Reduced Ventricular Response Irregularity Is Associated With Increased Mortality in Patients With Chronic Atrial Fibrillation

Akira Yamada, MD; Junichiro Hayano, MD; Seiichiro Sakata, MD; Akiyoshi Okada, MD; Seiji Mukai, MD; Nobuyuki Ohte, MD; Genjiro Kimura, MD

Background—Variations in the ventricular response interval (VRI) during atrial fibrillation (AF) may be reduced in patients with adverse clinical outcomes. The properties of VRI dynamics associated with prognosis remain undetermined.

Methods and Results—In 107 patients with chronic AF (age, 64±9 years), we analyzed a 24-hour ambulatory ECG for VRI variability (SD, SD of successive differences, and SD of 5-minute averages) and VRI irregularity (Shannon entropy of histogram, symbolic dynamics, and approximate entropy of beat-to-beat and minute-to-minute fluctuations [ApEnb-b and Antenm-m]). During a follow-up period of 33±16 months, 18 patients died (17%), 9 from cardiac causes, 7 from fatal strokes, and 2 from malignancies. Reductions in all VRI variability and irregularity measures were associated with an increased risk for cardiac death but not for fatal stroke. A significant association with cardiac death was also found for ejection fraction (relative risk, 1.10; 95% confidence interval [CI], 1.04 to 1.17, per 1% decrement) and ischemic AF (relative risk, 6.52; 95% CI, 1.62 to 26.3). After adjustment for these clinical variables, all irregularity measures except symbolic dynamics had predictive value (relative risks [95% CIs] per 1SD decrement: Shannon entropy of histogram, 2.03 [1.14 to 3.61]; ApEnb-b, 1.72 [1.14 to 2.60]; and Antenm-m, 1.90 [1.03 to 3.52]); however, the predictive power of variability measures was no longer significant. When the patients were stratified with the 33rd and 67th percentile values of ApEnb-b (1.83 and 1.94, respectively), the 5-year cardiac mortality rates for the upper, middle, and lower tertiles were 0%, 13%, and 43%, respectively (log-rank test, \(P=0.04\)).

Conclusions—Reduced VRI irregularity in a 24-hour ambulatory ECG has an independent prognostic value for cardiac mortality during long-term follow-up in patients with chronic AF. (Circulation. 2000;102:300-306.)

Key Words: atrial fibrillation ■ entropy ■ heart rate ■ mortality ■ nonlinear dynamics

During atrial fibrillation (AF), the sinus node loses its pacemaker function; rapid and random atrial impulses result. These impulses create disorganized atrioventricular nodal conduction and, thus, generate a highly irregular fluctuation of the ventricular response interval (VRI). Such conditions seem to preclude applications of standard heart rate variability (HRV) analysis. Nevertheless, some studies suggest that reduced HRV (VRI variability) may predict adverse prognosis, even in patients with chronic AF. However, these studies examined only conventional HRV measures assuming sinus rhythm; they may have overlooked important prognostic information existing in different properties of VRI dynamics. Recently, new mathematical methods were introduced for characterizing the nonlinear dynamics of biological signals. Such methods revealed that the complexity/irregularity of heart rate dynamics had prognostic value in cardiac patients with sinus rhythm. In this study, we applied these methods to the analysis of 2 different features of VRI dynamics, variability and irregularity, in patients with chronic AF and observed the associations of these features with the risk for mortality during long-term follow-up.

Methods

Patients
We studied 115 consecutive outpatients with chronic AF who underwent ambulatory ECG monitoring at Nagoya City University Hospital between 1993 and 1997. Patients were eligible if they were between 20 and 75 years of age and had chronic AF, as documented by at least bimonthly medical records for >1 year. Patients were excluded for the following reasons: (1) congestive heart failure of New York Heart Association class III or IV; (2) a myocardial infarction, stroke, or major surgical procedure within the previous 3 months; (3) high-grade atrioventricular block, bundle branch block, or pacemaker therapy; (4) sustained ventricular tachycardia or frequent ventricular ectopies >5% of 24-hour total beats; (5) class I, II, or III antiarrhythmic medication; or (6) insulin-dependent diabetes, chronic obstructive pulmonary disease, uncontrolled hypertension, active thyroid disease, severe renal or hepatic disease, or other conditions.
life-threatening disease. All patients gave written informed consent. The study protocols were in accordance with the ethical guidelines of Nagoya City University Medical School.

Baseline Measurements and Follow-Up

The ambulatory ECG was recorded with a 3-channel portable tape recorder (DMC-3253, Nihon Koden) during the patient's usual daily activities. Analyzable data were obtained in only 109 patients; data were lost due to technical failure in 5 patients and due to frequent ventricular ectopies in 1 patient.

The patients were followed-up in the outpatient clinic of the Nagoya City University Hospital or by their family doctors. The ventricular rate was controlled, if necessary, by digoxin. Anticoagulation therapy with warfarin was recommended in patients with nonidiopathic AF.

In August 1998, 108 of the 109 patients or their families completed a mailed inquiry and were interviewed by telephone about cardiovascular and noncardiovascular events by a physician blinded to the results of the VRI measurements. One patient with idiopathic AF was lost to follow-up after the baseline measurements. Death was the only endpoint; it was classified as (1) cardiac death (heart failure, fatal arrhythmia, and sudden unexpected death within 1 hour

![Figure 1. Scheme explaining the conceptual difference between variability and irregularity in time series data. Time series data in the same row have the same variability but different irregularities, whereas data in the same column have different variabilities but the same irregularity.](image)

![Figure 2. Trend-grams of VRI during 24-hour ambulatory ECG (top) and histograms of VRI during 24 hours (bottom) in a 71-year-old male patient who was alive 55 months after the recording (left) and in a 72-year-old male patient who died suddenly 11 months after the recording (right). Abbreviations are explained in Table 1.](image)

<table>
<thead>
<tr>
<th>TABLE 1. Measures of VRI Dynamics During 24 hours</th>
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<tbody>
<tr>
<td>Mean VRI</td>
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<tr>
<td>VRI variability</td>
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<tr>
<td>SDVRI</td>
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<td>VRI irregularity</td>
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<td>ApEn_{b-b}</td>
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<td>ApEn_{m-m}</td>
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We used an SAS program (SAS Institute)12 for statistical analysis. Statistical Analysis

Fluctuations [ApEnb-b and ApEn m-m] quantify the intrinsic unpredictability (unlikelihood of the reappearance of similar patterns). Analyses of representative patients are presented in Figure 2.

To characterize the 24-hour VRI dynamics, several measures were used; they are defined in Table 1. Variability and irregularity measures (SD, SD of successive differences [SDDVRI], and SD of 5-minute averages [SDAVRI]) quantify the variability of VRI dynamics (Figure 1). The irregularity measures (Shannon entropy of histogram [ShEn], symbolic dynamics [SymDyn], and approximate entropy of beat-to-beat and minute-to-minute fluctuations [ApEnb-b and ApEn m-m]) quantify the intrinsic unpredictability (unlikelihood of the reappearance of similar patterns). Analyses of representative patients are presented in Figure 2.

Data Processing

The ambulatory ECG tapes were digitized (128 Hz, 12 bit) with a Holter scanner (DMC-4100, Nihon Koden). The ECG lead with the least distinct f-wave relative to R-wave height was selected for detecting and labeling QRS complexes. The results were reviewed, and all errors were edited manually. Data were transferred to a supercomputer (S-7/7000U, Fujitsu), on which VRI dynamics were analyzed. The detailed procedure has been reported elsewhere.7

To characterize the 24-hour VRI dynamics, several measures were used; they are defined in Table 1. Variability and irregularity measures represent different properties of VRI dynamics (Figure 1). The variability measures (SD, SD of successive differences [SDDVRI], and SD of 5-minute averages [SDAVRI]) quantify the magnitude of deviation from the mean. The irregularity measures (Shannon entropy of histogram [ShEn], symbolic dynamics [SymDyn], and approximate entropy of beat-to-beat and minute-to-minute fluctuations [ApEnb-b and ApEn m-m]) quantify the intrinsic unpredictability (unlikelihood of the reappearance of similar patterns). Analyses of representative patients are presented in Figure 2.

Statistical Analysis

We used an SAS program (SAS Institute)12 for statistical analysis. Differences in quantitative and categorical data were evaluated by Student’s t tests and χ2 tests with Yates’ correction, respectively, and relationships between quantitative variables were assessed by Spearman’s rank correlation analysis. A Cox proportional hazards regression model was used for survival analysis. To remove the impact of conditions with a high fatality rate, patients who died within 2 months of follow-up were excluded. The independent prognostic value of VRI measures was determined by multivariate Cox models that included clinical variables with a significant univariate association. The best predictive model was made with step-wise variable selection in which P=0.05 was used for entering and removing a variable. Kaplan-Meier survival curves were calculated for patients stratified by VRI measures into high, middle, and low tertiles. Quantitative data were expressed as the mean±SD, and risk for death was expressed as relative risk (RR) and 95% confidence interval (CI). P<0.05 was considered significant.

Results

Clinical Characteristics

The duration of follow-up ranged from 12 to 67 months (mean, 33±16 months) for surviving patients. During the follow-up, 19 patients (18%) died; 9 died from cardiac causes (5 of progressive heart failure and 4 of sudden cardiac death), 8 from fatal strokes (7 infarctions and 1 bleeding), and 2 from malignancies. One fatal stroke occurred within 2 months of measurement, and this patient was excluded from further analysis. The mean age of the remaining 107 patients was 64±9 years at entry; 28 of them (26%) were female. The duration of chronic AF was 8.8±7.3 years. The cause of AF was idiopathic in 50 patients (47%), valvular in 33 patients (31%), and nonvalvular in 24 patients (22%). The survival duration of the 18 nonsurvivors ranged from 3 to 67 months (mean, 27±21 months).

Idiopathic AF was less frequent in the patients who died from fatal stroke and from all causes than in the surviving patients (Table 2). Nonvalvular AF, particularly ischemic AF, was less common in the survivors than in the nonsurvivors. The survivors and nonsurvivors did not differ in age, sex, duration of AF, left ventricular ejection fraction, left atrial diameter, or medication, except for warfarin, which had been prescribed more often in those who died from fatal stroke.

Although mean VRI did not differ significantly between the survivors and nonsurvivors, all variability measures (SDVRI, SDDVRI, and SDAVRI) and one irregularity measure (ApEn m-m) were lower in the patients who died from...
cardiac causes than in the surviving patients (Table 3). No such differences were observed between the patients who died of fatal stroke and the surviving patients.

In the entire patient population, close mutual correlations were observed among variability measures and some irregularity measures (ShEn and ApEn\textsubscript{m-m}), whereas other irregularity measures (SymDyn and ApEn\textsubscript{b-b}) were relatively independent (Table 4). SDVRI, SDAVRI, and ShEn correlated positively with left ventricular ejection fraction, and all VRI measures except ApEn\textsubscript{b-b} correlated with left atrial diameter. Except for SDAVRI, which was greater in female patients, none of the measures was associated with age, sex, duration of AF, or medication (digoxin, diuretics, calcium antagonists, or angiotensin-converting enzyme inhibitors).

**Survival Analysis**

Reductions in all VRI measures showed a significant univariate association with the risk for cardiac death (Table 5). All irregularity measures except ApEn\textsubscript{m-m} were also univariate predictors of all-cause death, but none of the measures predicted fatal stroke. Among clinical variables, left ventricular ejection fraction was a univariate predictor of cardiac death (RR, 1.10; 95% CI, 1.04 to 1.17, per 1% decrement) and, in ischemic AF, it was a predictor of cardiac and all-cause death (RRs, 6.52 and 7.54; 95% CIs, 1.62 to 26.3 and 2.74 to 20.7, respectively). No predictive value was observed for AF duration, left atrial diameter, or medication at baseline.

Even after adjusting for left ventricular ejection fraction and ischemic AF, all irregularity measures except SymDyn had a predictive value for cardiac death; however, after adjustment, the predictive power of variability measures was no longer significant for any cause of death (Table 5). Multivariate Cox regression with step-wise model building revealed that the risk for cardiac death was best predicted by left ventricular ejection fraction (RR, 1.08; 95% CI, 1.01 to 1.16, per 1% decrement) and ApEn\textsubscript{b-b} (RR, 1.75; 95% CI, 1.13 to 2.71, per 1SD decrement) and that all-cause death was best predicted by ischemic AF (RR, 14.2; 95% CI, 3.76 to 53.6) and ShEn (RR, 1.65; 95% CI, 1.10 to 2.47, per 1SD decrement). No significant predictive model was obtained for fatal stroke.

Finally, we stratified patients into tertiles using the 33rd and 67th percentile values of ApEn\textsubscript{b-b} (1.83 and 1.94, respectively). A Kaplan-Meier plot for cardiac death revealed that

<table>
<thead>
<tr>
<th>TABLE 3. VRI Measures in Patients Grouped by Survival</th>
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<tbody>
<tr>
<td>Survivors (n = 89)</td>
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<tr>
<td>Mean VRI, ms</td>
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<tr>
<td>SDVRI, ms</td>
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<td>SDDVRI, ms</td>
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<td>SDAVRI, ms</td>
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<tr>
<td>ShEn</td>
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<tr>
<td>SymDyn</td>
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<tr>
<td>ApEn\textsubscript{b-b}</td>
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<td>ApEn\textsubscript{m-m}</td>
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</table>

Data are mean ± SD.
*P < 0.05, †P < 0.005 vs survivors.

<table>
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<tr>
<th>TABLE 4. Relationships Between Clinical Features and VRI Measures</th>
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<tbody>
<tr>
<td>Mean VRI</td>
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<tr>
<td>SDVRI</td>
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<td>SDDVRI</td>
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<td>SDAVRI</td>
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<td>ShEn</td>
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<td>SymDyn</td>
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<td>ApEn\textsubscript{b-b}</td>
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<td>ApEn\textsubscript{m-m}</td>
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<tr>
<td>Age</td>
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<td>Duration of AF</td>
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<td>Ejection fraction</td>
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<tr>
<td>Left atrial diameter</td>
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<td>Sex</td>
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Data represent Spearman’s rank correlation coefficient or mean ± SD.
*P < 0.05, †P < 0.005.
5-year cardiac mortality rates for the upper, middle, and lower tertiles were 0%, 13%, and 43%, respectively (Figure 3; log-rank test, $P<0.04$).

**Discussion**

**Major Findings**

To our knowledge, this is the first study to examine the prognostic value of VRI irregularity in patients with chronic AF. Even after adjustments for coexisting cardiovascular conditions, VRI irregularity (as assessed by entropy measures) was a significant predictor of cardiac death, but mean VRI and VRI variability had no independent prognostic value.

**Previous Studies**

Stein et al.² examined 24-hour VRI variability in 21 patients with chronic AF due to nonischemic mitral regurgitation. During a 5.2-year follow-up, 5 patients died of cardiac causes and 8 underwent mitral valve replacement surgery. Although none of the measures predicted mortality, the authors observed a univariate association between reduced SDAVRI and combined risk (mortality and mitral valve surgery). Frey et al.³ also examined 24-hour VRI variability in 35 patients with chronic AF and advanced heart failure. During a 12-month follow-up, 8 patients clinically deteriorated (3 died and 5 underwent heart transplantation). They reported that reduced SDAVRI was the only independent predictor of event-free survival. In the present study, we failed to find an independent predictive value of SDAVRI. Although this may be due to the heterogeneity of our patient population, we did find that 24-hour VRI fluctuation had an angular spectral structure with a distinct breakpoint in the frequency range reflected by SDAVRI, which may cause instability in this measure.⁷

**Prognostic Relevance of VRI Dynamics**

Although our observations suggest that important prognostic information is more likely to exist in irregularity than variability measures of VRI, one of the irregularity measures (SymDyn) had no independent prognostic value. In the algorithm for SymDyn, the resolution of analysis (symbol separation) was defined as the 24-hour SD of VRI in each patient. The larger the VRI variability, the lower the resolution, which resulted in relative insensitivity to small changes in VRI. However, ApEn₉₉ and ApEm₉₉ were computed with a fixed resolution (tolerance value [r] for vector comparison) for all patients, and ShEn was calculated with the same resolution as VRI measurement. These findings suggest that prognostic information may exist in fine (low amplitude) VRI irregularity. Indeed, ApEn₉₉ and ApEm₉₉, which were computed with a tolerance normalized by individual VRI variability (20% of individual SD), had no significant predictive value (data not shown).

**Possible Mechanisms**

Because of the observational nature of the present study, it is difficult to determine whether decreased VRI irregularity is a part of the mechanisms of increased mortality in patients with chronic AF or if it is merely a marker of poor prognosis among them. However, VRI irregularity had prognostic value for cardiac death but not fatal stroke, which indicates that the association between irregularity and mortality is unattributable to the potential effect of VRI irregularity on atrial thrombogenesis. Also, the prognostic value of these measures

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**TABLE 5.** Univariate and Adjusted RR of VRI Measures by Cox Proportional Hazards Regression Analysis

<table>
<thead>
<tr>
<th>VRI Measure</th>
<th>Cardiac Death</th>
<th>Fatal Stroke</th>
<th>All-Cause Death</th>
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<tbody>
<tr>
<td></td>
<td>Univariate RR (95% CI)</td>
<td>Adjusted* RR (95% CI)</td>
<td>Univariate RR (95% CI)</td>
</tr>
<tr>
<td>Mean VRI</td>
<td>1.20 (0.57–2.52)</td>
<td>0.95 (0.41–2.19)</td>
<td>0.82 (0.40–1.68)</td>
</tr>
<tr>
<td>SDVRI</td>
<td>2.96 (1.30–6.73)†</td>
<td>2.29 (0.94–5.57)</td>
<td>0.74 (0.32–1.72)</td>
</tr>
<tr>
<td>SDDVRI</td>
<td>3.16 (1.28–7.83)†</td>
<td>2.25 (0.97–5.23)</td>
<td>0.76 (0.34–1.71)</td>
</tr>
<tr>
<td>SDAVRI</td>
<td>2.58 (1.16–5.73)†</td>
<td>2.13 (0.89–5.06)</td>
<td>0.88 (0.35–2.18)</td>
</tr>
<tr>
<td>ShEn</td>
<td>2.67 (1.68–4.27)†</td>
<td>2.03 (1.14–3.61)†</td>
<td>0.64 (0.21–1.93)</td>
</tr>
<tr>
<td>SymDyn</td>
<td>1.86 (1.22–2.83)‡</td>
<td>1.45 (0.95–2.21)</td>
<td>0.90 (0.33–2.48)</td>
</tr>
<tr>
<td>ApEn₉₉</td>
<td>2.09 (1.44–3.01)†</td>
<td>1.72 (1.14–2.60)†</td>
<td>0.50 (0.09–2.89)</td>
</tr>
<tr>
<td>ApEn₉₉₉₉</td>
<td>2.20 (1.35–3.58)‡</td>
<td>1.90 (1.03–3.52)‡</td>
<td>0.66 (0.24–1.80)</td>
</tr>
</tbody>
</table>

Data represent relative risk corresponding to 1-SD decrement in each VRI measure.

*Relative risks adjusted for left ventricular ejection fraction and ischemic AF.
†$P<0.05$, ‡$P<0.005$.
was independent of both left ventricular ejection fraction and origin of AF. Thus, these findings are not a simple reflection of poor ventricular performance or the characteristics of known cardiac diseases, although we cannot exclude the possibility that reduced VRI irregularity identifies patients with other unmeasured differences in disease severity that themselves influence survival in this population.

Multivariate Cox models revealed the best independent predictive value was with beat-to-beat VRI irregularity (\(\text{ApEn}_{\text{m-m}}\)). \(\text{ApEn}_{\text{m-m}}\) could be modified by many factors. Atrial expansion and, thereby, induced reflex vagal excitation may increase the dispersion of atrial refractoriness and VRI irregularity.\(^{13-15}\) The atrial electrical remodeling induced by AF itself\(^ {16}\) may shorten atrial refractoriness, thereby increasing the number and frequency of f-waves, which could increase VRI irregularity by enhancing concealed conduction within the atrioventricular node.\(^ {15,17}\) Although atrial expansion and electrical remodeling might progress as a pathological process of chronic AF, we observed that neither left atrial diameter nor the duration of chronic AF had prognostic value; furthermore, these factors, if involved, would increase VRI irregularity. Much evidence from HRV analysis during sinus rhythm suggests an adverse prognostic value of decreased vagal activity in cardiac patients.\(^ {18-20}\) Decreased vagal activity may prolong atrial refractoriness and reduce its dispersion, resulting in reduced VRI irregularity.\(^ {15,21}\) These factors suggest that vagal dysfunction is the most likely mediator of the association between reduced beat-to-beat VRI irregularity and cardiac mortality, although this attractive hypothesis deserves further study.

**Limitations**

We collected VRI data from patients under medication. We cannot exclude the possible influence of such medication on VRI dynamics, although we observed no significant associations of any drug with any VRI measure or prognosis. We must consider the possible effects of clinical decisions made for the patients during the follow-up. However, the end point of this study was simply death, and the patients were managed as recommended by recent standards.\(^ {22}\) Thus, our observations seem to reflect current general practice. Our patient population, however, was heterogeneous in the origin of chronic AF, although the prognostic value of VRI irregularity was independent of AF pathogenesis. Our observations may not be directly applicable to other populations with different AF origins. Finally, as a technical issue, the presence of the f-wave may have affected the precision of R-R interval measurement by distorting the R-wave forms. However, we selected the ECG lead with the least distinct f-wave. Furthermore, the measures derived from average VRI values, SDAVRI, and \(\text{ApEn}_{\text{m-m}}\) were less influenced by the effect, and \(\text{ApEn}_{\text{m-m}}\) was guarded from this because the tolerance for vector comparison (r) was set at 43 ms, indicating that 2 VRIs were considered identical unless they differed >43 ms. However, the other measures may have been influenced, which then might have deteriorated their prognostic value.

**Clinical Implications**

The prognostic implications of chronic AF are serious, even beyond the increased risk for thromboembolic events.\(^ {23}\) Growing evidence indicates that, in patients with heart failure, those with AF have excess mortality when compared with those who have sinus rhythm\(^ {4,24}\); the same holds true for patients after myocardial infarction.\(^ {26,27}\) A recent report on the Framingham cohort indicated that AF was associated with a 1.5- to 1.9-fold increased risk of mortality, even after adjustment for preexisting cardiovascular conditions.\(^ {28}\) Given the recent progress in pharmacological and nonpharmacological treatments for AF, risk stratification for mortality in these patients seems increasingly important. The analysis of VRI irregularity is applicable to routine ambulatory ECG recordings in almost all patients with chronic AF. Our method may add unique clinical information for identifying patients with an adverse prognosis, particularly those with an increased risk for cardiac death.

**Acknowledgments**

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