

Decreased heart rate variability is associated with higher levels of inflammation in middle-aged men

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Background Many traditional risk factors for coronary artery disease (CAD) are associated with altered autonomic function. Inflammation may provide a link between risk factors, autonomic dysfunction, and CAD. We examined the association between heart rate variability (HRV), a measure of autonomic function, and inflammation, measured by C-reactive protein (CRP) and interleukin-6 (IL-6).

Methods We examined 264 middle-aged male twins free of symptomatic CAD. All underwent ambulatory electrocardiogram monitoring and 24-hour ultra low, very low, low, and high-frequency power were calculated using power spectral analysis. C-reactive protein and IL-6 were measured, and risk factors including age, smoking, hypertension, lipids, diabetes, body mass index (BMI), depression, and physical activity were assessed.

Results Physical activity, BMI, high-density lipoprotein cholesterol, smoking, depression, and hypertension were directly associated with CRP and IL-6 and inversely associated with one or more HRV variables. There was a graded inverse relationship between all HRV parameters (except high frequency) and CRP and IL-6. After adjustment for age, BMI, activity, high-density lipoprotein, smoking, hypertension, depression, and diabetes, ultra low frequency and very low frequency remained significant predictors of CRP ($P < .01$).

Conclusions C-reactive protein is associated with decreased HRV, even after controlling for traditional CAD risk factors. Autonomic dysregulation leading to inflammation may represent one pathway through which traditional risk factors promote development of CAD. (Am Heart J 2008;156:759.e1-759.e7.)

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This study received financial support from the National Institutes of Health (Bethesda, MD) (K24HL077506, R01 HL68630, and R01 AG026255), Emory General Clinical Research Center (Atlanta, GA) (MO1-RR00039), and American Heart Association (Dallas, TX) (0245115N). United States Department of Veterans Affairs (Washington, DC) has supported the development and maintenance of the Vietnam Era Twin Registry. Invaluable assistance provided by VA Cooperative Study Program (Washington, DC); Department of Defense (Washington, DC); National Personnel Records Center (Overland, MO); National Archives, and Records Administration (College Park, MD); the Internal Revenue Service (Washington, DC); NIH (Bethesda, MD); National Opinion Research Center (Chicago, IL); National Research Council (Washington, DC); National Academy of Sciences (Washington, DC); and Institute for Survey Research (Washington, DC), Temple University (Philadelphia, PA).

Ambulatory electrocardiogram analysis software is provided by GE Medical, Milwaukee, WI.

Submitted March 11, 2008; accepted July 10, 2008.

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0002-8703/\$ - see front matter

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doi:10.1016/j.ahj.2008.07.009

Physiological and behavioral risk factors for the development of coronary artery disease (CAD), such as smoking, obesity, inactivity, hypertension, diabetes, hypercholesterolemia, and depression, are well known. The physiological pathways linking these factors to development of CAD, however, are incompletely understood. These risk factors alter autonomic function,¹⁻⁴ which in turn is associated with both the progression of CAD⁵ and increased mortality in the general population.^{6,7} Further, each of these well-known risk factors is associated with increased levels of inflammatory mediators⁸ associated with atherogenesis.⁹⁻¹¹ In laboratory experiments, alterations in both sympathetic and parasympathetic function activate proinflammatory cytokines.¹²⁻¹⁶ Thus, autonomic dysregulation resulting in inflammation could represent a pathway through which traditional risk factors lead to progression of CAD. Heart rate variability (HRV), a measure of beat-to-beat heart rate (HR) fluctuations over time, is an established measure of autonomic function.¹⁷ A relationship between HRV and inflammation, as measured by serum markers such as interleukin-6 (IL-6) and C-reactive protein (CRP), has been demonstrated in patients with congestive heart failure and acute coronary syndromes.¹⁸⁻²⁰ Studies of populations free of overt cardiac disease have suggested similar relationships.²¹⁻²³

The Twins Heart Study (THS) is an investigation of psychological, behavioral, and biological risk factors for subclinical cardiovascular disease using a twins design, which includes comprehensive autonomic evaluation. In this population, we investigated the interrelationships between 24-hour HRV, sympathetic activity, (norepinephrine), inflammatory markers (CRP and IL-6), and traditional risk factors.

Methods

Subjects

Twins included in THS were selected from the Vietnam Era Twin Registry, which includes 7,369 middle-aged male-male twin pairs, both of whom served in the United States military during the Vietnam War.²⁴ The THS included 180 monozygotic and dizygotic twin pairs (360 twins), all born between 1946 and 1956. The methods of construction of this sample have been described previously.^{4,25} Briefly, the twins were free of a self-reported previous diagnosis of cardiovascular disease based on survey data collected in 1990, including a previous diagnosis of myocardial infarction, coronary heart disease, angina, congestive heart failure, or stroke or a previous coronary angioplasty or coronary bypass surgery. From this group, random samples of twins in 2 strata were selected: one stratum included twins discordant for a lifetime history of major depression, and in a second stratum, neither twin had a history of depression. Subjects who had since developed cardiovascular disease based on current medical history ($n = 35$) were excluded. All twins were examined in pairs at the Emory University General Clinical Research Center (GCRC) (Atlanta, GA) between March 2002 and March 2006. All data collection occurred during the 27-hour GCRC admission under controlled conditions. Activity was limited to the environs of the GCRC and kept similar for each pair. This protocol was approved by the Institutional Review Board at Emory University. Informed consent was obtained from all subjects.

Measurement of HRV

Twins wore a Holter monitor (GE Medical SEER digital system, General Electric, Fairfield, CT) for 24 hours. The HRV data were analyzed in the frequency domain following published methodology.^{26,27} Holter recordings were digitally sampled and analyzed. Each tape was manually processed and edited for accurate identification of QRS complexes. A list of R-R intervals with annotations denoting normal beats, ectopics, and artifact was saved and later transferred to a computer workstation for further processing and analysis with customized software. The file was first edited to remove ectopics and artifact. Gaps in the time series were filled by interpolation with linear splines. The R-R interval file was then resampled at 3.41 Hz (1,024 samples per 5 minutes) to create a uniformly spaced time series. The power spectrum was computed from the fast Fourier transform of the time series modified by a Parzen window to reduce spectral leakage and corrected for window attenuation and boxcar sampling. Because long-term autonomic function was the goal of this study, the fast Fourier transform was performed on the 24-hour R-R interval file. The power spectrum was integrated over 4 discrete frequency bands²⁷: ultra low frequency (ULF), <0.0033 Hz; very low frequency (VLF), 0.0033 to <0.04 Hz; low frequency (LF), 0.04 to <0.15 Hz; high

Table I. Subject characteristics (N = 260)

| Variables | Values |
|----------------------------------|-------------------|
| Age, y | 54.4 \pm 2.85 |
| Smoker, current/former/never | 43 / 111 / 106 |
| Hypertension, yes/no | 114 / 146 |
| Diabetes, yes/no | 21 / 239 |
| Physical activity | 7.51 \pm 1.58 |
| BMI, kg/m ² | 29.1 \pm 4.61 |
| SBP, mm Hg | 128.4 \pm 16.03 |
| DBP, mm Hg | 80.6 \pm 10.64 |
| TC, mg/dL | 189.1 \pm 37.96 |
| HDL-C, mg/dL | 38.6 \pm 9.49 |
| LDL-C, mg/dL | 125.2 \pm 33.72 |
| Glucose, mg/dL | 100.0 \pm 16.26 |
| Norepinephrine, μ g per 24 h | 23.6 \pm 16.9 |
| BDI scores | 4.88 \pm 6.72 |
| IL-6, pg/mL | 2.29 \pm 2.04 |
| CRP, mg/L | 2.32 \pm 3.12 |
| HR, beat/min | 66.4 \pm 8.75 |
| Ln ULF | 9.14 \pm 0.56 |
| Ln VLF | 7.63 \pm 0.57 |
| Ln LF | 6.69 \pm 0.72 |
| Ln HF | 5.41 \pm 0.88 |

Mean \pm SD for continuous variables and count number for categorical variables. SBP, Systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol.

frequency (HF), 0.15 to <0.40 Hz. Subjects with $>20\%$ interpolated R-R intervals or <18 recorded hours were excluded. Our main measures of interest were ULF and VLF, which reflect overall autonomic balance²⁸ and were the measures previously most closely correlated with cardiovascular outcomes.²⁷

Markers of inflammation

Plasma IL-6 was assessed using commercially available ELISA kits (R and D Systems, Minneapolis, MN), and all samples run in duplicate. Inter- and intra-assay variability of this assay is reliably $<10\%$. Plasma CRP was measured with the Beckman Coulter High Sensitivity CRP assay on the Synchron LX-20 analyzer (Both made by Beckman Coulter Diagnostics, Fullerton, CA). Subjects with values of IL-6 above mean plus 3 times the SD were excluded, as correction for outliers.

Other measurements

A medical history and a physical examination were obtained from all twins. Blood pressure was measured in sitting position after 10 minutes of rest, using the average of 2 measurements 5-minute apart. Venous blood samples were drawn after an overnight fast. Total triglycerides were determined by enzymatic methods (Beckman Coulter Diagnostics). Direct high-density lipoprotein (HDL) and low-density lipoprotein cholesterol were measured with homogeneous assays (Equal Diagnostics, Exton, PA). Glucose levels were measured on the Beckman CX7 chemistry autoanalyzer. Norepinephrine concentration was measured in 24-hour urine collections, reflecting long-term sympathetic responses,²⁹ during the period of Holter monitoring, using high-performance liquid chromatography coupled with dual-electrode Coulometric electrochemical detection (reductive mode). Physical activity was

Table II. Correlation coefficients between HRV, inflammatory markers, and covariates

| Variables | Ln ULF | Ln VLF | Ln LF | Ln HF | Ln IL-6 | Ln CRP |
|-------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Age | 0.02 | 0.09 | −0.05 | −0.10 | 0.07 | 0.09 |
| Smoking | −0.23 [†] | −0.24 [†] | −0.20 [†] | −0.09 | 0.18 [†] | 0.21 [†] |
| Hypertension | −0.14 | −0.15 | −0.18 [†] | −0.19 [†] | 0.03 | 0.12 [*] |
| Diabetes | −0.12 | −0.12 | −0.13 | −0.04 | 0.12 | 0.12 |
| Physical activity | 0.12 | 0.23 [†] | 0.18 [†] | 0.06 | −0.25 [†] | −0.28 [†] |
| BMI | −0.05 | −0.06 | −0.14 [*] | −0.05 | 0.10 | 0.29 [†] |
| HR | −0.59 [†] | −0.66 [†] | −0.41 [*] | −0.35 [†] | 0.17 [†] | 0.29 [†] |
| SBP | −0.03 | 0.04 | 0.01 | −0.04 | −0.01 | 0.07 |
| DBP | −0.09 [†] | 0.02 | 0.06 | −0.03 | −0.14 [†] | 0.02 |
| TC | 0.04 | 0.08 | 0.06 | 0.08 | −0.06 | 0.002 |
| HDL-C | 0.10 | 0.19 [†] | 0.11 | 0.09 [*] | −0.23 [†] | −0.24 [†] |
| LDL-C | 0.11 | 0.15 | 0.16 | 0.13 | −0.01 | 0.03 |
| Glucose | −0.01 | −0.08 | −0.13 | −0.07 | 0.04 | 0.07 |
| Norepinephrine | −0.16 [*] | −0.23 [†] | −0.16 [*] | −0.02 | 0.20 [†] | 0.21 [†] |
| BDI scores | −0.22 [†] | −0.24 [†] | −0.15 [*] | −0.08 | 0.21 [*] | 0.14 |
| Ln IL-6 | −0.21 [*] | −0.23 [†] | −0.19 | −0.02 | — | — |
| Ln CRP | −0.29 [†] | −0.26 [†] | −0.22 [†] | −0.04 | 0.55 [†] | — |

P value is adjusted for correlations within twin pairs.

^{*}*P* < .05.

[†]*P* < .01.

assessed by the Baecke Questionnaire of Habitual Physical Activity (global physical activity score). Cigarette smoking was classified into current versus never or past smoker. Diabetes mellitus was defined as fasting glucose level >126 mg/dL or taking antidiabetic medications. Depression was measured by the Beck Depression Inventory.

Statistical analyses

Correlations between HRV parameters, inflammatory markers, and CAD risk factors as listed in [Tables I and II](#) were assessed using Pearson correlations for continuous variables and Spearman correlations for categorical variables. The association of inflammation with HRV, adjusting for age, body mass index (BMI), physical activity, HDL cholesterol (HDL-C), smoking, hypertension, diabetes, and depression, was tested using generalized estimating equations (GEEs) to account for the dependency between siblings (SAS PROC GENMOD). To improve the distributional properties of the HRV parameters and inflammatory markers, data were transformed to the logarithmic scale. Analyses were repeated controlling for use of antihypertensive, cholesterol-lowering, and diabetic medications.

Twins share maternal factors and familial and childhood/adolescent environment such as socioeconomic, lifestyle, and other factors shared by individuals of similar family background. The matched nature of the co-twin control design minimizes confounding by these factors. If the paired effects are smaller than the effects seen when twins are analyzed as separate individuals, this is evidence that there is confounding by factors shared by co-twins. In addition, daily activities and other environmental factors during the ambulatory electrocardiogram recording are controlled in paired analyses because co-twins were examined at the same time and under identical conditions. Therefore, we also conducted a matched-pair analysis in which CRP levels were compared within twin pairs discordant for HRV-tertile for ULF (tertile cutoffs 7.49-8.90/8.90-9.41/9.42-10.56) and VLF (tertile cutoffs 5.17-7.43/7.44-

7.87/7.89-9.19), that is, pairs whose members had HRV values that fell into different tertiles of the HRV sample distribution, for example, one twin had ULF in the highest tertile and his brother in a lower (n = 49 twin pairs). Analyses were performed using the statistical software SAS, version 9.0 (SAS, Inc, Cary, NC).

Results

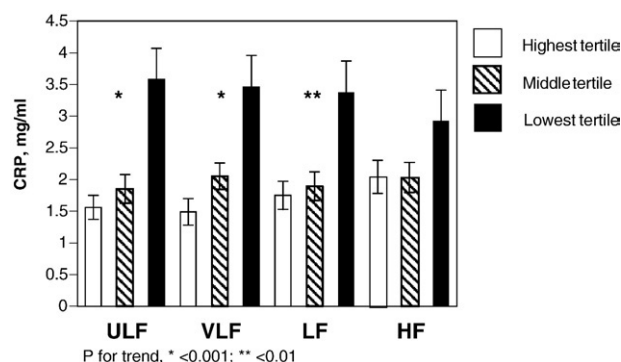
Study population

Of the 325 twins free of cardiovascular disease, 264 had ambulatory electrocardiogram data adequate for analysis. Two subjects and their co-twins were excluded due to IL-6 levels above the outlier threshold. The remaining 260 subjects comprise the study population. The mean age was 54 years (range, 47-60). Eight percent had diabetes, 44% hypertension, and 17% were current smokers. Subject characteristics are listed in [Table I](#).

Associations between HRV, inflammatory markers, and clinical factors

Bivariate correlations between HRV, inflammatory markers, and clinical factors are shown in [Table II](#). Physical activity, BMI, HDL-C, smoking, hypertension, and depression were directly associated with CRP and/or IL-6 and inversely associated with one or more HRV variables.

Both CRP and IL-6 were correlated with all HRV variables except HF, most strongly with ULF and VLF. When the group was categorized into tertiles based on HRV variables ([Figure 1](#)), CRP increased as HRV decreased. Plasma concentrations of CRP of those in the lowest tertile of ULF and VLF were more than twice that of those in the highest tertile. A similar pattern was seen for IL-6.

Figure 1

Levels of CRP for each HRV variable, with grouping by tertile.

Interrelationships among HRV, inflammatory markers, and clinical factors

In GEE regression models, after adjustment for age, BMI, physical activity, HDL-C, smoking, hypertension, diabetes, and depression, which were the CAD risk factors found significantly associated with HRV and/or inflammation in bivariate analyses, ULF and VLF remained significant predictors of CRP, as was HR (all $P < .01$; Table III). In a subsequent model, inclusion of use of antihypertensive, cholesterol-lowering, and diabetic medications did not alter any associations, nor did inclusion of β -blocker use (data not shown). In a model adjusting for HR, ULF remained an independent predictor of CRP.

The co-twin matched pair analysis confirmed the above results. As shown in Table IV, the twin with VLF in a higher tertile of the sample distribution had significantly lower CRP than his brother whose VLF fell in a lower tertile, with a similar trend seen for ULF. These associations were similar in monozygotic and dizygotic twin pairs, with no significant interaction between zygosity and HRV tertile.

Sympathetic activity, HRV, and inflammation

Twenty-four-hour urine norepinephrine concentration was correlated in bivariate analysis with both HRV variables and inflammatory markers (Table II). In multi-variable analysis, however, HRV variables remained independently associated with CRP, whereas norepinephrine did not ($\beta = .007$, $P = .15$).

Discussion

In middle-aged men free of cardiovascular disease, autonomic dysfunction, as demonstrated by decreased HRV, was associated with higher levels of the inflammatory biomarkers CRP and IL-6. Decreased long-term HRV (ULF and VLF) remained an independent predictor of

plasma concentration of CRP after adjustment for CAD risk factors associated with both autonomic dysfunction and inflammation.

Clinical implications

Although the role of physiological and behavioral risk factors in the pathogenesis of CAD is well established, the pathways through which these factors exert their atherogenic effect remain incompletely understood. These risk factors all alter autonomic regulation,¹⁻³ which in turn is linked to progression of atherosclerosis⁵ as well as mortality.^{6,7} Further, these factors all increase inflammatory processes,⁸ which promote many phases of atherogenesis, from T-cells entering the intima, to smooth muscle proliferation, to growth, and finally rupture of the atherosclerotic plaque.⁹ C-reactive protein, an acute phase reactant produced in the liver in response to IL-6 and other inflammatory cytokines,⁹ was strongly associated with decreased HRV in this study. Although the exact role of CRP in the atherosclerotic process is debated, CRP may actively promote atherogenesis.³⁰ Our findings suggest that inflammatory and autonomic processes may be linked and that many CAD-risk factors may be proinflammatory in part due to autonomic dysregulation. Further investigation is needed to evaluate whether therapy that improves HRV, such as β -blockers,²⁶ may be beneficial in decreasing inflammatory processes, as suggested by basic studies.¹⁶ Whether autonomic dysfunction, as measured by HRV, is a mediator of the inflammatory effects of traditional risk factors or rather is a marker for the overall physiologic impact of risk factors on the individual including their inflammatory effects requires further study.

The inflammatory process is complex, and only 2 markers were examined in this study. Although the association between HRV and CRP remained significant after controlling for other factors, that between HRV and IL-6 did not. Interleukin-6 has a short half-life³¹ and varies throughout the day, showing circadian variation,³¹ whereas CRP levels remain stable over 24 hours.³² This may explain why HRV, measured over 24 hours, showed a stronger association with CRP than IL-6.

Previous studies

Group means for HRV variables here are similar to those previously reported for middle-aged individuals free of cardiovascular disease, although those in the lowest tertiles for HRV, who also displayed the highest levels of inflammatory markers, had HRV in the ranges reported for individuals with CAD.³³ Measured IL-6 was somewhat higher than that reported for healthy individuals,¹¹ as was CRP.¹⁰ Body mass index, cholesterol, and blood pressure were similar to those in the Atherosclerosis Risk in Communities (ARIC) study in subjects free of cardiovascular disease.⁶ Mean Beck depression inventory (BDI) score for the group was within the reference range.⁴

Table III. Multivariate-adjusted GEE regression models for the association of HRV and HR with CRP and IL-6

| HRV Index * | Dependent variable: Ln CRP | | | | Dependent variable: Ln IL-6 | | | |
|-------------|----------------------------|-------|-------|------|-----------------------------|-------|-------|-----|
| | 95% CI | | | | 95% CI | | | |
| | β | Lower | Upper | P | β | Lower | Upper | P |
| Ln ULF | -0.43 | -0.69 | -0.17 | .001 | -0.12 | -0.30 | 0.05 | .16 |
| Ln VLF | -0.38 | -0.63 | -0.13 | .003 | -0.15 | -0.34 | 0.04 | .12 |
| Ln LF | -0.17 | -0.37 | 0.03 | .10 | -0.08 | -0.24 | 0.07 | .30 |
| Ln HF | 0.03 | -0.13 | 0.19 | .72 | 0.03 | -0.08 | 0.15 | .54 |
| HR | 0.02 | 0.01 | 0.04 | .003 | 0.01 | -0.01 | 0.02 | .34 |

*Each HRV parameter and HR were included in a separate model. All models were adjusted for age, BMI, physical activity, HDL-C, depressive symptoms, smoking, hypertension, and diabetes. CI, Confidence interval.

Table IV. Within-pair comparison of CRP plasma levels in twin pairs discordant for ULF or VLF tertile

| | CRP (mg/L) | |
|------------------------------|-----------------|-----------------|
| | Ln ULF | Ln VLF |
| Twin with lower HRV tertile | 2.66 \pm 4.69 | 2.51 \pm 2.41 |
| Twin with higher HRV tertile | 1.63 \pm 1.41 | 1.61 \pm 1.65 |
| Within-pair difference | 1.03 \pm 4.35 | 0.89 \pm 2.15 |
| Wilcoxon test | P = .15 | P = .003 |

Values are expressed as means \pm SD.

Previous studies have demonstrated associations between inflammatory markers and HRV in patients with congestive heart failure,¹⁸ and in stable¹⁹ and unstable CAD.²⁰ In studies of individuals without cardiovascular disease,²¹⁻²³ HRV, assessed by varying methods, is inversely associated with CRP and/or IL-6. The current findings confirm these associations with a rigorous study design, through controlling for activity, known to influence long-term HRV,³⁴ and through the use of the twins design, which allowed us to control for potential unmeasured confounders, such as socioeconomic, life-style, and other factors shared by individuals of similar family background. This study further expands prior findings, through inclusion of ULF, the HRV variable most predictive of mortality in some studies.²⁷

Many of these studies hypothesized that inflammation altered HRV. We hypothesized the opposite directional relationship: that autonomic changes would be proinflammatory. As described below, data from basic science support both possibilities.

Potential biological mechanisms

Experiments at the cellular, animal, and human levels support the link between autonomic and inflammatory processes. Experimentally, both exposure to acetylcholine and direct vagal stimulation inhibits release of cytokines by macrophages, termed the “cholinergic anti-inflammatory

pathway.”¹² Sympathetic activation, conversely, is proinflammatory. In isolated adipocytes, β -stimulation increases IL-6, and in humans, IL-6 levels increase with isoproterenol infusion.¹⁵ β -Blockers dampen the IL-6 increase normally seen in response to stress in rats.¹⁶

Ultra low frequency and VLF, the HRV variables most closely linked with inflammation in the current study, as well as being most predictive of mortality in previous studies,²⁷ may be markers for many processes contributing to overall autonomic dysregulation.²⁸ Heart rate variability in the VLF, LF, and HF band are all influenced in large part by parasympathetic activity,^{17,28} whereas VLF may also be influenced by other neurohormonal influences such as the renin-angiotensin-aldosterone system,²⁸ and LF by sympathetic influences in addition.²⁸ Ultra low frequency may be influenced by day-night changes, especially when activity is controlled,^{34,35} which in turn are influenced by autonomic activity.

In this study, both urinary norepinephrine and HRV were associated with inflammation. In multivariable analysis, HRV appeared a more important predictor of inflammation than norepinephrine, suggesting that parasympathetic dysregulation bore greater responsibility for our findings than did sympathetic excess. However, urinary norepinephrine may be an imprecise measure of sympathetic activity, and although studies show a good correlation between plasma and cardiac norepinephrine,³⁶ the correlation between plasma and central nervous system measures of norepinephrine is less clear ($r = 0.48$ in one study).³⁷ Sympathetic stimulation inhibits vagal output,³⁸ and it is also possible that the relationships seen here between HRV and inflammation were a reflection of sympathetic effects (ie, that low HRV was a marker for increased sympathetic activity) or that the 2 may have independent effects.

Other experimental studies suggest the opposite directional relationship, with inflammation causing autonomic changes. For example, IL-6 deactivates nitric oxide, which augments vagal activity as measured by

HRV.¹³ Marz et al¹⁴ has shown that rat sympathetic neurons both respond to and produce IL-6, suggesting that the association between inflammation and autonomic regulation is bidirectional.

Limitations

As in any cross-sectional study, the directionality of the association seen between HRV and inflammation in this study cannot be determined. Further, the possibility that a third, unmeasured variable may be responsible for the relationship between inflammation and autonomic dysfunction cannot be excluded. In addition, female twin pairs were not included in the Vietnam Era Twin Registry given their extremely low representation among Vietnam era military personnel. Gender influences HRV in some³³ (although not all) studies, and similarly, gender may effect inflammation.³⁹ Whether the relationship between inflammation and the autonomic nervous system differs in women is an important area of future investigation.

Conclusions

Markers of inflammation are associated with decreased HRV, even after controlling for clinical CAD risk factors. Autonomic dysregulation leading to inflammation may represent one pathway through which traditional risk factors promote the development of CAD.

We gratefully acknowledge the continued cooperation of the members of the Vietnam Era Twin Registry.

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