*Left Ventricular Function*

# Left Ventricular Systolic Function is Sensitive to Cycle-Length Irregularity in Patients with Atrial Fibrillation and Systolic Dysfunction

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***Background:*** Left ventricular (LV) systolic function during atrial fibrillation (AF) is positively correlated with an index of ventricular cycle-length irregularity, the ratio of preceding R-R interval to pre-preceding R-R interval ($RR_p/RR_{pp}$). This study was designed to elucidate the relationship between the $RR_p/RR_{pp}$ ratio and LV function, and to identify factors which influence the relationship.

***Methods:*** Beat-to-beat variation of LV function was determined by biplane Simpson's ejection fraction (EF) over 20 beats in 120 patients with chronic AF. The relationship of normalized EF (y) versus the $RR_p/RR_{pp}$ ratio (x) were analyzed by the regression equation $y = a + bx$. The relation-slope b describes the steepness of the relationship and is a measure of the sensitivity of LV function to ventricular cycle-length irregularity.

***Results:*** Mean EF and mean heart rate were factors affecting the relation slope. Negative correlations between mean EF and the relation slope were similarly present at faster heart rates (≥ 80/min, $r = -0.81$, $p < 0.001$) and slower heart rates (< 80/min, $r = -0.85$, $p < 0.001$). A steeper relationship with faster heart rates was present in patients with normal LV function ($r = 0.67$, $p < 0.001$) but not in patients with LV dysfunction ($r = 0.23$, $p = 0.09$).

***Conclusion:*** Beat-to-beat variation of LV systolic function (LV EF) is more sensitive to ventricular cycle-length irregularity during AF in patients with lower EF or higher heart rate.

**Key Words:** Atrial fibrillation • Ejection fraction • Left ventricular function

## INTRODUCTION

Atrial fibrillation (AF) is characterized by beat-to-beat variation of ventricular cycle lengths, resulting in considerable variability of left ventricular (LV) performance.[1-5] These beat-to-beat changes in LV performance are produced by the variations in LV filling and contractility, acting through the effects of the Frank-Starling mechanism and the interval-force relationship.[6,7] The beat-to-beat contractility in AF can be reasonably predicted from the ratio of preceding R-R interval to pre-preceding R-R interval ($RR_p/RR_{pp}$) that couples two important mechanisms of the interval-force relationship: mechanical restitution and post-extrasystolic potentiation.[8-10] The $RR_p/RR_{pp}$ ratio has been utilized as an index of ventricular cycle-length irregularity during AF.[11] The LV contractility is more sensitive to this index during fast AF than during slow AF; this relationship to some extent explains the clinical benefits of rate control in patients with AF.[11]

Previous studies indicated that the interval-force re-

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lationship is not affected by the presence of coronary artery disease, and the interval-dependent potentiation of LV contractility appears to be greater in patients with low ejection fraction (EF) than in patients with normal EF.[12-14] Limited information exists regarding the factors that may affect the relationship between ventricular cycle-length irregularity and LV systolic function during AF. Accordingly, the aim of this study was to identify factors that influenced the relationship between LV systolic function and $RR_p/RR_{pp}$ ratio during AF, and to assess the interrelationships between these factors.

## METHODS

### Patients

The study population was comprised of consecutive patients with chronic AF who were referred for echocardiographic examination between August 2005 and July 2006. Patients with poor quality echocardiographic images, frequent ventricular premature beats, complete atrioventricular block, mitral stenosis, cardiac tamponade or constrictive pericarditis were excluded. No patient was excluded based on gender, age, degree of hemodynamic impairment or history of cardiac surgery. Upon enrollment, patients provided their clinical histories and baseline characteristics. The presence of coronary artery disease (CAD) was defined as one of the following criteria: 1) significant epicardial coronary artery stenosis (more than 50%); 2) perfusion defect on radionuclide imaging, 3) ischemic ECG changes on a treadmill exercise test; or 4) history of coronary revascularization. Informed consent was obtained from each patient and the ethics committee approved the study protocol.

### Echocardiography and electrocardiography

Simultaneous biplane echocardiographic examination was performed using a commercially available echo machine (Sonos 7500; Philips Medical Systems, Andover, MS, USA) equipped with a matrix-array transducer.[15] Four-chamber and two-chamber views of the LV were obtained via the apical window simultaneously and displayed as a split-screen image. Biplane imaging of the LV was recorded for 25 consecutive cardiac cycles; these images were analyzed offline. Using Simpson's biplane rule, LV stroke volume and EF were derived from LV volumes at the end-diastolic and end-systolic phases over 20 cardiac cycles for each subject. Simultaneous electrocardiograms were utilized to measure R-R intervals. For a given cardiac beat, two characteristic ventricular cycle lengths, $RR_p$ and $RR_{pp}$, were determined with the LV function parameters during AF. The $RR_p$ is the cycle length immediately preceding the analyzed beat, and the $RR_{pp}$ is the cycle length preceding the $RR_p$. The $RR_p/RR_{pp}$ ratio was applied in the following calculations associated with the analyzed beat as an index of ventricular cycle-length irregularity.[11]

### Data analysis

For each subject, biplane LV volumes and EF of 20 consecutive beats were analyzed. Ventricular premature beats and the immediately following beat were excluded from the analysis. Patients were divided into four groups-those with normal (EF ≥ 55%), mildly abnormal (EF: 54-45%), moderately abnormal (EF: 30-44%) and severely abnormal (EF < 30%) LV systolic function according to their mean EF over 20 cardiac cycles, as per the recommendations for chamber quantification from the American Society of Echocardiography.[16] For each cardiac cycle, LV EF was normalized as a percentage of mean value over 20 cardiac cycles, plotted against the $RR_p/RR_{pp}$ ratio. The relation of normalized EF over 20 beats versus $RR_p/RR_{pp}$ was fitted to the linear regression equation, normalized EF = a + b × $RR_p/RR_{pp}$ (Figure 1). The slope (b) of the regression line describes the steepness of the relationship between normalized EF and $RR_p/RR_{pp}$ ratio, and is therefore a measure of the sensi-

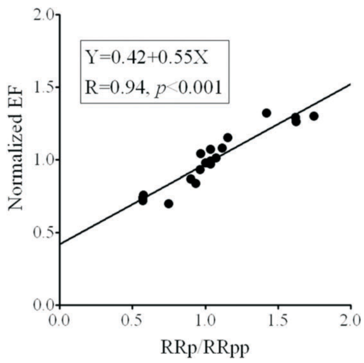


*Figure 1. Representative relationship between normalized ejection fraction (EF) and ratio of preceding/pre-preceding R-R intervals ($RR_p/RR_{pp}$). The relationship was fitted to the linear equation: y = a + b*x where y = normalized EF and x = $RR_p/RR_{pp}$.*

tivity of LV systolic function to ventricular cycle-length irregularity. Larger slope b indicates greater sensitivity of LV systolic function to ventricular cycle-length irregularity.

### Statistical analysis

Baseline descriptive statistics are expressed as mean ± standard deviation for continuous variables, or as numbers with percentages for categorical variables. Differences between variables in patients with abnormal systolic function and those with normal function were examined by Student's *t* test or the Mann-Whitney *U* test, depending on the normality of data for continuous data and by a $\chi^2$ test or Fisher's exact test for categorical variables. The relationships between slope b, mean heart rate and mean EF were evaluated by linear correlation. Scatterplots were utilized to evaluate the relationship between $RR_p/RR_{pp}$ ratio and normalized EF of pooled data from all subjects. In all analyses, a p value < 0.05 was considered to be statistically significant.

## RESULTS

Complete data were obtained for 120 patients with chronic AF. Patient characteristics are shown in Table 1. Of these 120 patients, 56 (47%) had LV dysfunction (EF < 55%). There was no significant difference in age, gender, presence of diabetes mellitus, or hypertension between patients with normal LV function and those with LV dysfunction. Patients with LV dysfunction had a higher prevalence of coronary artery disease, faster heart rate, larger LV end-diastolic volume, greater stroke volume, and larger LV mass as compared with patients with normal function. Additionally, patients with LV dysfunction had a steeper slope of the normalized EF-$RR_p/RR_{pp}$ relationship than those with normal LV function. This indicated that the beat-to-beat variation of LV function during AF was more sensitive to ventricular cycle-length irregularity in patients with LV dysfunction than in patients with normal LV function. In contrast, normalized EF was quite close to one at $RR_p/RR_{pp} = 1$ in all patients, which indicated the values at $RR_p/RR_{pp} = 1$ closely estimated the average values over all cardiac cycles during AF, regardless of LV function.

Mean heart rate negatively correlated with mean EF (r = -0.44, p < 0.001). The influence of interactions between these two independent factors on the slope of the normalized EF-$RR_p/RR_{pp}$ relationship is illustrated in Figure 2. A steeper relation slope with faster mean heart

**Table 1.** Demographic and echocardiographic characteristics of all patients in four study groups

| | Total (n = 120) | Normal (n = 64) | Abnormal systolic function | | |
|---|---|---|---|---|---|
| | | | Mildly (n = 25) | Moderately (n = 24) | Severely (n = 7) |
| Age (y, mean ± SD) | 66 ± 13 | 66 ± 13 | 66 ± 13 | 68 ± 13 | 67 ± 11 |
| Male sex, n (%) | 76 (63) | 36 (56) | 17 (68) | 17 (71) | 6 (86) |
| Diabetes mellitus, n (%) | 20 (17) | 9 (14) | 2 (8) | 7 (33) | 2 (29) |
| Hypertension, n (%) | 38 (32) | 21 (33) | 8 (32) | 8 (33) | 1 (14) |
| Coronary artery disease, n (%) | 19 (16) | 5 (8) | 2 (8) | 8 (33)* | 4 (57)* |
| LV end-diastolic volume (ml/$m^2$) | 53 ± 18 | 48 ± 15 | 47 ± 13 | 61 ± 13* | 92 ± 28* |
| LV stroke volume (ml/$m^2$) | 27 ± 9 | 31 ± 9 | 24 ± 6* | 23 ± 5* | 21 ± 5* |
| LV mass (ml/$m^2$) | 114 ± 38 | 111 ± 35 | 100 ± 31 | 126 ± 33 | 159 ± 57* |
| Relative wall thickness | 0.45 ± 0.09 | 0.46 ± 0.07 | 0.48 ± 0.12 | 0.42 ± 0.07* | 0.36 ± 0.06* |
| LV ejection fraction (%) | 54 ± 15 | 65 ± 7 | 50 ± 3* | 37 ± 4* | 23 ± 4* |
| Left atrial size (mm) | 46 ± 10 | 47 ± 11 | 43 ± 8 | 44 ± 7 | 51 ± 9 |
| Mean cycle length (ms) | 786 ± 148 | 842 ± 138 | 728 ± 131* | 721 ± 140* | 701 ± 127* |
| Mean heart rate (beats/min) | 79 ± 15 | 73 ± 13 | 85 ± 15* | 86 ± 15* | 88 ± 17* |
| Normalized EF = a + b × $RR_p/RR_{pp}$ | | | | | |
| Intercept constant (a) | 0.57 ± 0.22 | 0.71 ± 0.10 | 0.52 ± 0.11* | 0.39 ± 0.14* | 0.02 ± 0.13* |
| Slope (b) | 0.42 ± 0.21 | 0.28 ± 0.10 | 0.46 ± 0.11* | 0.59 ± 0.13* | 0.94 ± 0.10* |
| a + b (normalized EF at $RR_p/RR_{pp}$ = 1) | 0.98 ± 0.02 | 0.99 ± 0.01 | 0.98 ± 0.01 | 0.97 ± 0.02 | 0.96 ± 0.04 |
| Correlation coefficient (r) | 0.87 ± 0.06 | 0.87 ± 0.06 | 0.87 ± 0.06 | 0.89 ± 0.06 | 0.90 ± 0.06 |

LV, left ventricular; $RR_p/RR_{pp}$, ratio of preceding/pre-preceding R-R intervals. *p < 0.05 compared with patients with normal systolic function.

rates was present in patients with normal function (r = 0.67, p < 0.001), but not in patients with abnormal systolic function (r = 0.23, p = 0.09) (Figure 2A). Subgroup analysis revealed non-significant effects of heart rate on the relation slope in patients with mild (r = 0.32, p = 0.06), moderate (r = 0.30, p = 0.16), and severe (r = 0.10, p = 0.84) degree of systolic dysfunction. With comparable heart rates as in patients with normal LV function, the relation slope was usually larger in patients with LV dysfunction, indicating higher sensitivity of LV function to ventricular cycle-length irregularity. A similar negative relation between the mean EF and the slope was present at faster mean heart rates (≥ 80/min, r = -0.81, p < 0.001), and slower mean heart rates (< 80/min, r = -0.85, p < 0.001) (Figure 2B).

The standard deviation of the $RR_p/RR_{pp}$ ratio negatively correlated with the slope of normalized EF-$RR_p/RR_{pp}$ relationship (r = -0.4, p = 0.003). In contrast to the interrelation between mean heart rate and EF, there was no significant correlation between the standard deviation of $RR_p/RR_{pp}$ ratio and mean heart rate (r = 0.02, p = 0.88), or between the standard deviation of $RR_p/RR_{pp}$ ratio and mean EF (r = 0.07, p = 0.61). The standard deviation of mean EF positively correlated with the standard deviation of R-R interval (r = 0.49, p < 0.001) and correlated more strongly with the standard deviation of $RR_p/RR_{pp}$ ratio (r = 0.72, p < 0.001). Similarly, the standard deviation of stroke volume positively correlated with the standard deviation of R-R interval (r = 0.49, p < 0.001) and correlated more strongly with the standard deviation of $RR_p/RR_{pp}$ ratio (r = 0.68, p < 0.001).

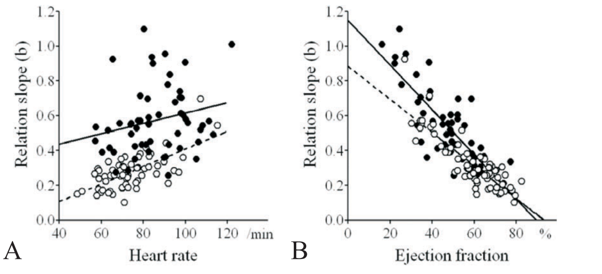


*Figure 2. Diagrams demonstrating interrelation between mean heart rate (A) and mean ejection fraction (B) on the slope of the normalized EF-$RR_p/RR_{pp}$ relationship. Steeper slopes with higher heart rates were present in patients with normal systolic function (open circles) but not in patients with abnormal function (closed circles) (A). Steeper slopes with lower ejection fractions were present at faster mean rates (≥ 80/min, closed circles) and slower mean rates (< 80/min, open circles) (B).*

All patient data were pooled to assess the impact of systolic abnormality on the normalized EF-$RR_p/RR_{pp}$ relationship. Fig. 3 shows the scatterplots of normalized EF versus $RR_p/RR_{pp}$ ratio in the four groups with different systolic function. The relationship between normalized EF and $RR_p/RR_{pp}$ ratio was somewhat curvilinear. The beat-to-beat variability of normalized EF was smaller for the normal group than that for the abnormal groups. As systolic abnormality increased, dependence on the $RR_p/RR_{pp}$ ratio augmented and the relationship became increasingly steeper. All regression lines intersect at the points where $RR_p/RR_{pp}$ ratio and normalized EF equal one (Figure 3). This finding indicated that the values at $RR_p/RR_{pp}$ = 1 in the curvilinear fit approximated the average values over 20 cardiac cycles during AF, regardless of LV function.

The beat-to-beat variations in LV systolic function, cycle lengths, and $RR_p/RR_{pp}$ ratio during AF were expressed as standard deviations and coefficients of variance. Variability data for the four groups with different mean EFs are presented in Table 2. The beat-to-beat variability, measured by coefficients of variance, of EF or stroke volume increased with the degree of systolic abnormality despite similar variability of R-R intervals or $RR_p/RR_{pp}$ ratio. Expressing the variability as the standard deviations of these parameters did not see the stepwise increase in variability of LV function.

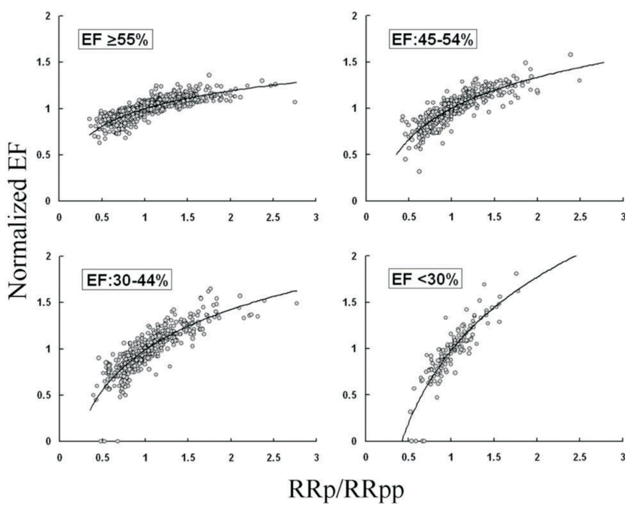


*Figure 3. Scatterplots of normalized ejection fraction (EF) versus ratio of preceding/pre-preceding R-R intervals in patients with normal, mildly abnormal, moderately abnormal and severely abnormal systolic function (EF ≥ 55%, 45-54%, 30-44%, and < 30%), respectively.*

**Table 2.** Beat-to-beat variations of left ventricular function, R-R intervals and $RR_p/RR_{pp}$

| | Normal (n = 64) | Abnormal systolic function | | |
|---|---|---|---|---|
| | | Mildly (n = 25) | Moderately (n = 24) | Severely (n = 7) |
| Standard deviation | | | | |
| R-R interval (ms) | 167 ± 58 | 144 ± 54 | 161 ± 47 | 120 ± 26* |
| $RR_p/RR_{pp}$ ratio | 0.29 ± 0.09 | 0.30 ± 0.09 | 0.33 ± 0.09 | 0.23 ± 0.06 |
| Stroke volume (ml) | 8.0 ± 3.2 | 8.8 ± 3.4 | 10.3 ± 3.5* | 10.5 ± 4.0 |
| Ejection fraction (%) | 5.8 ± 1.7 | 7.6 ± 2.4 | 7.7 ± 2.1* | 5.7 ± 1.2 |
| Coefficient of variance | | | | |
| R-R interval (ms) | 0.20 ± 0.06 | 0.20 ± 0.07 | 0.22 ± 0.05 | 0.18 ± 0.04 |
| $RR_p/RR_{pp}$ ratio | 0.28 ± 0.08 | 0.28 ± 0.08 | 0.32 ± 0.09 | 0.23 ± 0.06 |
| Stroke volume (ml) | 0.16 ± 0.05 | 0.23 ± 0.07* | 0.27 ± 0.07* | 0.28 ± 0.07* |
| Ejection fraction (%) | 0.09 ± 0.03 | 0.15 ± 0.05* | 0.21 ± 0.06* | 0.25 ± 0.07* |

$RR_p/RR_{pp}$, ratio of preceding/pre-preceding R-R intervals. *$p < 0.05$ compared with patients with normal left ventricular function.

## DISCUSSION

This study demonstrated a significant relationship between ventricular cycle-length irregularity (as determined by the $RR_p/RR_{pp}$ ratio) and beat-to-beat variation of LV systolic function in patients with AF. LV systolic function was more sensitive to this index in patients with lower EF, or in those with a faster heart rate. The increased variability of LV function parameters during AF results from the enhanced sensitivity to this index, and not from greater variability of R-R intervals or $RR_p/RR_{pp}$ ratio. Moreover, the LV EF at $RR_p/RR_{pp} = 1$ in the regression line closely estimated the average value over all cardiac cycles during AF, regardless of LV function.

Prior studies have shown that LV contractility is not constant during AF, and that beat-to-beat variability is regulated via mechanisms of mechanical restitution and potentiation.[8-10] Although these mechanisms depend nonlinearly on $RR_p$ and $RR_{pp}$ coupling intervals, a distinctive linear relationship has been illustrated between LV contractility and $RR_p/RR_{pp}$ ratio.[17-19] In the following studies, researchers observed similar linear relationships between $RR_p/RR_{pp}$ ratio and several hemodynamic parameters.[18,20-23] The present study extends previous findings by elucidating factors that affect the relationship between LV systolic function and ventricular cycle-length irregularity.[11] Our data suggested that mean heart rate and mean EF independently influenced the normalized EF-$RR_p/RR_{pp}$ relationship.

The influence of heart rate on the relationship between ventricular performance and $RR_p/RR_{pp}$ ratio has been shown in a canine model.[11] In 10 anesthetized dogs, the relationship was curvilinear and the curvilinearity decreased with faster heart rates.[11] Rate control in AF reduces the sensitivity of ventricular performance to the $RR_p/RR_{pp}$ ratio and therefore improves ventricular performance.[11,24] This is in line with the present data demonstrating greater sensitivity of normalized EF to the $RR_p/RR_{pp}$ ratio at faster heart rates. However, the influence of heart rate was less pronounced in patients with reduced EF than in those with normal EF. Of note this finding did not preclude the clinical benefits of rate control in patients with fast AF and low measured EF. Since LV EF might be measured artificially lower during fast AF, reduced EF in patients with rapid AF usually improves after rate control.

The interaction between mean heart rate and mean EF is well recognized and has been demonstrated in the current study. Our data suggested that LV systolic function had a major impact on the normalized EF-$RR_p/RR_{pp}$ relationship and outweighed the effect of heart rate in patients with reduced EF. This was confirmed by the comparable negative relationships between mean EF and the relation slope at faster and slower mean heart rates. The non-existence of significantly positive relationships between mean heart rate and the relation slope in patients with reduced EF also supports this notion.

Previous studies have not assessed the effects of LV systolic function on the EF-$RR_p/RR_{pp}$ relationships. Mechanisms invoked to explain the steeper relationships in patients with reduced EF include dependence of the LV systolic function on the interval-related restitution and post-extrasystolic potentiation of LV contractility (the interval-force relationship). It has been shown that the interval-dependent restitution is not affected by the presence of cardiomyopathy or coronary artery disease.[12,13] Moreover, the interval-dependent potentiation of contractility is not only preserved, but even greater in those with low EF than in those with normal EF.[14] As a result, LV systolic function is more sensitive to the $RR_p/RR_{pp}$ ratio in patients with low EF than in those with normal EF through the force-interval relationship. Although, on the basis of prior studies, end-diastolic volume, in company with contractility, is an independent determinant of the variations in ventricular performance during AF,[7,25] our data suggest that the Frank-Starling mechanism is not an important factor in determining the normalized EF-$RR_p/RR_{pp}$ relationship.

This study identified that the beat-to-beat variability of LV systolic function in AF increased with the extent of systolic abnormality, and that the increased variability of LV function parameters was related to the sensitivity to the $RR_p/RR_{pp}$ ratio. The result is not concordant with that obtained in the previous work that assessed the influence of heart rate and LV function on stroke volume variation during AF.[26] Kerr et al investigated the relationship between resting heart rate, LV function, and beat-to-beat variation in LV function as determined by aortic time-velocity integrals. They found that stroke volume variation was more sensitive to ventricular cycle-length irregularity at higher rates, but that this relationship was not influenced by baseline LV function. The diverse conclusions result from different measures of variability and different grouping of patients. The study by Kerr el al utilized standard deviation as a measure of variability and divided patients into normal (normal or mildly impaired function), and abnormal groups (the remaining patients) by a semi-quantitative rating method.[26] Coefficient of variation rather than standard deviation would be a better measure of variability for comparing two groups that had different mean variables. The increased variability of LV systolic function in patients with reduced EF results from the enhanced sensitivity to the $RR_p/RR_{pp}$ ratio, and not from the variability of R-R intervals or $RR_p/RR_{pp}$ ratio.

Beat-to-beat variation of hemodynamic parameters is a signature of AF.[1,4,6] A previous study demonstrated the role in assessment of LV filling pressure by Doppler in the presence of AF.[27] Nagueh et al observed that patients with elevated LV filling pressure (> 15 mmHg) had less variability in the peak acceleration and deceleration time of early mitral inflow than those with low pressure. In this study, patients with normal EF had less variability in LV stroke volume and EF than those with reduced EF. These findings have several clinical implications. First, the presence of substantial variations in LV outflow during AF should raise a suspicion of systolic dysfunction. Second, the standard protocol for acquiring an accurate assessment of LV function during AF requires averaging an arbitrary number of consecutive beats. To obtain the same level of variability, one needs to measure more consecutive beats in patients with LV dysfunction than in patients with normal LV function. Third, despite the increased variability of LV function in patients with low EF, LV function measured at beats with equal $RR_p$ and $RR_{pp}$ (i.e., $RR_p/RR_{pp} = 1$) closely estimates the average value over all cardiac cycles during AF.

There were several limitations in this study. First, a curvilinear equation has been proposed as a better model for describing the relationship between LV function and ventricular cycle-length irregularity.[11,24,25] The current study utilized linear regression rather than curvilinear regression to assess this relationship in each individual with a limited number of beats. The observed value deviated from the linear fit at both extremes of the $RR_p/RR_{pp}$ ratio. Deviation from linearity can underestimate the dependence of LV function on the $RR_p/RR_{pp}$ ratio. Second, most of the patients took medications for rate control or heart failure prior to enrollment. This study did not examine the effect of rate control or medications that may change the relationship between cycle-length irregularity and LV function. Finally, although we sought to evaluate all possible factors affecting the relationship between cycle-length irregularity and LV function, this study did not examine the effect of diastolic dysfunction, mechanical dyssynchrony or conduction block – any of which may affect this relationship.

## CONCLUSION

The index of ventricular cycle-length irregularity is a strong predictor of LV systolic function in patients with AF. The present study provides strong evidence that beat-to-beat variation of LV systolic function (LV EF) during AF is more sensitive to this index in patients with lower EF, or faster heart rate. Despite the increased variability of LV function in patients with systolic dysfunction, the values at beats with equal $RR_p$ and $RR_{pp}$ closely estimates the average LV function over all cardiac cycles.

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