VCL. *$P < 0.001$ applies for the difference between the reported four values in each column.
anistically its beat-to-beat irregularity is governed in part by the effects of restitution and potentiation (26). While both of these effects depend nonlinearly on the RRp and RRpp coupling intervals (31), a unique linear relationship has been described between contractility and the RRp/RRpp (26). In fact, we have proposed a similar linear relationship as a tool for evaluation not only of contractility but also for assessment of a broader selection of hemodynamic parameters during AF (27).

The present study extends previous observations by elucidating the role of the prevailing average ventricular rate (or average VCL) during AF and by defining the relaxation-interval relationships during AF. In particular, we established that nonlinear dependence on the RRp/RRpp better describes ventricular performance, especially during longer average VCL, and thus provided a more comprehensive explanation for the benefits of the slowed ventricular rate during AF.

Assessment of LV mechanical performance and relaxation during AF. Evaluating cardiac contractility during AF is still problematic in view of the absence of a standard approach. The maximum rate of change of the LV pressure (+dP/dtmax) has been frequently used to evaluate cardiac contractility during AF (28), although its usefulness is limited by beat-to-beat variations in preload. The LV maximal elastance (E_max, the slope of end-systolic pressure-volume relationships) is frequently referred to as the “gold standard” measure of cardiac contractility (12). This parameter is preload independent, but its determination requires the generation of a family of stable pressure-volume loops while varying the diastolic filling. The determination of an accurate E_max during AF is therefore associated with significant difficulties (30) and a model-derived theoretical normalized E_max (26, 31), has been proposed as an approximation.

In this study, we found a good correlation between LV_max power and the normalized E_max calculated as a function of the RRp and RRpp intervals, using the equation derived by Suzuki et al. (26) and Yue et al. (31). As shown in Fig. 2, these two variables were closely and positively correlated. Furthermore, we also demonstrated that both the experimentally measured LV_max power (Fig. 5) and the calculated normalized E_max (Fig. 3) exhibit a nonlinear dependence on the ratio RRp/RRpp. Despite these similarities, however, the present data establish only the LV_max power as a practically convenient index of LV mechanical performance during AF, rather than as a surrogate of E_max.

In accordance with previous studies by Prabhu and Freeman (18–20), we used both τ and dP/dt_min as relaxation parameters. While both parameters showed nonlinear behavior with a “plateau” (Fig. 5), the latter was more pronounced for τ. A possible explanation for this observation is that values for this parameter had a distribution that was highly skewed to the left.

Irregularity ratio RRp/RRpp as predictor of cardiac performance during AF. It has been well established that the varying contractile function during AF depends on the complex interaction of mechanisms that are triggered by changes in both volume and interval. The former refers to the Frank-Starling relationship (14), which predicts that increased venous return (and thus end-diastolic volume) would produce greater stroke volume during the next heart cycle. However, the precise molecular mechanisms governing the Frank-Starling relationship (17) and its involvement during AF remain unclear (7, 9).

On the other hand, cardiac performance in a given beat during AF depends also on the particular time sequence of several preceding beats (30). However, a good approximation is achieved by taking into account just the RRp and the RRpp intervals underlying the mechanisms of mechanical restitution and potentiation, respectively (31). Both canine (30) and human (3) studies found that RRp and RRpp were the predominant predictors of contractility in AF.

Recently, several investigators (26, 30) noted that, in addition to RRp and RRpp, the ratio RRp/RRpp is a strong predictor of LV performance during AF. In particular, a linear relationship between LV systolic parameters and the ratio RRp/RRpp has been reported.

### Table 3. Parameters characterizing nonlinear relationship dP/dt_min – RRp/RRpp during fast AF and during AF with three prolonged-average VCL

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Plateau, mmHg/s</th>
<th>Minimum RRp/RRpp</th>
<th>Curvature C</th>
<th>dP/dt_{min}, mmHg/s at RRp/RRpp = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast AF</td>
<td>-2.614 ± 1.265*</td>
<td>0.59 ± 0.16†</td>
<td>0.76 ± 0.45†</td>
<td>-1.015 ± 341†</td>
</tr>
<tr>
<td>AF with VCL, 75% SCL</td>
<td>-2.241 ± 0.787*</td>
<td>0.55 ± 0.10†</td>
<td>0.45 ± 0.11†</td>
<td>-1.490 ± 488§</td>
</tr>
<tr>
<td>AF with VCL, 100% SCL</td>
<td>-1.929 ± 0.612*</td>
<td>0.43 ± 0.08†</td>
<td>0.32 ± 0.14†</td>
<td>-1.553 ± 470§</td>
</tr>
<tr>
<td>AF with VCL, 125% SCL</td>
<td>-1.710 ± 0.390*</td>
<td>0.40 ± 0.07†</td>
<td>0.21 ± 0.09†</td>
<td>-1.577 ± 309§</td>
</tr>
</tbody>
</table>

Values are means ± SD. dP/dt_{min}, minimum of the first derivative of LV pressure. P values apply for the difference between the reported four values in each column. *P = 0.04; †P < 0.007; §P < 0.0001.

### Table 4. Parameters characterizing the nonlinear relationship τ – RRp/RRpp during fast AF and during AF with three prolonged-average VCL

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Plateau, ms</th>
<th>Curvature C</th>
<th>τ, ms at RRp/RRpp = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast AF</td>
<td>19 ± 45</td>
<td>0.36 ± 0.31</td>
<td>76 ± 25*</td>
</tr>
<tr>
<td>AF with VCL, 75% SCL</td>
<td>29 ± 15</td>
<td>0.30 ± 0.09</td>
<td>67 ± 19*</td>
</tr>
<tr>
<td>AF with VCL, 100% SCL</td>
<td>33 ± 9</td>
<td>0.27 ± 0.16</td>
<td>55 ± 11*</td>
</tr>
<tr>
<td>AF with VCL, 125% SCL</td>
<td>40 ± 9</td>
<td>0.16 ± 0.05</td>
<td>47 ± 13*</td>
</tr>
</tbody>
</table>

Values are means ± SD. τ, time constant of relaxation. *P < 0.0001 applies for the difference between the reported four values in last column.
Moreover, it was demonstrated that values at \(RR_p/RR_{pp} = 1\) in the linear regression lines can estimate the average values of various parameters (Doppler stroke volume, ejection fraction, peak aortic flow rate, and \(+dP/dt_{max}\) during AF (27).

Nonlinear relationship between ventricular performance and \(RR_p/RR_{pp}\) ratio during AF. In view of the nonlinear dependence of both the restitution and the \(RR_p/RR_{pp}\) intervals, respectively, the previously reported existence of a linear relationship between a number of systolic left ventricular performance parameters during AF and the ratio \(RR_p/RR_{pp}\) appears somewhat surprising (26, 27, 30).

However, our mathematical modeling (Fig. 3) and careful inspection of the data by Yue et al. (31) suggest that this linearity holds true only for a certain range of average VCL during AF. The simple linear equation used for description of the force-interval relations during fast AF may be inadequate if the average R-R interval during AF is prolonged. Such prolongation, of course, is not just an experimental utility. It is a major therapeutic goal during treatment of patients with AF (15).

Our experimental data showed that the normalized theoretical \(E_{max}\) (31), as well as all measured LV performance parameters deviated from linear dependency on \(RR_p/RR_{pp}\) with prolongation of the VCL (Fig. 5). The curvilinear effects were less noticeable during fast AF (Fig. 5, A, F, and K), and were progressively accentuated as the cycle length was prolonged to 75% (Fig. 5, B, G, and L), 100% (Fig. 5, C, H, and M), and 125% (Fig. 5, D, I, and N) of the spontaneous SCL. Our data also showed that all hemodynamic parameters estimated at \(RR_p/RR_{pp} = 1\) exhibited an improvement when the VCL was prolonged (Fig. 5, E, J, and O). This resulted from the combined effect of the VCL prolongation on the plateau, \(C\), and position of the studied relationships (Tables 2–4).

Finally, the relaxation-interval relationships were more curvilinear than the \(LV_{max}\) power-interval relationship (Tables 1 and 4, Fig. 5). This confirms previous observations that extrasystolic relaxation restitution is faster (more curvilinear) than the mechanical one (18).

Clinical implications and limitations. Our findings suggest that in patients with AF and controlled slower average ventricular rates (e.g., by appropriate pharmacological agents, such as \(\beta\)-blockers, Ca\(^{2+}\) channel blockers, or adenosine), the clinical benefit of AF conversion with subsequent regularization of the rate may be relatively small. Such a speculation is further supported by recent clinical studies that found that rate control is more important than rhythm regularization for improving quality of life and exercise capacity in patients with permanent AF (15). We should stress, however, that our experiments were performed on anesthetized open-chest dogs, which precludes direct clinical extrapolation.

To describe the characteristics of the observed nonlinear components for multiple parameters, we used simple exponential equations, which are widely used in the assessment of biological processes. However, no specific physiological correlates of our monoequivalent fitting parameters were given, and possibly, another model may better reflect intrinsic organ behavior, especially in humans.

In conclusion, our data imply that ventricular rate has a major impact on curvilinearity of \(LV_{max}\) power and relaxation-interval relationships. A computer simulation indicating similar behavior of contractility index \(E_{max}\) strengthens this observation. These findings may have a major implication in assessing novel AF treatment strategies, based on controlled slowing of the ventricular rate (29, 32).

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