

# Reduced Heart Rate Variability and New-Onset Hypertension

## Insights Into Pathogenesis of Hypertension: The Framingham Heart Study

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**Abstract**—Heart rate variability (HRV) is a useful noninvasive tool to assess cardiac autonomic function. The purpose of this study was to (1) compare measures of HRV between hypertensive and normotensive subjects and (2) examine the role of HRV as a predictor of new-onset hypertension. The first 2 hours of ambulatory ECG recordings obtained from 931 men and 1111 women attending a routine examination at the Framingham Heart Study were processed for HRV. Three time-domain and 5 frequency-domain variables were studied: standard deviation of normal RR intervals (SDNN), percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds, square root of the mean of squared differences between adjacent normal RR intervals, total power (0.01 to 0.40 Hz), high frequency power (HF, 0.15 to 0.40 Hz), low frequency power (LF, 0.04 to 0.15 Hz), very low frequency power (0.01 to 0.04 Hz), and LF/HF ratio. On cross-sectional analysis, HRV was significantly lower in hypertensive men and women. Among 633 men and 801 women who were normotensive at baseline (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg and not receiving antihypertensive treatment), 119 men and 125 women were newly hypertensive at follow-up 4 years later. After adjustment for factors associated with hypertension, multiple logistic regression analysis revealed that LF was associated with incident hypertension in men (odds ratio per SD decrement [OR], 1.38; 95% confidence interval [CI], 1.04 to 1.83) but not in women (OR, 1.12; 95% CI, 0.86 to 1.46). SDNN, HF, and LF/HF were not associated with hypertension in either sex. HRV is reduced in men and women with systemic hypertension. Among normotensive men, lower HRV was associated with greater risk for developing hypertension. These findings are consistent with the hypothesis that autonomic dysregulation is present in the early stage of hypertension. (*Hypertension*. 1998;32:293-297.)

**Key Words:** heart rate ■ hypertension, essential ■ Framingham Heart Study ■ autonomic nervous system  
■ pathogenesis

There is considerable evidence to suggest that the autonomic nervous system plays an important role in blood pressure regulation and in the development of hypertension.<sup>1,2</sup> Spectral analysis of HRV can partially distinguish parasympathetic from sympathetic influences on the heart<sup>3,4</sup> and may provide important insights into the role of the autonomic nervous system in the pathogenesis of essential hypertension.<sup>5</sup>

Although previous studies from Framingham<sup>6</sup> and elsewhere<sup>7-11</sup> have identified abnormal HRV in systemic hypertension, there is a paucity of data examining the association between HRV and blood pressure. Also, even though sympathetic nervous system overactivity has been demonstrated in early hypertension,<sup>1,2</sup> little is known about the impact of altered HRV on the development of new-onset hypertension. The purpose of this study was to (1) compare the measures of HRV in Framingham Heart Study subjects with and those

without hypertension and (2) assess the role of HRV as a predictor of new-onset hypertension during 4 years of follow-up.

### Methods

#### Subjects

The Framingham Heart Study is a prospective epidemiological study established in 1948 to evaluate potential risk factors for coronary heart disease. The original cohort included 5209 men and women aged 28 to 62 years. In 1971, 5124 additional subjects were entered into the Framingham Offspring Study. Study design and selection criteria have been published.<sup>12-14</sup>

Subjects for the present study were original Framingham Heart Study participants and Offspring Study subjects who underwent ambulatory ECG recordings between 1983 and 1987 during a routine scheduled examination at the Framingham Heart Study clinic. Subjects were excluded if they met any of the following criteria: (1)

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**Selected Abbreviations and Acronyms**

HF	= high frequency power
HRV	= heart rate variability
LF	= low frequency power
LF/HF	= ratio of low frequency to high frequency power
OR	= odds ratio
pNN50	= percentage of differences between normal RR intervals >50 ms based on 2-hour recordings
r-MSSD	= root-mean square of successive differences
SDNN	= standard deviation of normal RR intervals
TP	= total power

history or clinical evidence of myocardial infarction or congestive heart failure, (2) atrial fibrillation, (3) diabetes mellitus, (4) use of antihypertensive or cardioactive medication at the index examination, and (5) technically inadequate ambulatory ECG recordings. The diagnoses of myocardial infarction and congestive heart failure were established by a committee of 3 physicians who evaluated records from the Framingham Heart Study clinic examinations, interim hospitalizations, and visits to personal physicians in accordance with published criteria.<sup>15</sup> At the index examination, body height and weight measurements, medical history, physical examination, and 12-lead resting and ambulatory ECG results were routinely obtained.

**Blood Pressure Measurements**

At each routine examination, blood pressure was measured in the left arm twice, with the subject in the seated position, by the examining physician using a mercury column sphygmomanometer. The averaged values were then used to derive the respective examination systolic and diastolic blood pressures. The index examination was the one performed at the time of the ambulatory ECG recording.

**HRV Assessment**

The first 2 hours of ambulatory ECG recordings were processed for HRV. All ambulatory recordings included 2 channels of ECG information and were obtained on standard 4-track cassette tapes with the use of either a Cardiodata PR2 or PR3 pace recorder (Cardiodata Corp). The tape speed was 1 mm/s, and 1 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), sampling each ECG channel at 180 samples per second. Beat-to-beat RR interval data were obtained from the "beat stream file." A linearly interpolated beat was substituted for intervals of ectopic beats or artifact  $\leq 2$  RR intervals. The fast Fourier transform was calculated on 100-second blocks of RR interval data. A continuous curve was formed by linear interpolation between RR intervals; this was subjected to a Hamming window and resampled at 1.28 times per second. 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 usable period. Power density spectrum was estimated by taking the sum of the squares of the magnitude of the 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. Recordings with transient or persistent nonsinus rhythm, premature beats  $> 10\%$  of beats,  $< 1$  hour of recording time, or processed time  $< 50\%$  of recorded time were excluded.

Because clinic examinations typically lasted for 2 to 3 hours, only the first 2 hours of data were analyzed for HRV. The time-domain variables measured were the standard deviation of normal RR intervals (2-hour SDNN), percentage of differences between adjacent normal RR intervals exceeding 50 milliseconds (pNN50), and the square root of the mean of squared differences between adjacent normal RR intervals (r-MSSD). The frequency domain variables included total power (TP, 0.01 to 0.40 Hz), high frequency power

(HF, 0.15 to 0.40 Hz), low frequency power (LF, 0.04 to 0.15 Hz), very low frequency power (0.01 to 0.04 Hz), and LF/HF ratio. Further details of HRV assessment have been outlined in a previous report.<sup>6</sup>

**Follow-up**

Blood pressure level measured 4 years after the index examination was used to identify incident hypertension. New-onset hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or use of antihypertensive medications on follow-up in a subject who was normotensive at the index examination.<sup>16</sup> Subjects who developed congestive heart failure or who had a history of myocardial infarction at the follow-up examination were excluded.

**Statistical Analysis**

All statistical analyses were gender specific. Measures of HRV were natural-log transformed because their distributions were highly skewed. Linear regression analyses were used to estimate and test the strengths of associations between blood pressure measurements and 4 preselected variables considered to be most physiologically linked to blood pressure: LF, HF, LF/HF ratio, and 2-hour SDNN. Multi-variable regression analysis was used to evaluate these relations after adjustment for clinical covariates (age, gender, body mass index, alcohol consumption, and cigarette smoking) that could affect autonomic function.<sup>17</sup> With the use of linear regression analysis, age-adjusted increments in blood pressure were estimated for 1-SD increments in the HRV measures.

The principal outcome, incident hypertension, was coded as no/yes and was analyzed with logistic regression models.<sup>18</sup> Each of the 4 selected HRV variables was assessed separately and adjusted for age, body mass index, cigarette smoking, and alcohol consumption, as well as baseline systolic and diastolic blood pressures. Heart rate did not enter the model. Results are summarized by OR and 95% confidence interval, with the OR expressed for a 1-SD decrement in the log-transformed HRV variable. In addition, HRV measures were compared between subjects who developed hypertension and those who remained normotensive at the 4-year follow-up examination. An association was considered statistically significant at a value of  $P < 0.05$ . All analyses were done on a Sparcstation 2 (SUN Microsystems) using the Statistical Analysis System (SAS).<sup>19</sup>

**Results****Subjects Selected**

HRV data were available for 2722 subjects; 567 subjects using antihypertensive medication and 113 with a history of myocardial infarction or congestive heart failure were excluded from analysis: therefore, 931 men and 1111 women were eligible for the study. For the analyses of incident hypertension, 472 subjects (245 men and 227 women) were excluded because of presence of hypertension at the index examination, and 136 subjects did not attend the examination 4 years later. Of the subjects eligible (633 men and 801 women) for the incidence study, 119 men and 125 women developed hypertension at the follow-up examination 4 years later.

**Clinical and HRV Characteristics**

At the index examination, subjects with hypertension were older than those with normal blood pressure (Table 1). After age adjustment, body mass index, baseline systolic and diastolic blood pressures, and mean heart rate were higher in hypertensive men and women compared with the normotensives. Alcohol consumption was higher in hypertensive men, whereas no significant difference was observed for smoking

**TABLE 1. Mean Age and Age-Adjusted Clinical Characteristics of Hypertensive and Normotensive Subjects at Index Examination**

Characteristic	Men		Women	
	NT (n=686)	HTN (n=245)	NT (n=884)	HTN (n=227)
Age, y	48.4±0.5	56.7±0.6*	49.3±0.4	61.6±0.8*
BMI, kg/m <sup>2</sup>	26.4±0.2	27.7±0.3	24.5±0.2	26.0±0.3
Cigarettes/d	6.5±0.5	7.9±0.8	5.7±0.5	5.3±0.9
Alcohol, oz/wk	3.9±0.2	5.1±0.3†	2.0±0.2	2.1±0.3
Coffee, cups/d	2.7±0.1	2.5±0.2	2.0±0.8	1.8±0.2
SBP, mm Hg	120±0.5	143±0.7*	117±0.4	145±0.8*
DBP, mm Hg	77±0.3	89±0.5*	73±0.3	86±0.5*
Heart rate, bpm	71.0±0.4	74.5±0.6*	75.1±0.3	77.5±0.7*

NT indicates normotensive; HTN, hypertensive; BMI, body mass index; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Results are expressed as mean±SEM.

\*P<0.0001, †P<0.0002.

and coffee consumption (Table 1). After adjustment for the clinical covariates, all HRV measures, with the exception of the LF/HF ratio, were significantly reduced in subjects with hypertension compared with those with normal blood pressure (Table 2).

**Progression to Hypertension**

The baseline adjusted HRV values in normotensive men who developed hypertension during 4 years of follow-up were reduced in comparison to those who remained normotensive (Table 3). In women, LF and HF were lower at baseline in those who developed hypertension during follow-up. Table 3 also shows the adjusted OR corresponding to a 1-SD decrement of each HRV measure. These analyses revealed that LF was associated with new-onset hypertension in men (OR, 1.38; 95% confidence interval, 1.04 to 1.83).

On the basis of this model, crude probabilities of progression to hypertension as a function of LF are displayed in

**TABLE 2. Comparison of Adjusted Measures of Heart Rate Variability Between Hypertensive and Normotensive Subjects at Index Examination**

Variable	Men		Women	
	NT (n=686)	HTN (n=245)	NT (n=884)	HTN (n=227)
In SDNN	4.52±0.01	4.42±0.02*	4.46±0.01	4.36±0.02*
In LF	6.82±0.02	6.62±0.04*	6.56±0.02	6.37±0.05†
In HF	5.46±0.03	5.31±0.05§	5.48±0.03	5.31±0.05§
In LF/HF	1.36±0.02	1.31±0.03	1.08±0.01	1.06±0.03
In Very LF	7.63±0.02	7.47±0.02†	7.46±0.02	7.30±0.04‡
In TP	8.10±0.02	7.93±0.04*	7.92±0.02	7.75±0.04†
In r-MSSD	3.43±0.02	3.34±0.03§	3.41±0.01	3.31±0.03§
In pNN50	1.72±0.04	1.42±0.08‡	1.64±0.04	1.35±0.08§

NT indicates normotensive; HTN, hypertensive. All HRV measures are natural log (ln) transformed values, expressed as mean±SEM. All measures are adjusted for age, body mass index, smoking, and alcohol consumption.

\*P<0.0001, †P<0.0005, ‡P<0.001, §P≤0.01.

**TABLE 3. ORs for Incident Hypertension on Follow-up Among Normotensive Subjects According to HRV Measures at Baseline**

HRV Variables	Adjusted Mean HRV Values at Baseline		Adjusted OR for HTN per 1 SD Decrement in ln HRV	
	NT*	HTN*	1 SD	OR (95% CI)
Men (n=633)	(n=514)	(n=119)		
In SDNN	4.56	4.52	0.277	1.23 (0.96–1.57)
In LF	6.96	6.84	0.688	1.38 (1.04–1.83)
In HF	5.57	5.48	0.855	1.17 (0.90–1.52)
In LF/HF	1.39	1.36	0.451	1.09 (0.87–1.38)
Women (n=801)	(n=676)	(n=125)		
In SDNN	4.49	4.51	0.306	1.01 (0.79–1.28)
In LF	6.68	6.66	0.762	1.12 (0.86–1.46)
In HF	5.58	5.57	0.897	1.13 (0.87–1.45)
In LF/HF	1.09	1.10	0.449	0.95 (0.76–1.20)

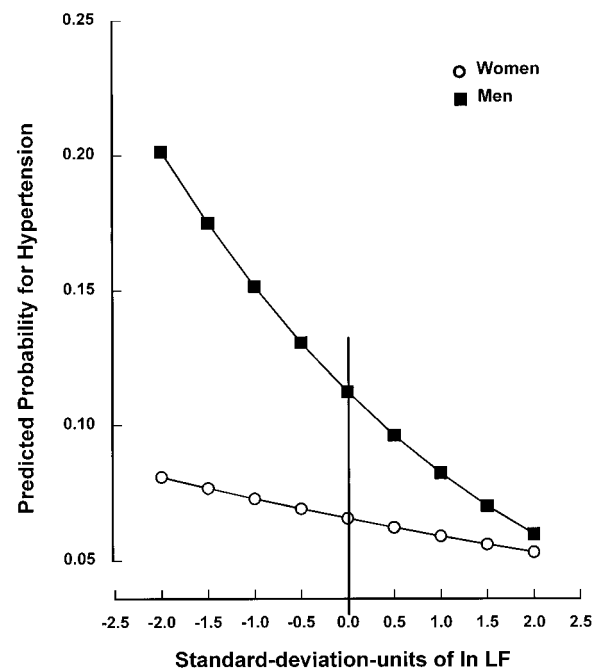
NT indicates normotensive; HTN, hypertensive; and CI, confidence interval. Mean HRV values adjusted for age, body mass index, smoking, and alcohol intake. OR adjusted for age, body mass index, smoking, alcohol intake, and baseline systolic and diastolic blood pressures.

\*Hypertension status on follow-up.

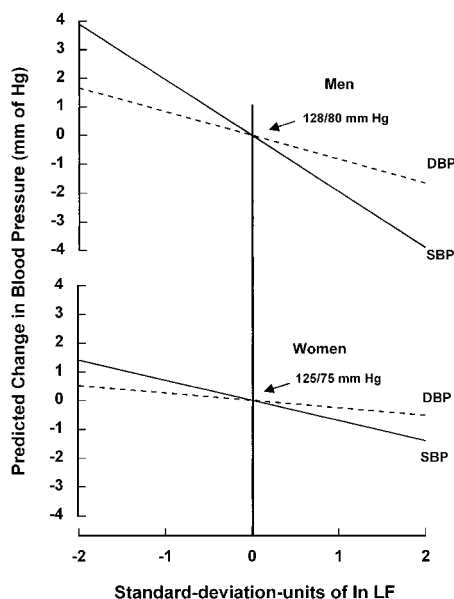
Figure 1. This has been plotted for nonsmoking men and women (with mean values for other covariates) at 0.5-SD decremental units. There is a steep curvilinear relation between LF and the incidence of hypertension in men; this relation was less striking in women.

**Change in Blood Pressure**

The impact of LF on longitudinal blood pressure change as a continuous variable was analyzed using multiple linear re-



**Figure 1.** Plots of probability of developing hypertension during 4-year follow-up as a function of natural-log transformed low frequency power (ln LF). The crude probability of developing hypertension is displayed for men and women per 0.5-SD units of natural-log transformed LF.



**Figure 2.** Line plots of predicted changes in blood pressure during 4-year follow-up as a function of the natural-log transformed low frequency power ( $\ln$  LF). This line graph was plotted for nonsmoking men and women with mean values for other covariates. The crude predicted rise in blood pressure (both systolic and diastolic) is displayed per 1-SD unit of natural-log transformed LF.

gression analysis. After adjustment for clinical covariates and baseline blood pressure, a 1-SD decrement in LF was associated with a mean increase of 1.95 mm Hg in systolic and 0.83 mm Hg in diastolic blood pressure in men and 0.70 mm Hg in systolic and 0.26 mm Hg in diastolic blood pressure in women. Figure 2 displays the linear relations between blood pressure changes during follow-up and LF. The magnitude of change in blood pressure as a function of LF was larger in men than in women, with a shallower trend observed for changes in diastolic compared with systolic blood pressure.

## Discussion

Our findings suggest the presence of reduced LF in men who are at risk for developing hypertension. The presence of reduced HRV in hypertensive subjects and the association of LF with new-onset hypertension are consistent with the hypothesis that dysregulation of the autonomic nervous system plays a role in the pathogenesis of hypertension.

Because changes in blood pressure affect autonomic tone and vice versa, HRV measures differ in hypertensive subjects when compared with those with normal blood pressure. Our findings of reduced HRV in systemic hypertension concur with results from 3 recently published population-based studies.<sup>6,7,11</sup> These studies were either restricted to men<sup>7</sup> or examined HRV in men and women pooled together<sup>6,11</sup> and included subjects on a variety of cardioactive medications.<sup>6,7</sup> In contrast, our study included a larger population-based sample in which referral bias was inherently minimal. We examined the association between HRV and blood pressure separately in healthy middle-aged men and women free from the confounding effects of cardioactive medications.

The absence of a difference in the LF/HF ratio between normotensive and hypertensive individuals could be explained by variable responsiveness of the neural regulatory mechanisms between individuals<sup>20</sup> and the fact that the LF/HF ratio correlated poorly with other HRV measures.<sup>6</sup>

## Predictors of Hypertension

After adjustment for age, body mass index, smoking, alcohol consumption, and baseline systolic and diastolic blood pressures, the LF component of the power spectral analysis remained predictive of the development of hypertension in men. Earlier work from Framingham has shown adiposity to be a strong predictor of hypertension in men and women.<sup>21</sup> A noteworthy finding in our study was that the LF component of HRV in men was observed to be a stronger predictor of hypertension than body mass index, a measure of obesity. These findings are in contrast to those of a recent study that identified HF to be a better predictor of incident hypertension when compared with LF.<sup>11</sup> This difference can be explained by methodological differences; Liao et al<sup>11</sup> studied ECG recordings of 2 minutes in duration, which may be insufficient in length to appropriately measure the LF. The association between HF and incident hypertension in that report<sup>11</sup> was similar in direction but stronger compared with our study. This could be explained by the fact that the authors did not adjust for baseline differences in body mass index and baseline blood pressure in the multivariable estimation of incident hypertension. A total of 244 subjects developed hypertension (cumulative incidence of 17%) in the present report compared with 64 (5%) in the study by Liao et al.<sup>11</sup>

Gender differences in baseline HRV,<sup>6,22</sup> hormonal changes accompanying essential hypertension,<sup>23</sup> and cyclic changes of HRV observed in women<sup>24</sup> may help explain the poorer predictive value of HRV in women. The weak relation observed between HRV and diastolic blood pressure as opposed to systolic blood pressure (Figure 2) could be a reflection of the low incidence of diastolic hypertension in the middle-aged Framingham Heart Study population. Subjects with diastolic hypertension at the index examination also may have been more likely to receive drug treatment and therefore be excluded from follow-up for changes in diastolic blood pressure than those with systolic hypertension; this could have attenuated the relation between HRV and diastolic blood pressure.

## Strengths and Limitations

An important strength of this study is the well-characterized study sample through the many years of follow-up. This information allowed us to select subjects who were free of clinically apparent cardiovascular disease, which can alter autonomic function and HRV measurements. Additionally, the relatively large number of subjects who developed hypertension allowed more precise estimation of the risk of hypertension and permitted adjustment for age and baseline blood pressure.

This study was based on intermediate-duration recordings, which yield different values for SDNN than shorter or longer recordings. The recordings were obtained when subjects underwent an extensive clinical evaluation and are not rep-

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 resting blood pressure measurements. It is uncertain in which direction this would have biased our results.

### Clinical Implications

The present study extends the clinical utility of HRV beyond its role in the surveillance of diabetics and patients after myocardial infarction.<sup>25,26</sup> A reduction in HRV is associated with an increased risk of cardiac mortality<sup>27</sup> and has been shown to predict risk for cardiac events<sup>25,28</sup> and overall mortality.<sup>25,27</sup> Additional research is needed to determine whether reduced HRV contributes to the increased cardiac mortality in hypertension. It is possible that an assessment of HRV may help guide the selection of antihypertensive therapy.<sup>29</sup>

### Conclusions

HRV is reduced in men and women with systemic hypertension. Among normotensive men, lower HRV was associated with greater risk for developing hypertension. Estimation of LF using spectral analysis of ambulatory ECG recordings improves the prediction of risk of hypertension in men above that which can be obtained from measurements of baseline systolic and diastolic blood pressures, body mass index, and age. These findings are consistent with the hypothesis that autonomic dysregulation is present in the early stage of hypertension.

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