Nighttime Vagal Cardiac Control and Plasma Fibrinogen Levels in a Population of Working Men and Women

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Background: Elevated plasma fibrinogen levels have prospectively been associated with an increased risk of coronary artery disease in different populations. Plasma fibrinogen is a measure of systemic inflammation crucially involved in atherosclerosis. The vagus nerve curtails inflammation via a cholinergic antiinflammatory pathway. We hypothesized that lower vagal control of the heart relates to higher plasma fibrinogen levels.

Methods: Study participants were 559 employees (age 17–63 years; 89% men) of an airplane manufacturing plant in southern Germany. All subjects underwent medical examination, blood sampling, and 24-hour ambulatory heart rate recording while kept on their work routine. The root mean square of successive differences in RR intervals during the night period (nighttime RMSSD) was computed as the heart rate variability index of vagal function.

Results: After controlling for demographic, lifestyle, and medical factors, nighttime RMSSD explained 1.7% ($P = 0.001$), 0.8% ($P = 0.033$), and 7.8% ($P = 0.007$), respectively, of the variance in fibrinogen levels in all subjects, men, and women. Nighttime RMSSD and fibrinogen levels were stronger correlated in women than in men. In all workers, men, and women, respectively, there was a mean ± SEM increase of 0.41 ± 0.13 mg/dL, 0.28 ± 0.13 mg/dL, and 1.16 ± 0.41 mg/dL fibrinogen for each millisecond decrease in nighttime RMSSD.

Conclusions: Reduced vagal outflow to the heart correlated with elevated plasma fibrinogen levels independent of the established cardiovascular risk factors. This relationship seemed comparably stronger in women than men. Such an autonomic mechanism might contribute to the atherosclerotic process and its thrombotic complications.

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Fibrinogen is a large glycoprotein that is synthesized by the liver and circulates in normal concentrations of 200–450 mg/dL in plasma.[1] Meta-analyses showed a prospective association between elevated plasma fibrinogen levels even in the normal range and an increased risk of coronary artery disease (CAD) in different populations.[2,3] This relationship exists independently of established cardiovascular risk factors, which are also correlates of fibrinogen.[2] Fibrinogen is higher in women than in men and in smokers than in nonsmokers.[1,2] Fibrinogen increases with age, higher body mass index, higher blood pressure, dyslipidemia, impaired glucose tolerance, and diabetes.[1,2,4] In contrast, fibrinogen levels are lower with regular physical activity and alcohol consumption.[1,2]

The mechanisms by which fibrinogen contributes to the initiation and progression of the

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atherosclerotic process and its thrombotic complications are likely manifold and as yet not completely understood.[1] In addition to its major functions in the coagulation cascade as a precursor of fibrin and as a cofactor for platelet aggregation, fibrinogen is a major acute-phase protein.[1] During the acute-phase response, proinflammatory cytokines are secreted, among them interleukin-6 that stimulates the liver to synthesize and release fibrinogen resulting in a 2- to 10-fold increase in its plasma level.[5,6] Chronic inflammation at a lower level than during the acute phase is crucially involved in atherosclerosis.[7] In this process, elevated fibrinogen might simply be viewed as an innocent bystander indicating ongoing low-grade systemic inflammation.[1] By playing a more active role, however, fibrinogen that escapes the vasculature in response to endothelial cell retraction at sites of inflammation might give rise to fibrin accumulation in atherosclerotic lesions.[8] Moreover, circulating fibrinogen was shown to stimulate macrophages to produce inflammatory mediators.[9]

Via stimulation of acetylcholine receptors on tissue macrophages in the heart and other organs, the vagus nerve exerts a tonic inhibitory control on proinflammatory cytokine production.[10] Impaired vagal control of this cholinergic anti-inflammatory pathway might give rise to many inflammation-related diseases, including cardiovascular diseases.[11] One means of expressing vagal function is by measuring parasympathetic indices of heart rate variability such as high-frequency (HF) power and root mean square of successive differences in RR intervals (RMSSD).[12] In line with the reasoning of anti-inflammatory properties exerted by the vagus nerve,[10,11] some[13,14] but not all[15–19] studies showed an inverse relationship between HF power and RMSSD on the one hand and interleukin-6 and C-reactive protein on the other in healthy and patient populations.

Previous studies on a relationship between tonic vagal control of the heart and circulating fibrinogen concentrations are inconsistent. In community samples, fibrinogen correlated inversely with HF power and RMSSD in young men and women[16] and with HF power in middle-aged men but not in women.[20] No correlation between fibrinogen and RMSSD was observed in elderly men and women.[21] In patients with CAD, fibrinogen correlated inversely with HF power in women patients,[22] whereas no such correlation was found in male patients[17] or in depressed patients of either sex.[18] On the whole, part of these studies were performed in comparably small samples not allowing for extensive adjustment for correlates of fibrinogen,[18,20] in particular age groups,[16,20,21] and either women or men,[17,22] while not systematically investigating differences by gender.

This study aimed to further explore the relationship between vagal control of the heart and plasma fibrinogen levels in an ample sample of working men and women. We hypothesized an inverse relationship between parasympathetic outflow to the heart and fibrinogen concentration independent of previous correlates of fibrinogen levels. Because of emerging gender differences in the relationship between vagal function and cardiovascular risk factors and outcome,[23] we additionally stratified our analysis by gender.

MATERIALS AND METHODS

Study Participants

The study was approved by the institutional review board and all participants gave written informed consent. Subjects were recruited from an airplane manufacturing plant in southern Germany and spanned the entire work force between 17 and 63 years. A majority of participants were engineers or highly skilled mechanics. In total, 657 workers underwent a medical examination including a full-day recording of heart rate. Of these, 559 subjects had a complete data set in terms of gender, age, history of myocardial infarction, physical activity, alcohol intake, smoking status, body mass index, blood lipids, blood pressure, hematocrit, heart rate variability, and fibrinogen levels allowing us to perform full multivariate linear regression analysis. The 98 subjects with incomplete data did not differ in age ($P = 0.67$) and the proportion of gender ($P = 0.51$) from those with a complete data set. Because of the epidemiological nature of our study, we did not exclude subjects based on their medical history and medication use but controlled for history of myocardial infarction.

Demographic, Lifestyle, and Medical Assessment

All participants were examined between 9 AM and 11 AM on a typical work day. Prior to the heart rate recording, a medical examination was performed. Age and gender were recorded and

subjects had their height and weight measured to compute body mass index. Blood pressure was obtained via sphygmomanometry from the dominant arm in the seated position after a 20-minute rest period. Participants completed a questionnaire asking into the amount of habitual physical activity, intake of alcoholic beverages, and smoking status.

Heart rate was recorded as beat-to-beat intervals with a Mini-Vitaport electrocardiogram (ECG) logger (Becker Medical Systems, Karlsruhe, Germany), sampling the three-electrode ECG at a rate of 400 Hz. Beat-to-beat intervals were calculated as the interval between two successive R-spikes. After instrumentation with the ambulatory ECG recorder, individuals proceeded with their daily work until 3.30 PM and then continued with their usual leisure and sleep activities. The next morning between 7.15 AM and 8.00 AM the ECG monitors were disconnected and fasting blood samples were collected.

Biochemical Analyses

Blood samples were immediately transported to a commercial laboratory (Synlab, Augsburg, Germany), where they were analyzed within 6 hours of sample collection. Plasma fibrinogen level was determined by a routine clotting assay following the Clauss method.[24] Serum lipid levels, plasma glucose, and hematocrit were determined by standardized methods using routine laboratory analyzers (Hitachi 911, Roche Diagnostics, Rotkreuz, Switzerland).

Heart Rate Variability

Raw data for the determination of heart rate variability were processed in accordance with previously published guidelines.[12] Beat-to-beat intervals corresponding to a heart rate below 30 or above 200 bpm were excluded, as well as any intervals resulting in an increase or drop in heart rate by more than 30% between successive intervals. RMSSD in RR intervals is an estimate of short-term components of heart rate variability and was calculated from all valid adjacent beat-to-beat intervals. RMSSD is currently understood as the most reliable time-domain-based index of high-frequency beat-to-beat variations. There is nocturnal predominance of parasympathetic activity, which moreover, can be recorded more reliably during the night than during the day when environmental factors interfere. Therefore, we used Night-Time RMSSD as our representative measure of parasympathetic neural regulation of the heart. Nighttime was defined as the sleep period from 30 minutes after falling asleep until 30 minutes prior to awakening verified by diary, accelerometer, and visual inspection of the heart rate data.

Statistical Analysis

All calculations were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P \leq 0.05$ (2-tailed). Independent samples *t*-test and chi-square test were used to test for group differences in continuous and categorical variables, respectively. Pearson correlation analysis was applied to estimate the bivariate association between two variables. Because men contributed a larger sample than women, the mere significance level of a correlation coefficient may be misleading. Therefore, we used Fisher's Z-transform of correlation coefficients to compare whether the strength of correlations between two variables would significantly differ between men and women.[25]

We employed hierarchical linear regression analysis, using forced entry, to test whether nighttime RMSSD is associated with fibrinogen levels independent of covariates. To reduce the risk of model overfitting given the relatively small sample of women, we performed data reduction[26] using mean arterial blood pressure and the low-density to high-density lipoprotein ratio as independent variables. The distribution of standardized residuals suggested multivariate normality (i.e., normal distribution of fibrinogen levels for each combination of values of the independent variables). Leverage statistic applying Cook's distance verified that no cases unduly influenced the regression models. Effect sizes were expressed as R square values.

RESULTS

Subject Characteristics

Table 1 shows the demographic, lifestyle, and medical factors of the entire sample and by gender. Women were significantly younger, drank less alcohol, and had expectedly lower hematocrit than men. Compared to men, women had a more favorable metabolic profile as evidenced by relatively lower levels of body mass index, serum lipids,

Table 1. Characteristics of Study Participants

	All (n = 559)	Men (n = 495)	Women (n = 64)	P-Value
Age [yrs]	41.1 ± 11.4	42.4 ± 10.9	34.1 ± 12.5	<0.001
History of MI [%]	1	1	0	1.000
Physical activity [%][a]	20, 23, 27, 30	21, 23, 27, 29	14, 26, 30, 30	0.597
Alcohol [g/d]	16.7 ± 17.1	18.0 ± 17.6	6.3 ± 5.8	<0.001
Smoker [%]	27	25	36	0.068
Body mass index [kg/m^2]	26.3 ± 4.0	26.6 ± 3.7	24.1 ± 5.0	<0.001
Triglycerides [mg/dL]	154.6 ± 131.2	158.2 ± 125.8	126.3 ± 165.6	0.067
LDL cholesterol [mg/dL]	131.5 ± 38.4	133.6 ± 37.7	115.0 ± 39.6	<0.001
HDL cholesterol [mg/dL]	54.6 ± 13.0	53.2 ± 12.0	65.2 ± 15.3	<0.001
LDL-to-HDL ratio	2.6 ± 1.0	2.6 ± 1.0	1.9 ± 1.0	<0.001
Fasting glucose [mg/dL]	91.9 ± 16.8	92.8 ± 17.4	85.4 ± 10.0	0.001
Systolic BP [mmHg]	122.6 ± 14.9	123.8 ± 14.6	113.9 ± 14.5	<0.001
Diastolic BP [mmHg]	80.2 ± 10.4	80.8 ± 10.3	75.7 ± 9.6	<0.001
Mean BP [mmHg]	94.4 ± 11.2	95.1 ± 11.1	88.4 ± 10.8	<0.001
Hematocrit [%]	45.2 ± 2.8	45.6 ± 2.4	41.5 ± 2.7	<0.001
Nighttime RMSSD [ms]	45.9 ± 22.6	45.8 ± 22.5	45.7 ± 23.0	.943
Fibrinogen [mg/dL]	294.3 ± 62.5	291.1 ± 59.2	318.8 ± 80.3	.009

Values are given as means ± SD.
[a]No exercise, regular exercise <1 h/wk, regular exercise 1–2 h/wk, regular exercise >2 h/wk.
BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; RMSSD = root mean square of successive differences in RR intervals.

plasma glucose, and blood pressure. While fibrinogen levels were higher in women than in men, nighttime RMSSD did not differ between male and female workers. Sixteen subjects (2.9%) had fibrinogen levels >450 mg/dL deemed to reflect an abnormally high plasma concentration.[1]

Bivariate Associations with Fibrinogen Level

There was a significant correlation between lower nighttime RMSSD values and higher plasma fibrinogen levels in the entire sample (Fig. 1A) as well as in men (Fig. 1B) and women (Fig. 1C). The correlation strength between nighttime RMSSD and fibrinogen levels was not different between men and women ($P = 0.53$).

Table 2 shows the bivariate relationships between plasma fibrinogen concentration and those subject characteristics that were subsequently entered as independent variables into the multivariate regression equation. In the entire sample, fibrinogen significantly correlated with virtually all demographic, lifestyle, and medical factors, except alcohol consumption. All associations were in the predicted direction with the exception of the inverse correlation between hematocrit and fibrinogen.

Higher levels of body mass index and of mean BP were associated with higher fibrinogen concentration in men and women. Older age, less physical activity, higher levels of triglycerides, and greater LDL-to-HDL ratio correlated with higher levels of fibrinogen in men. Lower amount of alcohol intake and higher fasting glucose levels showed a relationship with higher fibrinogen concentration in women. The correlation strength between fibrinogen levels and age ($P = 0.046$), alcohol intake ($P = 0.030$), and fasting glucose levels ($P = 0.018$) differed between men and women.

Multivariate Associations with Fibrinogen Level

Table 3 shows the partial correlation coefficients between plasma fibrinogen levels and demographics, lifestyle variables, medical factors, and nighttime RMSSD. While the full model accounted for 14.3% and 12.2% of the total variance in fibrinogen concentration in all subjects and men, respectively, it explained 49% of the variance in women. Lower nighttime RMSSD values significantly predicted higher fibrinogen levels in the entire sample as well as in men and women independent of the other covariates. After all covariates had been taken into account, nighttime RMSSD levels explained an additional 1.7%, 0.8%, and 7.8% of the variance in

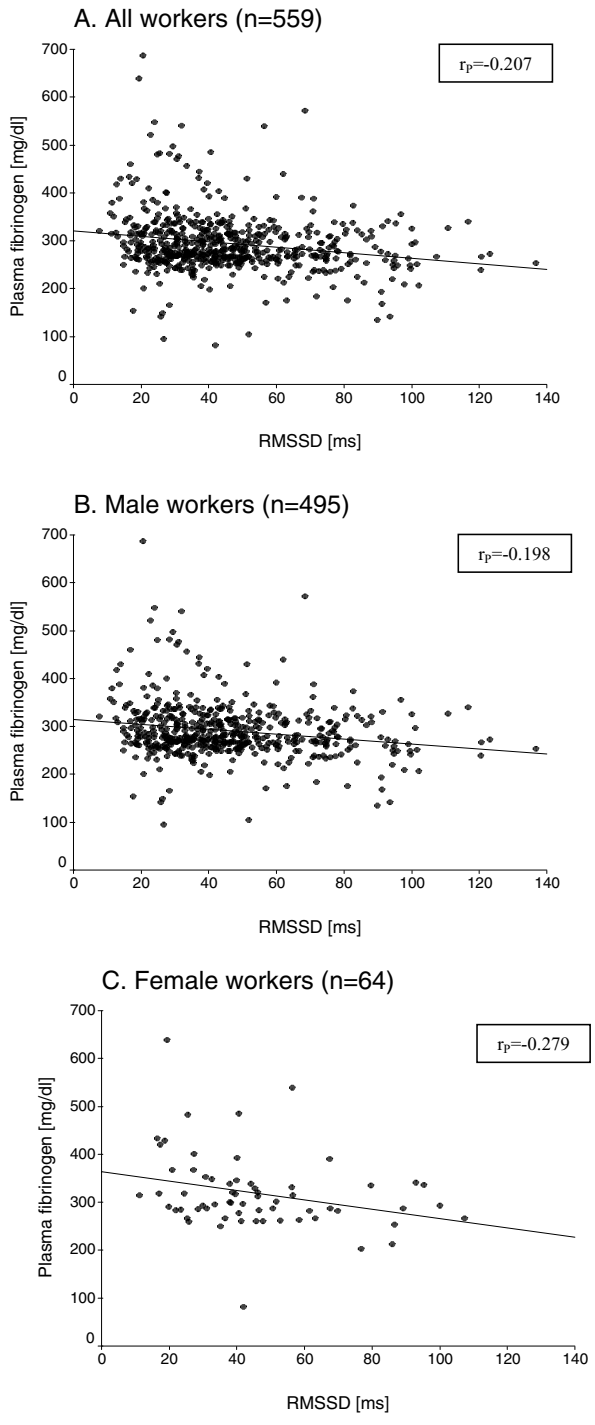

Figure 1. Relationship between heart rate variability and fibrinogen levels. Scatterplots for the univariate association between the root mean square of successive differences in RR intervals (RMSSD) during the nighttime and plasma fibrinogen concentration in all subjects (Panel A; $P < 0.001$), men (Panel B; $P < 0.001$), and women (Panel C; $P = 0.026$). r_P = Pearson correlation coefficient.

fibrinogen levels in all subjects, men, and women, respectively. The unstandardized regression coefficient (B) indicated that for each millisecond decrease in nighttime RMSSD, there was a mean ± SEM increase of 0.41 ± 0.13 mg/dL, 0.28 ± 0.13 mg/dL, and 1.16 ± 0.41 mg/dL fibrinogen in all subjects, men, and women, respectively.

In addition to nighttime RMSSD, female gender, smoking, higher body mass index and lower hematocrit emerged as independent predictors of higher fibrinogen levels in the entire sample. Older age, less physical activity, smoking, and higher body mass index, and lower hematocrit independently predicted higher fibrinogen levels in men. Younger age, less alcohol intake, and higher fasting glucose were revealed as independent predictors of higher fibrinogen concentration in women.

The correlation strength between fibrinogen and age ($P < 0.001$), physical activity ($P = 0.022$), alcohol consumption ($P = 0.037$), fasting glucose ($P = 0.007$), and nighttime RMSSD ($P = 0.033$) differed between women and men. Particularly, this analysis suggests that although lower nighttime RMSSD was independently associated with higher plasma fibrinogen concentration in men and women, this association was comparably stronger in women.

DISCUSSION

We found an inverse association between parasympathetic outflow to the heart and the plasma fibrinogen concentration in a working population of men and women. Notably, the relationship between relatively lower vagal cardiac control and higher plasma fibrinogen levels was independent of demographic, lifestyle, and medical factors previously shown to be correlates of fibrinogen concentration. The relationship was also not confounded by male employees with a previous myocardial infarction and hematocrit as an index of hemoconcentration, the latter commonly increasing fibrinogen concentration. Performing a subgroup analysis by gender, vagal tone was an independent predictor of plasma fibrinogen levels in male and female workers. Moreover, the independent correlation between lower vagal tone and higher fibrinogen was significantly stronger in women than men.

Corroborating previous work,[1–4] plasma fibrinogen showed bivariate correlations with virtually all established cardiovascular risk factors assessed in the total study population and to some extent

Table 2. Bivariate Correlation Coefficients with Plasma Fibrinogen Concentration

	All (n = 559)		Men (n = 495)		Women (n = 64)	
	Pearson corr.	P-value	Pearson corr.	P-value	Pearson corr.	P-value
Gender	−0.141	0.001	–		–	
Age*	0.145	0.001	0.229	<0.001	−0.038	0.766
History of MI	0.088	0.037	0.104	0.020	–	
Physical activity	−0.126	0.003	−0.151	0.001	−0.019	0.883
Alcohol intake*	−0.036	0.392	0.010	0.827	−0.278	0.026
Smoking	0.106	0.012	0.077	0.088	0.197	0.118
Body mass index	0.183	<0.001	0.177	<0.001	0.396	0.001
Triglycerides	0.108	0.011	0.117	0.009	0.138	0.278
LDL-to-HDL ratio	0.129	0.002	0.171	<0.001	0.164	0.194
Fasting glucose*	0.084	0.048	0.082	0.070	0.383	0.002
Mean blood pressure	0.121	0.004	0.126	0.005	0.317	0.011
Hematocrit	−0.116	0.006	−0.060	0.180	−0.032	0.802

* = significantly different correlation strength between men and women ($P < 0.05$).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

also in the subgroups of men and women. In the adjusted analysis, fibrinogen was higher in women than men and showed a direct relationship to smoking and increased body mass index in all subjects and the male group, while an inverse association with physical activity emerged in men only. In women, higher fibrinogen levels were predicted by lower alcohol intake and higher fasting glucose. Whereas increased fibrinogen level was independently predicted by older age in men, younger age was a rather unexpected predictor in women. Although not investigated, the latter could be explained by oral contraceptive use that increases plasma fibrinogen more strongly in younger than in older women.[27] Altogether, the observation of so many independent correlates of fibrinogen suggests that our analysis was appropriately controlled for important confounders of a relationship between vagal function and fibrinogen levels.

Table 3. Partial Correlation Coefficients with Plasma Fibrinogen Concentration

	All (n = 559)		Men (n = 495)		Women (n = 64)	
	Partial corr.	P-value	Partial corr.	P-value	Partial corr.	P-value
Gender	−0.124	0.004	–		–	
Age*	0.056	0.118	0.117	0.006	−0.351	0.009
History of MI	0.058	0.176	0.065	0.131	–	
Physical activity*	−0.067	0.117	−0.097	0.024	0.211	0.126
Alcohol intake*	−0.070	0.103	−0.049	0.253	−0.321	0.018
Smoking	0.112	0.009	0.084	0.050	0.230	0.095
Body mass index	0.133	0.002	0.090	0.035	0.245	0.074
Triglycerides	0.005	0.905	0.004	0.930	−0.093	0.501
LDL-to-HDL ratio	0.052	0.228	0.056	0.192	0.080	0.567
Fasting glucose*	0.003	0.949	−0.026	0.536	0.329	0.015
Mean blood pressure	0.052	0.224	0.030	0.481	0.149	0.281
Hematocrit	−0.097	0.024	−0.088	0.041	−0.049	0.723
Nighttime RMSSD*	−0.138	0.001	−0.091	0.033	−0.364	0.007
R square of full model	0.143		0.122		0.490	
Analysis of variance	$F_{13,545} = 7.0$, $P < 0.001$		$F_{12,482} = 5.6$, $P < 0.001$		$F_{11,52} = 4.6$, $P < 0.001$	

* = significantly different correlation strength between men and women ($P < 0.05$).
HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; RMSSD = root mean square of successive differences in RR intervals.

Less than 3% of our subjects had an abnormally high fibrinogen concentration. However, the cardiovascular risk associated with fibrinogen has been shown to increase with relatively elevated values already in the normal range (200–450 mg/dL) of the fibrinogen concentration of an apparently healthy population.[2,3] Therefore, our findings might suggest clinical relevance in several respects. First, the magnitude of the vagal effect on plasma fibrinogen concentration was comparable to that of several established cardiovascular risk factors. Specifically, in the entire sample, the independent variance of plasma fibrinogen explained by gender (1.3%), smoking (1.1%), and body mass index (1.5%) was of similar size to the 1.7% explained by nighttime RMSSD. In the subgroups of men and women, nighttime RMSSD also explained as much of the individual variance in fibrinogen levels as did other significant correlates of fibrinogen. Second, a previous meta-analysis yielded a relative CAD risk of 1.8 (95% CI 1.6–2.0) for individuals in the top third versus those in the bottom third of the population fibrinogen level.[3] In this meta-analysis, which was largely confirmed by a more recent one,[2] the absolute difference in plasma fibrinogen between cases and noncases was approximately 20 mg/dL. In comparison, we found that for 1 SD decrease in nighttime RMSSD (i.e., 23 ms), fibrinogen increased by 9 mg/dL, 6 mg/dL, and 27 mg/dL, respectively, in all subjects, men, and women. Third, several gender differences in cardiovascular disease-related associates and determinants of plasma fibrinogen have been emphasized.[28] In agreement with this notion, we found a significant difference between men and women in terms of the correlation strength between fibrinogen and age, alcohol consumption, physical activity, and glucose levels. In addition, due to their generally higher fibrinogen level, women could be at higher cardiovascular risk than men. In our women, the average fibrinogen level was 28 mg/dL higher than in men after covariate adjustment. Given that with each millisecond increase in RMSSD women achieved a lowering of 1.16 mg/dL fibrinogen, their nighttime RMSSD would need to increase by 1 SD to reach the average fibrinogen level of men. Identifying lowered vagal control of heart rate as a stronger contributor to elevated fibrinogen levels in women than men may support efforts to improve assessment and management of CAD in women.[23,28] For instance, it has been suggested that enhancing parasympathetic cardiac function by means of regular exercising and relaxation training might favorably affect inflammation[29] and associated cardiovascular disease outcome.[11,29] Physical conditioning may reduce plasma fibrinogen levels,[30] although it has not been explored whether this effect is more relevant in women than in men.[28] Mindfulness-based stress relaxation training recently resulted in a decrease in plasma levels of Interleukin-6,[31] which further downstream in the inflammation cascade, might theoretically mitigate fibrinogen production by the liver.[6]

The limitations and strengths of our study are to be viewed within the particular study population and design. Given the sizeable number of covariates, our sample of women was comparably small such that overadjustment and instability of the regression model might be an issue. This also precluded taking into account additional potentially important covariates of fibrinogen such as related to sleep and menopausal status.[32,33] However, the partial correlation coefficient of this relationship was greater than the bivariate one suggesting that the independent relationship between nighttime RMSSD and fibrinogen was not overly weakened by taking into account too many covariates. Also, the size of our sample of women allowed us to detect a significant association between nighttime RMSSD and fibrinogen, while a previous study did not find an association between HF power and fibrinogen in a sample of 50 women most of whom were also employees.[20] Our findings are not unequivocally transferable to CAD patients. In CAD, fibrinogen levels were generally found to be increased[34] and vagal cardiac control to be decreased.[35] In our bivariate analysis, men with a previous myocardial infarction had a significantly higher fibrinogen level than men without infarction. Particularly in male patients with CAD, the underlying disease might dilute the relationship between vagal tone and fibrinogen. In two previous studies investigating 52 men[17] and 44 men and women combined[18] all with CAD, HF power did not correlate with fibrinogen levels, whereas we found a significant association in women patients with CAD.[22] The predictive value of fibrinogen as a cardiovascular risk factor has consistently been shown across different age groups (i.e., 40–59, 60–69, and $\geq$70 years).[2] However, many of our subjects were below the age of 40. Therefore, whether an increase in fibrinogen in relation to nighttime RMSSD confers cardiovascular risk in our comparably young study population is equivocal. We

obtained one single measurement of fibrinogen. Repeated sampling on different days would clearly have increased the reliability of values. Nonetheless, this is common procedure in many epidemiological studies[1,2] and repeated sampling might have to consider seasonal variation in fibrinogen with relatively highest concentrations observed in the winter time.[36] Moreover, we determined fibrinogen during the morning hours when the risk of an acute coronary event is highest as compared to other diurnal and nocturnal time periods.[37] Importantly, it is assumed that fibrinogen-related increase in blood viscosity and decreased vagal tone both contribute to the heightened matutinal coronary risk.[38]

In summary, we found an inverse relationship between vagal cardiac control and circulating fibrinogen concentration in a population sample of working men and women. While this association was independent of correlates of fibrinogen, the strength of the association was seemingly greater in women than men. The findings provide one mechanistic explanation for how vagal function via an anti-inflammatory pathway might be involved in atherosclerosis progression complicated by atherothrombotic events. Since nighttime RMSSD accounted for a rather small proportion of the variance in fibrinogen levels, the clinical importance of this association remains to be demonstrated.

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