Autonomic Function and Prothrombotic Activity in Women after an Acute Coronary Event

Roland von Känel, M.D.¹ and Kristina Orth-Gomér, M.D., Ph.D.²

Abstract

Background: The link between decreased heart rate variability (HRV) and atherosclerosis progression is elusive. We hypothesized that reduced HRV relates to increased levels of prothrombotic factors previously shown to predict coronary risk.

Methods: We studied 257 women (aged 56 ± 7 years) between 3 and 6 months after an acute coronary event and obtained very low frequency (VLF), low frequency (LF), and high frequency (HF) power, and LF/HF ratio from 24-hour ambulatory ECG recordings. Plasma levels of activated clotting factor VII (FVIIa), fibrinogen, von Willebrand factor antigen (VWF:Ag), and plasminogen activator inhibitor-1 (PAI-1) activity were determined, and their levels were aggregated into a standardized composite index of prothrombotic activity.

Results: In bivariate analyses, all HRV indices were inversely correlated with the prothrombotic index explaining between 6% and 14% of the variance ($p < 0.001$). After controlling for sociodemographic factors, index event, menopausal status, cardiac medication, lifestyle factors, self-rated health, metabolic variables, and heart rate, VLF power, LF power, and HF power explained 2%, 5%, and 3%, respectively, of the variance in the prothrombotic index ($p < 0.012$). There were also independent relationships between VLF power and PAI-1 activity, between LF power and fibrinogen, VWF:Ag, and PAI-1 activity, between HF power and FVIIa and fibrinogen, and between the LF/HF power ratio and PAI-1 activity, explaining between 2% and 3% of the respective variances ($p < 0.05$).

Conclusions: Decreased HRV was associated with prothrombotic changes partially independent of covariates. Alteration in autonomic function might contribute to prothrombotic activity in women with coronary artery disease (CAD).

Introduction

HEART RATE VARIABILITY (HRV)—the physiological fluctuation in length of consecutive R-R intervals—is an established measure of vagal modulation of heart rate, with decreased HRV indicating abnormal autonomic input to the heart.¹ Different measures of decreased HRV predicted sudden arrhythmic death,² coronary atherosclerosis progression,³ prospective risk of acute coronary events,⁴ and death from coronary artery disease (CAD).⁴ Assessment of HRV thus may provide a useful tool to understand better how autonomic function could affect the atherosclerotic process and its mediators.⁵

In women with CAD, decreased HRV related to higher plasma levels of the proinflammatory cytokine interleukin-6 (IL-6),⁶ consistent with the paradigm of anti-inflammatory properties exercised by the vagus nerve via an anticholinergic pathway.⁷ In reasonably healthy subjects, we found a positive association between IL-6 and soluble tissue factor when HRV was low but not when it was high⁸ and an inverse association between HRV and plasma levels of plasminogen activator inhibitor-1 (PAI-1).⁹ Inflammation and coagulation interact in accelerating coronary atherosclerosis.¹⁰ Thus, reduced vagal control might elicit not only inflammation but also coagulation activation in women with CAD.

¹Department of General Internal Medicine and Cardiovascular Prevention and Rehabilitation, Swiss Cardiovascular Center Berne, Inselspital, Bern University Hospital, and University of Bern, Switzerland.

²Division of Preventive Medicine, Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden.

Financial support was provided by the NIH (RO1HL45785-02), the Swedish Science Foundation (521-2005-6921), and the Bank of Sweden Tercenary Fund (2000-0349-01-02) (all to K.O.-G.)

To test this assumption, we measured the relationship between indices of HRV and hemostatic factors in women patients who had survived an acute coronary event 3–6 months prior to the investigation. We measured plasma levels of activated clotting factor VII (FVIIa), fibrinogen, von Willebrand factor antigen (VWF:Ag), and PAI-1 activity. These factors have been associated with an increased risk of CAD,¹¹ with most evidence for fibrinogen and VWF:Ag coming from meta-analyses.^{12,13} We hypothesized that HRV indices show an inverse relationship with levels of hemostatic factors independent of variables commonly affecting HRV^{14–16} and hemostasis,^{11,17–19} such as sociodemographic and metabolic factors, lifestyle habits, and cardiac medication.

Materials and Methods

Patients and study design

The study protocol of the Stockholm Female Coronary Risk Study was approved by the Ethics Committee of the Karolinska Institutet, and all subjects provided informed consent. The details of the study design have been described elsewhere.²⁰ In brief, women patients aged ≤ 65 years who were hospitalized for acute myocardial infarction (AMI) or unstable angina pectoris (UAP) were included between 1991 and 1994. The diagnosis of AMI was made and quality assured following World Health Organization (WHO) criteria of typical chest pain, cardiac enzyme patterns, and diagnostic electrocardiographic (ECG) changes. UAP was defined as new onset of severe AP or deterioration of known stable AP in the 4 weeks before hospital admission. A total of 292 women (110 AMI, 182 UAP) were enrolled, that is, 87% of female patients identified during the defined time period. Of the 13% (43 patients) who could not be included in the study, 5 died during the 3 months between hospitalization and examination, 13 were too sick to come to the research center, 2 could not participate because of transportation difficulties, and 2 declined because they were recruited for other studies. Another 21 patients declined to participate for other reasons, including inability to speak Swedish fluently.

A questionnaire was mailed to subjects before their visit to the research clinic. The questionnaire included questions about educational level, smoking history, physical activity during leisure time categorized as sedentary or active, and daily alcohol intake.²⁰ Each questionnaire was checked by a research nurse for problems or missing data.

All patients were examined at the research clinic as outpatients between 3 and 6 months after discharge from the hospital, when they were considered to be in a stable cardiac, metabolic, and hemostatic condition. The first day of the study included a detailed cardiological examination, resting ECG, and placement of a 24-hour Holter ECG monitor. The second day included extensive interview and questionnaire assessments of lifestyle and behavioral characteristics, as well as anthropometric measures and full lipid and routine laboratory profiles, including hemostatic factors. Body mass index (BMI) and mean blood pressure (BP) were determined by standard methods. Cardiac medication (aspirin, oral anticoagulants, beta-blockers, statins, and angiotensin converting enzyme [ACE] inhibitors) were abstracted from hospital charts and verified on arrival at the research clinic. Self-rated health was assessed using one question with regard to limited activities due to the illness during the past 5

years rated on a Likert scale ranging from 1 (completely healthy) to 5 (never entirely free from illness).

Measurement of heart rate variability

Patients were hooked up with a two-channel ambulatory ECG device (Spacelab 90205, Spacelab Inc., Redmond, WA) for 24 hours while maintaining their medication. A commercial software (Aspect Holter System, Daltek, Borlänge, Sweden) identified arrhythmias and classified QRS complexes. Consecutive R-R intervals were expressed in centiseconds with 5-minute epochs. To be accepted for additional analysis, at least 96% of QRS complexes were required to be classified as normal by the Daltek system.²¹ The time series of R-R intervals were resampled with a frequency of two samples per second. Gaps in time series consequent to nonnormal R-R intervals were filled with values calculated by linear interpolation between adjacent normal R-R intervals. We computed the frequency domain measures high frequency (HF) power (0.15–0.40 Hz), low frequency (LF) power (0.04–0.15 Hz), and very low frequency (VLF) power (0.0033–0.04 Hz) in milliseconds squared; the LF/HF power ratio was also calculated. HRV recordings were available in 266 patients. Of these, we excluded 9 patients who had HRV measures >3 standard deviations (SD) above the transformed sample mean (i.e. outliers); therefore, we performed our analyses on a final sample of 257 women patients.

Laboratory measurements

Venous blood was drawn between 8 AM and 10 AM, fasting from midnight. Samples were immediately centrifuged at 3000g for 10 minutes at ambient temperature, and plasma was stored at -70°C . Fibrinogen was determined by a polymerization rate method.²² VWF:Ag was analyzed by an enzyme-linked immunosorbent assay (ELISA) (Asserachrom Stago, Asnières, France). FVIIa was determined by a clotting assay using soluble recombinant truncated tissue factor.²³ PAI-1 activity was measured by a functional spectrophotometric method (Biopool AB, Umea, Sweden). Interassay and intraassay coefficients of variation (CV) were 4% for fibrinogen, 2% for vWF:Ag, $<10\%$ for FVIIa, and $<12\%$ for PAI-1 activity. Cholesterol was determined by cholesterol oxidase phenol 4-aminoantipyrine peroxidase (CHOD-PAP) enzymatic methods with reagents from Boehringer Mannheim (Germany).

Statistical analysis

Data were analyzed using SPSS 13.0 software (SPSS Inc., Chicago, IL). The level of significance was set at $p < 0.05$ (two-tailed). Because of a nonnormal distribution (Kolmogorov-Smirnov test), LF power, HF power, heart rate, fibrinogen, FVIIa, and VWF:Ag values were logarithmically transformed; VLF power and PAI-1 values were square-root transformed, and age was normalized using Blom transformation. For clarity, we present all data in original units. For comparisons between different groups, we used Student's t test for continuous variables and chi-square test for categorical variables. Pearson correlations quantified the bivariate relationship between two variables.

To investigate the predictive value of HRV measures for levels of hemostasis factors, we computed hierarchical linear regression analysis adjusting for 18 *a priori* determined variables possibly affecting HRV and hemostasis. To statis-

tically account for multiple comparisons among four HRV measures and four hemostatic factors, we performed data reduction,²⁴ calculating a composite index of prothrombotic activity as previously described.²⁵ Standardized z-scores of transformed values of the four hemostasis factors were added up and divided by four, yielding a normally distributed score termed prothrombotic index. We first performed an omnibus test to confirm that the prothrombotic index significantly correlated with each HRV measure applying Bonferroni correction ($p < 0.013$). In *post hoc* analysis, we then

identified the predictive value of individual HRV measures for each hemostatic factor.

Results

Subjects' characteristics

Reliable HRV recordings were available in 257 patients, 91 of whom had AMI and 166 of whom had UAP. Table 1 shows the distribution of demographic, medical, and lifestyle factors and the proportion of occasionally missing data.

TABLE 1. CHARACTERISTICS OF 257 WOMEN WITH CORONARY ARTERY DISEASE^a

	n	% of sample	Mean	SD	Median	Range
Sociodemographic factors						
Age, years	257		56.2	6.9	58.0	37–66
Educational attainment						
Mandatory	159	62				
High school	50	19				
College/university	43	17				
Menopausal status						
Premenopausal	53	20				
Postmenopausal with HRT ^b	30	12				
Postmenopausal without HRT	172	67				
Medication use						
Aspirin	177	69				
Oral anticoagulants	15	6				
Beta-blocker	161	63				
Statins	19	7				
ACE inhibitors	27	11				
Lifestyle factors						
Smoking status						
Current	50	20				
Former	124	48				
Never	83	32				
Physical activity						
Sedentary	62	24				
Active	192	75				
Alcohol consumption, g/day						
≤5 (light drinker)	178	69				
>5 (moderate drinker)	68	27				
Self-rated health	260		3.34	1.22	3.0	1.0–5.0
Metabolic factors						
Body mass index, kg/m ²			27.0	4.5	26.5	18.6–44.1
Total serum cholesterol, mmol/L			6.5	1.2	6.5	3.2–11.4
Mean blood pressure, mm Hg			91.2	12.2	89.7	64.7–130.0
Diabetes mellitus diagnosis	33	13				
Heart rate, bpm	250		62.7	10.5	61.5	43–101
Heart rate variability measures						
Very low frequency power, msec ²	257		620	394	543	15–2052
Low frequency power, msec ²	257		420	351	346	7–2826
High frequency power, msec ²	257		312	424	218	12–4922
LF/HF power ratio	257		2.09	0.7	1.99	0.23–4.61
Hemostatic factors						
Prothrombotic index [z-score]	240		0.00	0.65	0.00	–1.50–2.23
Activated FVII, ng/mL	240		1.31	0.35	1.29	0.44–2.42
Fibrinogen, g/L	253		3.65	0.81	3.50	1.40–7.20
VWF antigen, IU/mL	253		1.53	0.78	1.35	0.62–7.32
PAI-1 activity, IU/mL	253		15.4	14.8	11.0	0–87.0

^aData were missing for educational attainment in 5 subjects (2%), for menopausal status in 2 subjects (1%), for physical activity in 3 subjects (1%), for alcohol consumption in 11 subjects (4%), for self-rated health in 6 subjects (2%), for cholesterol in 1 subject (<1%), for mean blood pressure in 6 subjects (2%), for diagnosis of diabetes in 18 subjects (7%), for heart rate in 7 subjects (3%), for prothrombotic index in 17 subjects (7%), for FVIIa in 17 subjects (7%), and for fibrinogen, VWF:Ag, and PAI-1 activity in 4 subjects each (2%).

^bACE, angiotensin converting enzyme; HRT, hormone replacement therapy.

Association between HRV and hemostatic factors

All HRV indices significantly correlated with the prothrombotic index ($p \leq 0.001$). The direction of these crude associations is illustrated in Figure 1, showing that lower HRV was consistently associated with higher prothrombotic activity. Table 2 shows the *post hoc* analysis with the bivariate correlation matrix of associations between the individual HRV measures and hemostatic factors. The vast majority of these associations were significant. The polarity of correlation coefficients suggested that a decrease in frequency domain measures was associated with an increase in all hemostatic factors.

HRV as predictor of prothrombotic index

Table 3 shows the results of the linear regression models. VLF power, LF power, HF power, and the LF/HF power ratio

significantly predicted the prothrombotic index after controlling for sociodemographic factors in block 1 ($p < 0.001$), for type of index event in block 2 ($p < 0.001$), for menopausal status in block 3 ($p < 0.001$), and for cardiac medication in block 4 ($p \leq .001$). When additionally controlling for lifestyle factors in block 5 ($p < 0.001$), self-rated health in block 6 ($p < 0.001$), metabolic factors in block 7 ($p < 0.003$), and heart rate in block 8 ($p < 0.012$), VLF power, LF power, and HF power, but not the LF/HF power ratio, maintained significance as independent predictors of the prothrombotic index. In the final models, VLF power, LF power, and HF power individually explained 2%, 5%, and 3%, respectively, of the variance in the prothrombotic index.

HRV as predictor of individual hemostatic factors

Table 4 shows the final models for the four hemostatic factors after all eight blocks of covariates had been adjusted (see

FIG. 1. Relationship between HRV and the prothrombotic index. The composite score of all hemostasis factors (prothrombotic index) correlated inversely with all HRV measures ($n = 240$). **(A)** Very low frequency (VLF) power ($r = -0.31$, $p < 0.001$). **(B)** Low frequency (LF) power ($r = -0.37$, $p < 0.001$). **(C)** High frequency (HF) power ($r = -0.26$, $p = 0.001$). **(D)** LF/HF power ratio ($r = -0.25$, $p < 0.001$). Log, logarithmically transformed values; Sqr, square-root transformed values.

TABLE 2. BIVARIATE ASSOCIATIONS BETWEEN HRV AND HEMOSTATIC FACTORS

Factor	VLF power	LF power	HF power	LF/HF ratio
FVIIa ^a	-0.13*	-0.16*	-0.15*	-0.12
Fibrinogen	-0.24***	-0.28***	-0.23***	-0.08
VWF:Ag	-0.24***	-0.32***	-0.19**	-0.23***
PAI-1:Act	-0.19**	-0.21***	-0.11	-0.20**

^aFVIIa, activated clotting factor VII; HF, high frequency; LF, low frequency; PAI-1:Act, plasminogen activator inhibitor-1 activity; VLF, very low frequency; VWF:Ag, von Willebrand factor antigen

Significance level of Pearson correlation coefficients: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 3 for detailed list of control variables). Lower levels of several HRV measures were independently associated with higher levels of prothrombotic factors. Specifically, lower levels of VLF power predicted higher levels of PAI-1 activity ($p = 0.011$), explaining 2% of the variance. Moreover, lower levels of LF power predicted higher levels of fibrinogen ($p = 0.016$), VWF:Ag ($p = 0.033$), and PAI-1 activity ($p = 0.004$), explaining between 2% and 3% of the respective variances. Lower levels of HF power predicted higher levels of FVIIa ($p = 0.027$) and of fibrinogen ($p = 0.020$), explaining 3% and 2% of the variance, respectively. Eventually, decreased sympathovagal balance was an independent predictor of increased PAI-1 activity ($p = 0.029$), explaining 2% of the variance.

Discussion

We showed an inverse relationship between HRV and both a composite prothrombotic index and individual levels of hemostatic factors, suggesting that decreased HRV is associated with prothrombotic changes in women with CAD. The associations between reduced VLF power, LF power, HF power, and higher prothrombotic index were independent of age, educational level, type of the index event, menopausal status, cardiac medication, lifestyle factors, self-rated health, metabolic variables, and resting heart rate. In con-

trast, the LF/HF power ratio was no longer an independent predictor of the prothrombotic index after cardiac medication had been taken into account. In terms of individual hemostatic factors, these showed crude associations with almost every HRV measure. Importantly, several of these relationships remained significant even after adjustment for covariates. PAI-1 activity level was independently predicted by lowered VLF power, LF power, and LF/HF power ratio, suggesting fibrinolytic capacity might be impaired when HRV is low. Increased fibrinogen was independently predicted by lowered LF power and lowered HF power. In addition, higher levels of VWF:Ag and FVIIa were independently predicted by lower levels of LF power and HF power, respectively. The metabolic syndrome is related to decreased HRV²⁶ and, moreover, confers a prothrombotic state that is characterized by increased levels of fibrinogen and PAI-1.¹⁸ Together with our previous finding of an increased PAI-1 concentration with reduced HRV, the findings from the present study suggest that the relationship between decreased HRV and the prothrombotic state is not fully accounted for by metabolic disturbances.

One particular HRV measure did not seem to predict individual hemostatic factors more strongly than any other. No consensus has been reached about whether some HRV measures are more useful than others in predicting cardiovascular risk.¹⁴ In fact, a decrease in different HRV measures²⁷ and an increase in various prothrombotic hemostatic factors have both been related to increased cardiovascular risk.¹¹ Also, the exact meanings of frequency-domain parameters of HRV as indices of autonomic function are only partially understood.¹⁴ Whereas the HF component particularly reflects vagal outflow (i.e., parasympathetic activity) to the heart, the LF component represents predominantly sympathetic outflow that to some extent is also influenced by parasympathetic modulation. The LF/HF power ratio is viewed as a quantification of the sympathetic/parasympathetic (i.e., sympathovagal) balance. The autonomic meaning of VLF power remains undetermined.¹⁴

As experts generally agree that vagal activity is the major contributor to the HF component of HRV,¹⁴ a cautious interpretation of our findings could be that reduced vagal control was associated with higher levels of prothrombotic ac-

TABLE 3. HIERARCHICAL LINEAR REGRESSION MODELS FOR PROTHROMBOTIC INDEX

Entered covariates (df)	VLF power	LF power	HF power	LF/HF ratio
1 3,231	-0.30/0.086	-0.36/0.122	-0.24/0.055	-0.25/0.59
2 4,230	-0.30/0.086	-0.36/0.122	-0.24/0.057	-0.24/0.054
3 5,227	-0.28/0.074	-0.36/0.113	-0.23/0.051	-0.23/0.051
4 10,222	-0.28/0.072	-0.35/0.107	-0.23/0.047	-0.22/0.045
5 13,206	-0.25/0.050	-0.33/0.083	-0.24/0.049	-0.14/0.014
6 14,201	-0.26/0.052	-0.34/0.087	-0.26/0.055	-0.13/0.013
7 18,177	-0.21/0.034	-0.29/0.058	-0.23/0.040	-0.11/0.009
8 19,175	-0.23/0.023	-0.32/0.048	-0.23/0.027	-0.12/0.010
R ² of entire model	0.373, $p < 0.001$	0.398, $p < 0.001$	0.377, $p < 0.001$	0.360, $p < 0.001$

Columns show standardized β -coefficients/ ΔR^2 (i.e., individual variance of prothrombotic index explained by the respective heart rate variability measure) after subsequent adjustment for eight blocks of covariates. Block 1: age, education (sociodemographic factors); block 2: type of index event; block 3: menopausal status; block 4: aspirin, oral anticoagulants, beta-blocker, statins, ACE inhibitors (cardiac medications); intake of each drug was coded as 1 = yes vs. 0 = no; block 5: smoking status, physical activity, alcohol consumption (lifestyle factors); block 6: self-rated health; block 7: BMI, total serum cholesterol, mean blood pressure, diabetes diagnosis (metabolic factors); block 8: resting heart rate. Significant β -coefficients after Bonferroni correction are given in bold ($p < 0.013$).

TABLE 4. FINAL LINEAR REGRESSION MODELS FOR INDIVIDUAL HEMOSTATIC FACTORS^a

Hemostatic factor	Degrees of freedom	VLF power	LF power	HF power	LF/HF ratio
FVIIa	19,175	−0.18/0.014 $R^2 = 0.225$, $p < 0.001$	−0.15/0.011 $R^2 = 0.222$, $p < 0.001$	−0.22/0.027 $R^2 = 0.238$, $p < 0.001$	−0.00/0.005 $R^2 = 0.211$, $p < 0.001$
Fibrinogen	19,188	−0.14/0.008 $R^2 = 0.214$, $p < 0.001$	−0.23/0.024 $R^2 = 0.230$, $p < 0.001$	−0.21/0.023 $R^2 = 0.229$, $p < 0.001$	0.03/0.001 $R^2 = 0.207$, $p < 0.001$
VWF:Ag	19,188	−0.06/0.001 $R^2 = 0.217$, $p < 0.001$	−0.20/0.019 $R^2 = 0.235$, $p < 0.001$	−0.12/0.001 $R^2 = 0.217$, $p < 0.001$	−0.13/0.012 $R^2 = 0.228$, $p < 0.001$
PAI-1 activity	19,188	−0.23/0.023 $R^2 = 0.348$, $p < 0.001$	−0.26/0.030 $R^2 = 0.355$, $p < 0.001$	−0.14/0.011 $R^2 = 0.336$, $p < 0.001$	−0.15/0.017 $R^2 = 0.342$, $p < 0.001$

^aColumns show standardized β -coefficients/ ΔR^2 (i.e., individual variance of hemostatic factors explained by the respective HRV measure) after subsequent adjustment for eight blocks of covariates as listed in the legend to Table 3. Significant β -coefficients are given in bold ($p < 0.05$).

tivity and of the individual hemostatic factors FVIIa and fibrinogen. In accordance with recently postulated anti-inflammatory properties of the vagus nerve,⁷ one could tentatively postulate an anticoagulant reflex exercised by the parasympathetic nervous system. More precisely, vagal function tonically inhibits release of proinflammatory cytokines from human macrophages.⁷ Unfortunately, we were unable to test for such a mechanism in the present study because we did not measure cytokines, which might have given rise to enhanced production of procoagulant molecules. For instance, tumor necrosis factor- α (TNF- α) may upregulate PAI-1 in adipose tissue such that the concentration of circulating PAI-1 increases.²⁸ Supporting this notion, we recently found that HF power was inversely associated with PAI-1 plasma concentration and, moreover, that a significant proportion of this relationship was mediated by the BMI.⁹ We also found a direct association between plasma IL-6 levels and procoagulant tissue factor when HF power was decreased.⁸

Apparent discrepancies exist in interpreting the LF component of HRV as viewed by some as a measure of sympathetic modulation and by others as a measure of both vagal and sympathetic activity.¹⁴ Increased plasma levels of fibrinogen were found after acute mental stress as well as in chronically stressed individuals.¹⁹ Plasma VWF:Ag levels increase in response to acute mental stress¹⁹ and to infusion of sympathomimetic compounds.²⁹ Elevated PAI-1 levels have been found in individuals under chronic psychological stress,¹⁹ and PAI-1 gene expression was responsive to stress hormones.³⁰ This could help explain why LF power that is critically affected by sympathetic tone¹⁴ was an independent predictor of the prothrombotic index and of levels of fibrinogen, VWF:Ag, and PAI-1 activity.

The observed relationship between decreased HRV and prothrombotic activity provides one mechanistic explanation of how reduced HRV could contribute to atherosclerosis progression and, ultimately, acute coronary events. A low-grade systemic hypercoagulable state promotes fibrin deposits within the atherosclerotic vessel wall, thereby accelerating plaque growth and coronary narrowing.³¹ Disturbed autonomic function might modulate hemostatic activity in a detrimental way to eventually cause overt atherosclerotic disease. Moreover, abundant research demonstrates that decreased HRV is associated with deleterious arrhythmia and

sudden cardiac death² often accompanied by thrombotic occlusions of coronary arteries, as demonstrated in autopsy.³² At times of atherosclerotic plaque rupture, concomitant hypercoagulability as kindled by autonomic dysfunction might promote coronary thrombus formation.

We mention several limitations of our study. The cross-sectional design does not allow interpretations of causality direction, although it seems unlikely that enhanced thrombotic activity would lead to an evident change in autonomic function. The individual variance in prothrombotic index and factors explained by HRV measures was rather small, and the clinical meaning remains unclear. We are unable to rule out the possibility of residual confounding because a range of additional factors might also contribute to HRV indices.¹⁴ For instance, part of vagal modulation could relate to both tissue destruction and the ongoing vascular process. We controlled for the type of index event and self-rated health as proxy measures of the degree of severity of the acute coronary event, but we had no more precise measures of myocardial damage available. The basic assumption that HRV reflects autonomic function in CAD is usually, but not always, true. Particularly, patients with a high degree of sinus arrhythmia from non-respiratory causes will not always have high HF power, so even excluding those with outlier values will not completely solve this issue.

In summary, we found evidence for the hypothesis that decreased HRV might contribute to CAD in women by its association with prothrombotic activity. Future research should attempt to show a causal or indirect relationship by more specifically identifying the biological mechanisms involved.

Disclosure Statement

There are no author conflicts of interest.

References

- Stein PK. Vagal tone: Myths and realities. *J Cardiovasc Electrophysiol* 2005;16:870.
- Hohnloser SH, Klingenhöfen T, Zabel M, Li YG. Heart rate variability used as an arrhythmia risk stratifier after myocardial infarction. *Pacing Clin Electrophysiol* 1997;20:2594.

3. Huikuri HV, Jokinen V, Syvanne M, et al. Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* 1999;19:1979.
4. Tsuji H, Larson MG, Venditti FJ Jr, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* 1996;94:2850.
5. Hamaad A, Lip GY, MacFadyen RJ. Heart rate variability estimates of autonomic tone: Relationship to mapping pathological and procedural stress responses in coronary disease. *Ann Med* 2004;36:448.
6. Janszky I, Ericson M, Lekander M, et al. Inflammatory markers and heart rate variability in women with coronary heart disease. *J Intern Med* 2004;256:421.
7. Tracey KJ. The inflammatory reflex. *Nature* 2002;420:853.
8. von Känel R, Nelesen RA, Mills PJ, Ziegler MG, Dimsdale JE. Relationship between autonomic tone, interleukin-6, and soluble tissue factor in reasonably healthy subjects. *Brain Behav Immun* 2008;22:461–468.
9. von Känel R, Nelesen RA, Ziegler MG, Mausbach BT, Mills PJ, Dimsdale JE. Relation of autonomic activity to plasminogen activator inhibitor-1 plasma concentration and the role of body mass index. *Blood Coagul Fibrinolysis* 2007;18:353.
10. Libby P, Simon DI. Inflammation and thrombosis: The clot thickens. *Circulation* 2001;103:1718.
11. Kannel WB. Overview of hemostatic factors involved in atherosclerotic cardiovascular disease. *Lipids* 2005;40:1215.
12. Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: An individual participant meta-analysis. *JAMA* 2005;294:1799.
13. Danesh J, Wheeler JG, Hirschfield GM, et al. C reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387.
14. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996;93:1043.
15. Horsten M, Ericson M, Perski A, Wamala SP, Schenck-Gustafsson K, Orth-Gomer K. Psychosocial factors and heart rate variability in healthy women. *Psychosom Med* 1999;61:49.
16. Thayer JF, Hall M, Sollers JJ 3rd, Fischer JE. Alcohol use, urinary cortisol, and heart rate variability in apparently healthy men: Evidence for impaired inhibitory control of the HPA axis in heavy drinkers. *Int J Psychophysiol* 2006;59:244.
17. Lee KW, Lip GY. Effects of lifestyle on hemostasis, fibrinolysis, and platelet reactivity: A systematic review. *Arch Intern Med* 2003;163:2368.
18. Nieuwdorp M, Stroes ES, Meijers JC, Buller H. Hypercoagulability in the metabolic syndrome. *Curr Opin Pharmacol* 2005;5:155.
19. von Känel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: A biobehavioral pathway to coronary artery disease? *Psychosom Med* 2001;63:531.
20. Orth-Gomér K, Mittleman MA, Schenck-Gustafsson K, et al. Lipoprotein(a) as a determinant of coronary heart disease in young women. *Circulation* 1997;95:329.
21. Nygard ME. An automated system for ECG monitoring. *Comput Biomed Res* 1987;12:181.
22. Vermynen C, de Vreker R, Verstraete M. A rapid enzymatic method for assay of fibrinogen fibrin polymerization time (FPT test). *Clin Chim Acta* 1963;8:418.
23. Morrissey JH, Macik BG, Neuenschwander PF, Comp PC. Quantitation of activated factor VII levels in plasma using a tissue factor mutant selectively deficient in promoting factor VII activation. *Blood* 1993;81:734.
24. Babyak MA. What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med* 2004;66:411.
25. von Känel R, Dimsdale JE, Patterson TL, Grant I. Acute procoagulant stress response as a dynamic measure of allostatic load in Alzheimer caregivers. *Ann Behav Med* 2003;26:42.
26. Brunner EJ, Hemingway H, Walker BR, et al. Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: Nested case-control study. *Circulation* 2002;106:2659.
27. Kleiger RE, Stein PK, Bigger JT Jr. Heart rate variability: Measurement and clinical utility. *Ann Noninvasive Electrocardiol* 2005;10:88.
28. Birgel M, Gottschling-Zeller H, Rohrig K, Hauner H. Role of cytokines in the regulation of plasminogen activator inhibitor-1 expression and secretion in newly differentiated subcutaneous human adipocytes. *Arterioscler Thromb Vasc Biol* 2000;20:1682.
29. von Känel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis *in vivo*. *Eur J Haematol* 2000;65:357.
30. Venugopal B, Sharon R, Abramovitz R, Khasin A, Miskin R. Plasminogen activator inhibitor-1 in cardiovascular cells: Rapid induction after injecting mice with kainate or adrenergic agents. *Cardiovasc Res* 2001;49:476.
31. Falk E, Fernandez-Ortiz A. Role of thrombosis in atherosclerosis and its complications. *Am J Cardiol* 1995;75:3B.
32. Virmani R, Burke AP, Farb A. Sudden cardiac death. *Cardiovasc Pathol* 2001;10:211.

Address reprint requests to:

Roland von Känel, M.D.

Professor of Medicine

Department of General Internal Medicine

University Hospital, Inselspital

CH-3010 Bern

Switzerland

E-mail: roland.vonkaenel@insel.ch