

Left Ventricular Beat-to-Beat Performance in Atrial Fibrillation: Contribution of Frank-Starling Mechanism After Short Rather Than Long RR Intervals

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Objectives. This study sought to evaluate control mechanisms of the varying left ventricular performance in atrial fibrillation.

Background. Atrial fibrillation is characterized by a randomly irregular ventricular response, resulting in continuous variation in left ventricular beat-to-beat mechanical behavior and hemodynamic variables.

Methods. Fourteen patients with chronic nonvalvular atrial fibrillation were studied, using a nonimaging computerized nuclear probe linked to a personal computer. Left ventricular ejection fraction, end-diastolic and end-systolic volume counts, stroke volume counts and filling time were calculated on a beat-to-beat basis during 500 consecutive RR intervals. Multiple regression analysis was used to assess how ejection fraction was predicted by these variables.

Results. The preceding RR interval and end-diastolic volume showed a positive relation, and prepreceding interval and end-systolic volume an inverse relation, with ejection fraction (all $p <$

Atrial fibrillation is characterized by a randomly irregular ventricular response (1), resulting in considerable variations in beat-to-beat left ventricular hemodynamic variables (2). These variations in left ventricular function during atrial fibrillation have been ascribed to beat-to-beat changes in preload, acting through the Frank-Starling mechanism (3-5), the interval-force relation (6-10) or a combination of both (11-13). Also, afterload changes may play a role in the variable left ventricular performance during atrial fibrillation (3,4,11). Although left ventricular performance during atrial fibrillation has been extensively studied, some of these studies have been liable to methodologic limitations because they generally did not allow for direct beat-to-beat assessment of left ventricular function in a sufficiently large number of consecutive beats in each

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0.0001). Sensitivity analysis suggested that the preceding interval and the end-diastolic volume were equally important in predicting ejection fraction. There was a relatively strong interaction between the preceding interval and end-diastolic volume, indicating that the influence of the end-diastolic volume on ejection fraction was diminished after long intervals. A second interaction showed that the effect of end-diastolic volume on ejection fraction was attenuated after short prepreceding cycles.

Conclusions. Cycle length-dependent contractile mechanisms, including postextrasystolic potentiation and mechanical restitution, determine the varying left ventricular systolic performance during atrial fibrillation over the entire range of intervals. Beat-to-beat changes in preload, consistent with the Frank-Starling mechanism, also play a role, but their influence is diminished after long preceding and short prepreceding intervals.

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individual patient. In addition, in some studies patients had mitral stenosis, which may have precluded proper assessment of interval-force and Frank-Starling mechanisms.

Continuous acquisition of left ventricular volume data from sequential RR intervals can be performed in only a few ways. We used a nonimaging computerized nuclear probe, allowing beat-to-beat assessment of the radionuclide time-activity curve with high temporal resolution, reflecting left ventricular volume changes instantaneously (13,14). The data obtained by the nuclear stethoscope were fed into a personal computer, enabling accurate beat-to-beat calculation (and storage) of relative left ventricular volume and ejection fraction for a large number of consecutive beats. The aims of the present study were to assess the beat-to-beat variations of left ventricular performance during atrial fibrillation and to evaluate the role of the interval-force relation and the Frank-Starling mechanism.

Methods

Patients and study protocol. Fourteen patients with chronic atrial fibrillation were included (Table 1). To avoid

Table 1. Characteristics of 14 Study Patients

Gender (male/female)	10/4
Age (yr)	58 ± 11
Underlying heart disease	
Ischemic heart disease	5
Hypertensive heart disease	2
"Lone" arrhythmia	7
Arrhythmia duration (mo)	24 ± 29
New York Heart Association functional class	1.6 ± 0.6
Left atrial diameter, long-axis view (mm)	39 ± 12
Left ventricular end-diastolic diameter (mm)	47 ± 16
Left ventricular end-systolic diameter (mm)	32 ± 12
Left ventricular fractional shortening (%)	32 ± 8
RR interval (ms)	640 ± 106
Left ventricular ejection fraction (%)	34 ± 11

Data presented are mean value ± SE or number of patients.

blunting of cycle length-dependent hemodynamic changes by valvular heart disease, in particular mitral stenosis (5,9), only patients with nonvalvular atrial fibrillation were studied. Before the study, all patients underwent an echocardiographic examination. All antiarrhythmic drugs, including digitalis and calcium antagonists, were stopped at least 5 drug half-lives before the study. The study was approved by the Institutional Review Board, and written informed consent was given by all patients.

Nuclear probe. To measure relative left ventricular volumes on a beat-to-beat basis, a commercially available computerized nuclear probe (Nuclear Stethoscope, Bios) was used (14,15). Equilibrium blood pool labeling was obtained by the in vivo labeling of red blood cells with 20 mCi of technetium-99m. To search for the optimal position of the detector, the technique recommended by the manufacturer was used (14), namely, monitoring the continuously displayed values of stroke counts and ejection fraction. At the optimal left ventricular position, the values of stroke counts and ejection fraction were maximal, and they were minimal for the background position. The analog output from the probe and the electrocardiogram (ECG) were fed into a personal computer with custom-developed software. This system allowed for continuous real-time display and permanent recording of a simultaneously acquired left ventricular time-activity curve (or background activity level) and the ECG signal (Fig. 1). After final probe positioning, beat-to-beat data were acquired during 500 consecutive beats.

Statistical analysis. The measurements were randomly classified into two groups. Fifty percent of the measurements per patient made up the cross-validation group (test group). The remaining data represented the experimental group, used for building the statistical model. Univariate analysis was used to estimate associations between the dependent variable ejection fraction and the following independent variables: preceding and prepreceding RR interval; preceding and prepreceding filling time; end-diastolic volume; preceding end-systolic volume; preceding filling volume; and preceding stroke volume.

Significant univariate variables were included in a stepwise

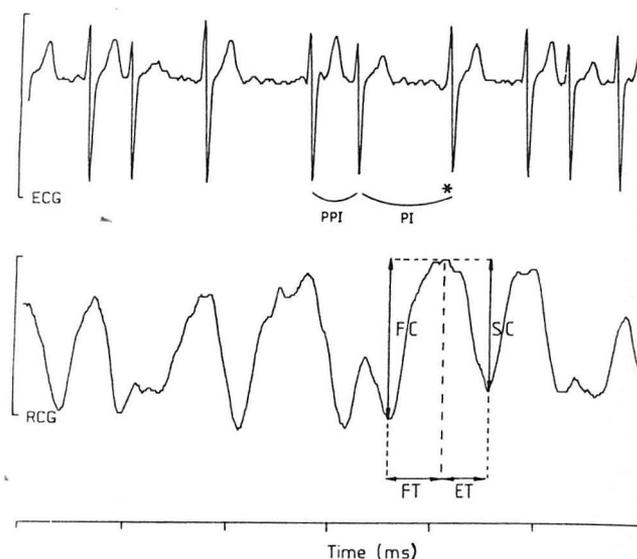


Figure 1. Recording from a study patient, showing electrocardiogram (ECG) (top) and radionuclide time-activity curve (radiocardiogram [RCG]) (bottom) reflecting left ventricular volume. The sixth beat is the index beat (asterisk). ET = ejection time; FC = filling counts; FT = filling time; PI = preceding RR interval; PPI = prepreceding interval; SC = stroke counts.

multiple regression model to assess the potentially independent determinants of ejection fraction. Variables were added one by one to the model at the 0.05 level. After a variable was added, all variables already included in the model were reconsidered, and any variable that did not produce an *F* statistic significant at the 0.05 level was dropped. Thereafter, potential two-way interaction terms were introduced into the model, using the same stepwise approach. Interaction terms (β_5 , β_6 and β_7) were incorporated or excluded at the 0.10 level.

Dummy variables were created to encode different subjects to account for the between-subject variability over repeated observations (16). The coding scheme for the dummy variables was 1, 0, -1 (Patient 14 was used as reference). Patient data were forced in the stepwise regression.

To account for multicollinearity introduced by the interaction terms, the independent variables were centered by subtracting the mean from the actual value. Multicollinearity was evaluated using Colinearity Diagnostics and Variance Inflation in SAS (SAS, version 6.08, SAS Corp.).

The final model used the following equation:

$$\begin{aligned}
 EF = & \text{Constant} + \sum_{i=1}^{13} P_i + \beta_1(EDV - \overline{EDV}) + \beta_2(pRR - \overline{pRR}) \\
 & + \beta_3(ppRR - \overline{ppRR}) + \beta_4(pESV - \overline{pESV}) + \beta_5(EDV \\
 & - \overline{EDV})(pRR - \overline{pRR}) + \beta_6(EDV - \overline{EDV})(ppRR - \overline{ppRR}) \\
 & + \beta_7(EDV - \overline{EDV})(pESV - \overline{pESV}), \quad [1]
 \end{aligned}$$

where EF = left ventricular ejection fraction; P_1 to P_{13} = fixed effects for the 13 patients in relation to Patient 14; β_1 to β_7 =

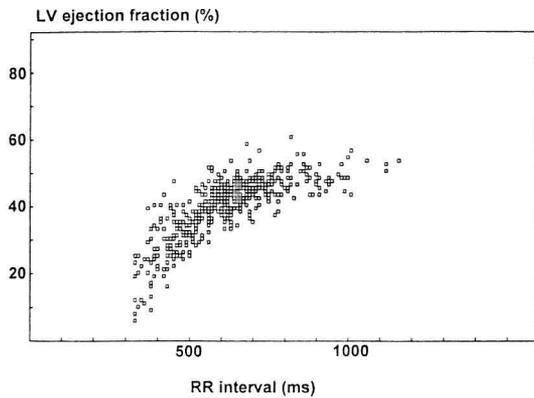


Figure 2. Relation between preceding RR interval and left ventricular (LV) ejection fraction.

regression coefficients for the independent variables and their interaction terms, which determine left ventricular systolic performance; EDV = end-diastolic volume; pRR and ppRR = preceding and prepreceding RR intervals, respectively; and pESV = preceding end-systolic volume. The independent variables were introduced as centered terms (equation 1). In addition, the model shows three interaction terms.

To detect potential nonuniformity of the data, the model fit was evaluated by examining residuals.

To test the accuracy of the regression equation, it was applied to the cross-validation group. The agreement between the predicted and observed ejection fractions was compared by linear regression analysis as well as the Bland and Altman statistical method (17).

Sensitivity analysis was used to determine the relative importance of the independent variables predicting ejection fraction in the multiple regression model. For this the following form was used:

$$\text{SENS}_{\text{EF} \cdot \text{pRR}} = \frac{\delta_{\text{EF}}}{\delta_{\text{pRR}}} \cdot \frac{\text{pRR}_{\text{baseline}}}{\text{EF}_{\text{baseline}}}, \quad [2]$$

where SENS = sensitivity of ejection fraction to the independent variable; and $\delta_{\text{EF}}/\delta_{\text{pRR}}$ = partial derivative of ejection fraction with respect to the independent variable (in this example pRR, the preceding RR interval). This procedure was repeated for all other statistically significant variables. For each variable the median value was taken as baseline. The relative importance of the independent variables in the multiple regression model was evaluated by comparison of the calculated absolute sensitivity values.

Results

Mean values for ejection fraction and RR intervals during 500 consecutive cardiac cycles for all patients are shown in Table 1. Figure 2 shows the relation between the preceding RR interval and ejection fraction in one of the patients. Figure 3 shows an example of the relation between end-diastolic volume counts and ejection fraction.

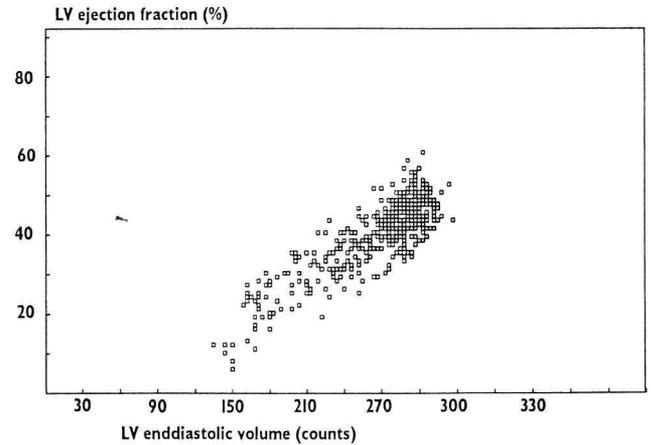


Figure 3. Relation between left ventricular (LV) end-diastolic volume counts and ejection fraction.

Multiple regression analysis. Table 2 summarizes the factors to which ejection fraction was significantly related in the multiple regression analysis. The residuals showed no systematic patterns. Therefore, it was decided to abandon transformation of data. After centering the independent variables and considering the final model, no significant multicollinearity was found.

Preceding stroke volume, filling time and filling volume as well as prepreceding filling time did not contribute significantly to the magnitude of ejection fraction. The preceding interval and the end-diastolic volume showed a positive relation with ejection fraction, whereas the prepreceding RR interval and the preceding end-systolic volume showed an inverse relation with ejection fraction. In addition, there were three separate statistically significant two-way interaction terms (see next section).

Effects of interactions on ejection fraction. The influence of interactions between the two preceding RR intervals and end-diastolic volume on ejection fraction, and between preceding end-systolic volume and end-diastolic volume on ejection

Table 2. Results of Multiple Regression Analysis*

Variable	Regression Coefficient	SE of Regression Coefficient	t Test Statistic
pRR	0.03	0.0012	25.79
ppRR	-0.016	0.00097	-17.33
EDV	0.12	0.006	19.75
pESV	-0.15	0.0094	-16.02
EDV·pRR	-0.00019	0.000016	-11.97
EDV·ppRR	0.000068	0.000016	4.24
EDV·pESV	0.00046	0.000074	6.16
Constant	37.20	0.21	175.79
R ²	0.73		

*p = 0.0001 for all comparisons. EDV·pESV = interaction between end-diastolic volume and preceding end-systolic volume; EDV·ppRR = interaction between end-diastolic volume and prepreceding RR-interval; EDV·pRR = interaction between end-diastolic volume and preceding RR interval.

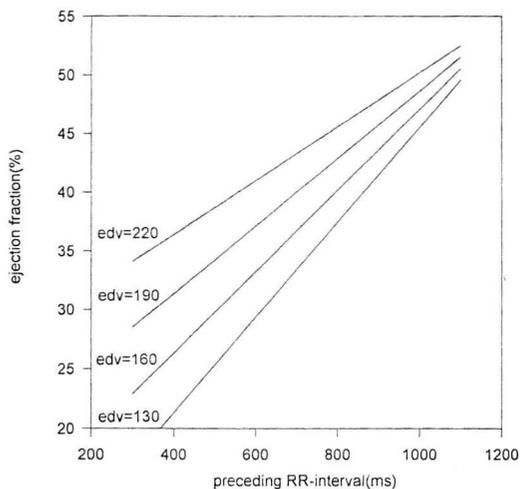


Figure 4. Effect of interaction between preceding RR interval and end-diastolic volume (edv) on ejection fraction. Curves were constructed on the basis of the multiple regression model. In this example the prepreceding interval was fixed at 640 ms (i.e., mean value of all RR interval observations). After longer preceding intervals, ejection fraction increases. However, the interaction shows that after short preceding RR intervals, the effect of end-diastolic volume on ejection fraction is relatively large, whereas after long intervals, left ventricular systolic performance hardly depends on the end-diastolic volume. The curves express the effect of varying mechanical restitution, which is considered complete only after intervals >800 ms. After a short preceding RR interval, mechanical restitution is incomplete; therefore, end-diastolic volume may have a larger effect (i.e., its effect is not outweighed by the interval-force relation).

fraction, is illustrated in Figures 4 to 6. There was a diminishing influence of the end-diastolic volume on ejection fraction with lengthening of the preceding RR interval (Fig. 4). This interaction was to some extent counteracted by a second interaction (i.e., between the prepreceding RR interval and end-diastolic volume) (Fig. 5). The influence of end-diastolic volume on ejection fraction was more marked if the prepreceding interval was long. In other words, longer prepreceding intervals enhanced the influence of end-diastolic volume on ejection fraction, whereas after short intervals, the end-diastolic volume affected the ejection fraction to a lesser extent. Figure 6 shows the interaction among preceding end-systolic volume, end-diastolic volume and ejection fraction. For a given increase in end-diastolic volume, ejection fraction was relatively less enhanced if the preceding end-systolic volume was low.

Sensitivity analysis. Sensitivity analysis suggested that preceding RR interval and end-diastolic volume were the most important variables predicting ejection fraction, followed by preceding end-systolic volume and prepreceding RR interval. In addition, the interactions among preceding RR interval, end-diastolic volume and ejection fraction were relatively strong, whereas the other two interactions were weaker. Over the range of prepreceding RR intervals, sensitivity of ejection fraction to preceding RR interval was 0.58, whereas sensitivity to end-diastolic volume varied between 0.49 and 0.55. For the

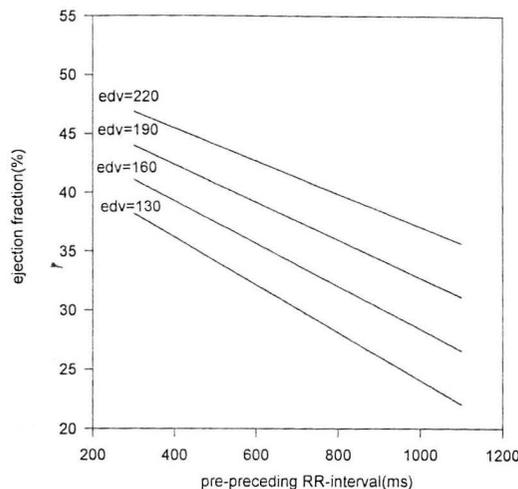
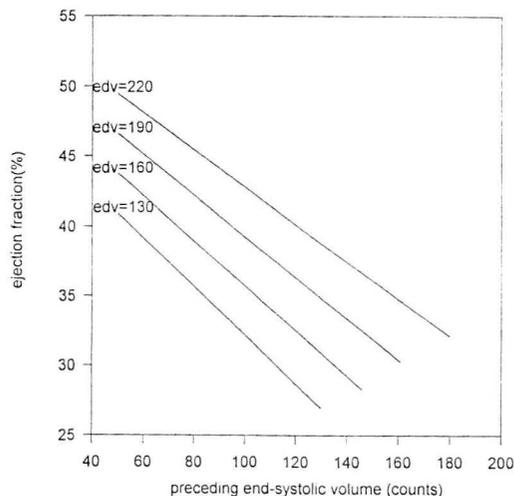


Figure 5. Effect of interaction between prepreceding RR interval and end-diastolic volume (edv) on ejection fraction: 1) Curves show the effect of postextrasystolic potentiation (i.e., increasing ejection fraction with shortening of the prepreceding interval). 2) After long prepreceding intervals, postextrasystolic potentiation does not play a large role as a determinant of ejection fraction. Presumably, this potentiation sets the stage for a more active Frank-Starling mechanism (i.e., there is a larger modifying effect of end-diastolic volume on ejection fraction after longer prepreceding intervals). In this example, the preceding interval was fixed at 640 ms (compare Fig. 4).

range of preceding end-systolic volumes, sensitivity of ejection fraction to preceding RR interval was 0.58, and to end-diastolic volume it ranged between 0.46 and 0.62.

Predicted versus observed ejection fractions. Linear regression analysis of the test set for predicted ejection fractions (obtained by the model) with observed ejection fractions showed a correlation coefficient of 0.96 ($p < 0.0001$), a

Figure 6. Effect of interaction between preceding end-systolic volume and end-diastolic volume (edv) on ejection fraction. For a given increase in end-diastolic volume, ejection fraction was relatively less enhanced if the preceding end-systolic volume was low. This result suggested that the role of the Frank-Starling mechanism is relatively limited after low preceding end-systolic volumes, possibly because under those circumstances afterload plays a more important role.



regression coefficient of 1.00 ± 0.003 (mean \pm SE) and a root-mean-square error of 7.66. The Bland and Altman statistical method showed nonsignificant, normally distributed differences with a mean difference (predicted minus observed ejection fraction) of 0.16 ± 7.66 , with 95% confidence limits of agreement ($-14.9, 15.2$). The 95% confidence limits for the lower and upper limits of agreement are ($-15.4, -14.4$) and ($14.7, 15.7$), respectively.

Discussion

Factors determining ejection fraction during atrial fibrillation. The present study demonstrates that in agreement with previous investigations (3-5), beat-to-beat left ventricular function in atrial fibrillation relates to a certain extent to beat-to-beat changes in end-diastolic volume. In general, a longer preceding cycle is accompanied by larger end-diastolic volume and ejection fraction. However, our findings also indicate that the influence of the end-diastolic volume on ejection fraction may depend on the two preceding RR intervals. The interaction between preceding RR interval and end-diastolic volume showed that end-diastolic volume relates to the variable left ventricular systolic function after short preceding RR intervals rather than long ones. Possibly, this is due to the limited variation of the end-diastolic volume seen after longer RR intervals compared with shorter ones. Ejection fraction also tends to level off after the longer preceding RR intervals, but the cycle length-dependent increase in ejection fraction remains present after long preceding RR intervals. In addition, ejection fraction shows a large variability even after long RR intervals (Fig. 2 and 4). These phenomena are caused by mechanical restitution or postextrasystolic potentiation. The latter describes the fact that the beats following a short prepreceding interval (the "extrasystolic" interval) are strengthened (10). Thus, at the same end-diastolic volume, ejection fraction may vary widely, depending on the duration of the preceding cycle.

An inverse relation was found between preceding end-systolic volume and ejection fraction. In the absence of a significant effect of the filling volume on subsequent ejection fraction, the latter relation suggested that a low afterload enhances the ejection fraction.

In summary, ejection fraction depends less on end-diastolic volume after long than after short RR intervals, but after both long and short diastoles, ejection fraction is controlled by mechanical restitution, postextrasystolic potentiation and possibly also by a lower afterload.

Effects of interactions on beat-to-beat variability of ejection fraction. As described earlier, the effect of end-diastolic volume on ejection fraction depends on the preceding RR interval. An intriguing observation was that the relative importance of end-diastolic volume in determining ejection fraction is enhanced if the prepreceding interval is long (Fig. 5). After longer prepreceding intervals (apparently these are not "extrasystolic"), postextrasystolic potentiation does not affect the following ejection, and systolic performance depends primarily

on whether mechanical restitution is complete. In this "unpotentiated" setting, it is conceivable that the end-diastolic volume can express itself as a separate determinant of ejection fraction. The third interaction (among preceding end-systolic and end-diastolic volumes and ejection fraction) indicated that for a given increase of end-diastolic volume, ejection fraction was relatively less enhanced if the preceding end-systolic volume was low. This finding suggested that the role of the Frank-Starling mechanism is relatively limited after low preceding end-systolic volumes, possibly because under those circumstances the afterload plays a more important role.

Frank-Starling mechanism. The contribution of the Frank-Starling mechanism to the varying left ventricular performance during atrial fibrillation remains a matter of doubt and debate (18-21). If such a contribution exists, it seems most marked with short cycle lengths, especially in view of the interaction among the preceding RR interval, end-diastolic volume and ejection fraction (Fig. 4). In addition, the Frank-Starling mechanism cannot explain the observation that ejection fraction is significantly influenced by the prepreceding cycle length. This finding is in agreement with several previous studies and can, as mentioned previously, be explained by postextrasystolic potentiation. Another explanation relates to a low afterload after a short prepreceding interval. After a short prepreceding cycle, only a small amount of blood will be ejected, and the increase in aortic pressure will be small. As a consequence, the runoff in the aorta will be considerable, and aortic impedance (i.e., afterload) during the next beat will be relatively low, resulting in an increased ejection fraction (4,11). This notion is further supported by the inverse relation between preceding end-systolic volume and subsequent ejection fraction as well as by the effect of the interaction between preceding end-systolic volume and end-diastolic volume on ejection fraction.

From the present study it is not possible to differentiate with certainty between the effects of aortic impedance and postextrasystolic potentiation. This differentiation would require, among others, simultaneous measurement of left ventricular volume and (aortic) pressure data on a beat-to-beat basis. Other beat-to-beat regulatory mechanisms have been described, including the positive and negative effects of ejection (22) and the previous beat contraction history (23). Unfortunately, in the absence of pressure data, these mechanisms could not be evaluated.

Importance of interval-force relation. In view of the abovementioned findings, the interval-force relation is one of the factors determining the variable left ventricular performance in atrial fibrillation. Although, on the basis of our observations, we cannot exclude the Frank-Starling mechanism as playing a role during short diastoles in atrial fibrillation, it is unlikely that it is the sole factor responsible for the variability of the size of the pulse in cases of auricular fibrillation, as first described by Einthoven and Korteweg in 1915 (2). An inverse correlation between the duration of the prepreceding interval and ventricular systolic performance was also noted by other investigators (6,8,11). They concluded that this was of an

inotropic rather than a hemodynamic origin. In another study (12) it was suggested that the interval-force relation played an important role only in patients with mitral regurgitation, whereas it was of no importance in other patients except probably those with coronary heart disease in combination with severe left ventricular dysfunction. However, a recent study by Hardman et al. (10) demonstrated the importance of postextrasystolic potentiation as a major determinant of variations in the pulse during atrial fibrillation.

Potential limitations. 1) The nonimaging characteristics of the nuclear probe may create positioning problems. Consequently, identification of the region of interest may not always be achieved easily and reliably (24). To preclude this problem, we used a standardized positioning procedure known to be associated with a low measurement variability. In addition, variability of ejection fraction remains unchanged with RR interval changes, such as during premature beats (14). Moreover, in the absence of error in background activity, the magnitude of inaccuracy of ejection fraction measurement is only 5% for an ejection fraction of 50% (14). Unfortunately, we cannot determine from our data the separate effects of measurement errors on stroke volume and end-diastolic and end-systolic volume assessments. 2) Although patients with valvular heart disease were excluded from the present study, patients were still relatively heterogeneous with respect to underlying heart disease. The latter, in combination with the small number of patients, precluded subgroup analysis.

Conclusions. The interval-force relation explains the varying left ventricular performance during atrial fibrillation over the entire range of RR intervals. Beat-to-beat variation in preload, consistent with the Frank-Starling mechanism, is more important after short than long intervals. From the present study, a possible role for afterload changes cannot be excluded. To elucidate this issue, one should measure not only left ventricular volume but also left ventricular and aortic pressure and blood flow velocity in relation to RR interval changes.

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