Is Baseline Autonomic Tone Associated with New Onset Atrial Fibrillation?: Insights from the Framingham Heart Study

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Background: Recent reports have indicated that autonomic tone fluctuations measured by heart rate variability (HRV) precede episodes of paroxysmal atrial fibrillation (AF). Little is known about the impact of baseline autonomic tone and the development of new onset AF in a population-based cohort. The purpose of this study was to assess the role of HRV as a predictor of new onset AF.

Method: Ambulatory ECG recordings obtained from the Framingham Heart Study subjects attending a routine examination were processed for HRV. The HRV variables analyzed included standard deviation of normal R-R intervals (SDNN), low frequency power (LF), high frequency power (HF), and LF/HF ratio. There were 1434 women and 1142 men (54 ± 14.1 years) eligible for the study.

Results: In 12 years of follow-up, 65 women and 67 men had new onset AF. The study had 80% power to detect a hazard ratio (HR) of 1.3 per standard deviation (SD) decrement in HRV. A one SD decrement in log LF/HF was associated with increased risk of developing AF (HR = 1.23; 95% confidence intervals (CI) = 1.06–1.44) in age- and sex-adjusted models; the association was no longer significant (HR = 1.15; 95% CI = 0.98–1.35) after adjusting for potential confounders.

Conclusion: Autonomic dysregulation at baseline, as reflected by an altered HRV is associated with risk of AF; however, this association does not persist after adjusting for potential confounders. Much of the apparent association between HRV and AF is mediated by traditional risk factors.

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Various experimental and clinical observations suggest changes in sympathetic and vagal neural regulatory mechanisms play a critical role in altering cardiac electrical properties and in promoting the occurrence of arrhythmic events.^{1–3} Recent reports have indicated that a transient augmentation of sympathetic tone or alterations in parasympathetic activity may be important in the onset of atrial fibrillation (AF).^{4–7}

HRV is a promising method for evaluating the interplay of sympathetic and vagal activity before the

onset of AF. Spectral analysis of HRV can partially distinguish parasympathetic from sympathetic influence on the heart^{8–11} and may provide important insights into the role of the autonomic nervous system in the development of AF.^{4–7} Persistent abnormalities in autonomic tone can result in atrial myopathies¹² and may predispose individuals to develop AF. Although short-term fluctuations in autonomic tone precede episodes of AF,^{4–7,13,14} little is known about the impact of an abnormal baseline autonomic tone on the development of new

onset AF in the population. We hypothesized that the presence of baseline autonomic dysregulation (reflected by a reduced HRV) would be associated with new onset AF. The purpose of this study was to assess the role of HRV as a predictor of new onset AF during 12 years of follow-up.

METHODS

Study Population

The Framingham Heart Study is a prospective epidemiological study established in 1948 to evaluate potential risk factors for cardiovascular disease. The original cohort included 5209 men and women, aged 28 to 62 years at enrollment. In 1971, 5124 additional subjects (offspring and their spouses) were entered into the Framingham Offspring Study. Study design and selection criteria have been published.¹⁵⁻¹⁷ The Boston University Medical Center Institutional Review Board approved the protocol, and all participants gave informed consent.

Subjects for the present study had ambulatory electrocardiographic recordings between 1983 and 1987 during a routine examination at the Framingham Heart Study clinic. Subjects were excluded if they met any of the following criteria at the index examination: (1) history or clinical evidence of myocardial infarction or congestive heart failure, (2) AF/atrial flutter, (3) technically inadequate ambulatory ECG recordings, and (4) antiarrhythmic medication. A committee of three physicians evaluated records from the Framingham Heart Study clinic examinations, visits to personal physicians, and interim hospitalizations to establish the diagnoses of myocardial infarction and congestive heart failure in accordance with published criteria. AF was diagnosed upon review by a Framingham Heart Study cardiologist if either AF or atrial flutter were demonstrated on an electrocardiogram or Holter from Framingham clinic, outside physician office, or hospitalization tracings. Valve disease was considered present if any diastolic murmur or a greater than 2/6 systolic murmur was auscultated at baseline or prior Framingham clinic examination. At the index examination, body height and weight measurements, medical history, physical examination, 12-lead resting and ambulatory electrocardiography were routinely obtained.

Heart Rate Variability Assessment

The first 2 hours of ambulatory ECG recordings were processed for HRV. All ambulatory recordings included two channels of ECG information and were obtained on standard four-track cassette tapes with the use of either a Cardiodata PR2 or PR3 pace recorder (Cardiodata Corp., Northboro, MA). The tape speed was 1 mm/s, and one channel was used to record a 32-Hz crystal-controlled timing track. For analysis, the tapes were played back at 120 times real time on the Cardiodata/Mortara Mk5 Holter analysis system (Mortara Instrument Co., Milwaukee, WI) sampling each ECG channel at 180 samples/s. Potential errors in recorder speed control were compensated for by the use of a playback system incorporating a phase-locked loop using the recorded timing track. Beat-to-beat R-R interval data were obtained from the beat stream file. Intervals of ectopic beats or artifact less than or equal to two R-R intervals were substituted with a linearly interpolated beat. The fast Fourier transform was calculated on 100-second blocks of R-R interval data. A continuous curve was formed by linear interpolation between R-R intervals; this was subjected to a Hamming window and resampled at 1.28 times/s. If there was a run of arrhythmia or artifact >1 beat long, the 100-second block was terminated, the partial block was discarded, and a new block was started at the end of the unusable period. Power density spectrum was estimated by taking the sum of the squares of the magnitude of fast Fourier transform performed on all usable 100-second blocks. The resulting 100-second power spectra were corrected for attenuation resulting from sampling and the Hamming window and were averaged. The 100-second method was intended to avoid any assumptions about sinus node activity in consecutive arrhythmias in which the sinus node activity was unknown. With the shorter time blocks the minimal frequency at which the power spectrum can be measured is >0.01 Hz. We computed the 2-hour power spectral density and calculated the following measures: low frequency power (LF, 0.04–0.15 Hz), high frequency power (HF, 0.15–0.40 Hz), and low frequency/high-frequency ratio (LF/HF). The time domain measure, SD of normal R-R intervals (SDNN), was calculated from the 100-second segments used to calculate the frequency domain variables. Further details of HRV assessment have been outlined in a previous report.¹⁸

Continuous visual monitoring during the process of scanning helped identify arrhythmias and normal QRS intervals. Recordings with transient or persistent nonsinus rhythm, premature beats >10% of beats, <1-hour recording time, or processed time <50% of recorded time were excluded.

Statistical Analyses

Measures of HRV were natural-log-transformed to normalize their skewed distributions. The principal outcome, new onset AF, was analyzed with proportional hazards regression models.¹⁹ Each of the four pre-selected HRV variables (the low frequency power, high frequency power, low-frequency-to-high-frequency power ratio, and the 2-hour SDNN) were assessed separately and adjusted for age, sex, body mass index, valve disease on physical examination, diabetes, cigarette smoking, baseline systolic and diastolic blood pressure, alcohol intake, and cardiac medications. Results are summarized by hazard ratio (HR) and 95% confidence interval, with the HR expressed for a one SD decrement in the log-transformed heart rate variability variable. In addition, HRV measures were compared between subjects who developed AF and those that remained free of AF during follow-up. In a secondary analysis, the population was divided into quartiles and the association between the two extreme subgroups of HRV (highest and lowest) and new onset AF were examined. An association was considered statistically significant at a value of $P < 0.05$. All analyses were done on an SPARCstation 2 (SUN Microsystems) using the Statistical Analysis System (SAS).²⁰

RESULTS

Subjects

HRV data were available for 2576 subjects, that is, 1434 women and 1142 men. During follow-up (average 10.5 years, maximum 12), 65 women and 67 men developed new onset AF. Table 1 depicts the baseline characteristics of subjects according to whether or not they developed AF in follow-up. Compared with subjects who remained in sinus rhythm, subjects with incident AF were older, more likely to be male, and more likely to have valve disease and higher systolic blood pressure. The baseline unadjusted mean heart rate variability measures were significantly lower in the group of subjects that went on to develop AF (Table 2).

Table 1. Baseline Clinical Characteristics of Subjects (Age- and Sex-Adjusted) According to Whether They Developed Atrial Fibrillation (AF) during Follow-up

	Atrial Fibrillation (n = 132)	Normal Sinus Rhythm (n = 2444)
Age (years)	67 ± 12	53 ± 14
Sex (male %)	51	44
Valve disease (%)	6	3
BMI (kg/m ²)	26.3 ± 4.4	26.1 ± 4.5
Smoker (%)	21	25
Heart rate (bpm)	74.8 ± 11.3	73.4 ± 10.3
SBP (mmHg)	131 ± 19	128 ± 16
DBP (mmHg)	78 ± 10	78 ± 9
Diabetes (%)	5	6
Cardiac medications (%)	12	10
Alcohol (oz/week)	3.0 ± 4.5	3.0 ± 4.3

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; oz/week, ounces of alcohol consumed per week; bpm, beats per minute. Results are expressed as mean ± SD or as percentage.

New Onset AF

HRV measures adjusted for sex and age were similar in subjects who developed AF compared with those who did not, except for ln LF/HF (Table 3). The proportional hazards analyses revealed that ln LF/HF was associated with new onset AF (HR = 1.23, 1.06–1.44). The age- and sex-adjusted probabilities of progression to AF as a function of ln LF/HF are displayed in Figure 1 for a hypothetical "average" subject.

The association between ln LF/HF and AF were no longer significant (HR = 1.15; 95%

Table 2. Baseline Unadjusted Measures of Heart Rate Variability between Subjects with New Onset AF and Those with Normal Sinus Rhythm

Variables	New Onset AF (n = 132)	Normal Sinus Rhythm (n = 2444)
Ln SDNN (ms)	4.2 ± 0.4	4.4 ± 0.3 ^a
Ln LF (ms ²)	5.9 ± 1.0	6.5 ± 0.9 ^a
Ln HF (ms ²)	5.0 ± 1.0	5.4 ± 0.9 ^b
Ln LF/HF	0.9 ± 0.6	1.1 ± 0.5 ^a

All heart rate variability measures are natural log (ln) transformed values, expressed as mean ± standard error of mean. SDNN, standard deviation of normal RR intervals; LF, low frequency power; HF, high frequency power; LF/HF, ratio of low frequency to high frequency power.

^aP < 0.0001; ^bP < 0.0005.

Table 3. Hazards Ratio for New Onset AF on Follow-up According to HRV Measures at Baseline

Variables	Sex- and Age-Adjusted Values at Baseline		Fully Adjusted Hazards Ratio for AF ^a
	New Onset AF	NSR	
ln SDNN (ms)	4.4 ± 0.03	4.4 ± 0.01	1.13 (0.94, 1.38)
ln LF (ms ²)	6.4 ± 0.06	6.5 ± 0.01	1.09 (0.89, 1.33)
ln HF (ms ²)	5.5 ± 0.07	5.3 ± 0.02	0.97 (0.80, 1.16)
ln LF/HF	1.0 ± 0.04	1.1 ± 0.01	1.15 (0.98, 1.35)

All HRV measures are natural log (ln) transformed values, expressed as mean ± standard error of mean.

^aThe fully adjusted model includes sex, age, body mass index, smoking, diabetes, valve disease, systolic and diastolic blood pressure, alcohol intake, and cardiac medications. SDNN, standard deviation of normal R-R intervals; LF, low frequency power; HF, high frequency power; LF/HF, ratio of low frequency to high frequency power, NSR = normal sinus rhythm; CI = confidence intervals.

CI = 0.98–1.35, Table 3) after adjusting for other potential confounders (body mass index, valve disease, diabetes, smoking, baseline systolic and diastolic blood pressure, alcohol intake, and cardiac medications). Including heart rate in the multivariate models did not materially alter the findings. In a secondary analysis, there was no significant association between the two extreme quartiles of HRV and new onset AF. Based on observed standard errors of proportional hazards regression coefficients for ln HRV variables, the study had 80% power to detect a hazards ratio (HR) of 1.3 per SD decrement in ln HRV.

Figure 1. Age- and sex-adjusted probabilities of developing AF over a 12-year follow-up period for a hypothetical subject (with mean values of all covariates). Curves are plotted for the mean ± 1 SD of the ln LF/HF ratio.

DISCUSSION

Our findings suggest that although HRV is reduced in subjects who develop AF, much of the apparent association between HRV and AF is mediated by traditional risk factors. To our knowledge, this is the first study to examine the role of baseline HRV as a predictor of AF in a population-based cohort.

Autonomic Activity and AF

There is evidence to suggest that abnormal atrial electrophysiology^{1,21} coupled with changes in the autonomic tone^{21,22} plays an important role in the genesis of AF. The autonomic nervous system modulates dispersion of atrial refractory periods²¹ and intraatrial conduction and therefore influences the initiation and maintenance of AF. Vagal influences tend to favor macroentry, whereas sympathetic activity favors automaticity and delayed afterpotentials; the two major patterns of AF.²⁰ Predicting AF, by assessing the sympatho-vagal balance preceding AF, may prove to be a useful strategy for targeting drug therapy and preventing AF.

HRV has been shown to be a valuable non-invasive marker of autonomic tone, as well as an important tool for evaluating prognosis in patients with heart disease.^{12,24,25} Temporal changes in HRV have indicated diurnal differences in autonomic activity preceding AF episodes, with increased parasympathetic activity preceding nocturnal AF, contrary to daytime AF.^{5–7} It is quite likely that variations, rather than basal autonomic tone, are important in the genesis of AF.^{13,14} Also, the fact

that autonomic tone vacillations do not induce AF in all healthy persons, implies that the occurrence of AF may further be dependent on the sensitivity of the atrial substrate to these triggering factors.^{1,12,22} This could potentially explain why measurements of baseline autonomic tone might not be predictive of a dynamic event like AF in the population. Moreover, HRV is a dynamic measurement and varies over time and it is quite likely that the HRV measured at baseline may have been different from the HRV just preceding the onset of AF.

Strengths and Limitations

An important strength of this community-based study is that subjects have been well characterized through many years of follow-up. Hence, we were able to select subjects who were free of clinical cardiovascular disease (which can alter autonomic function and HRV measurements), and able to construct multivariable models adjusting for important potential confounders. This study was based on intermediate-duration recordings that yield different values for SDNN than shorter or longer recordings. The recordings were obtained when subjects underwent an extensive clinical evaluation and are not representative of basal resting conditions. Such activity can precipitate short-term changes in the autonomic tone that can confound the relation of autonomic tone to new onset AF.

The study sample was predominantly Caucasian and it is possible that results from the present study may not be generalizable to other ethnic and racial groups. Since the diagnosis of AF was dependent on the documentation of its presence on an electrocardiogram or Holter from the Framingham clinic, outside physician office or hospitalization tracings, it is quite likely that the patients in this study were more likely to have persistent or permanent AF. It is conceivable that episodes of paroxysmal AF escaped documentation.

CONCLUSION

Atrial fibrillation is a dynamic event, with inciting autonomic mechanisms specific for the individual. A population-based approach showed that HRV is reduced in subjects who go on to develop AF. However, basal autonomic tone measured by HRV does not provide additional value above conventional risk factors as a predictor for new onset AF.

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