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Heart rate variability predicts levels of inflammatory markers: Evidence for the vagal anti-inflammatory pathway

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ABSTRACT

Evidence from numerous animal models shows that vagal activity regulates inflammatory responses by decreasing cytokine release. Heart rate variability (HRV) is a reliable index of cardiac vagal regulation and should be inversely related to levels of inflammatory markers. Inflammation is also regulated by sympathetic inputs, but only one previous paper controlled for this. In a larger and more representative sample, we sought to replicate those results and examine potential sex differences in the relationship between HRV and inflammatory markers. Using data from the MIDUS II study, we analyzed the relationship between 6 inflammatory markers and both HF-HRV and LF-HRV. After controlling for sympathetic effects measured by urinary norepinephrine as well as a host of other factors, LF-HRV was found to be inversely associated with fibrinogen, CRP and IL-6, while HF-HRV was inversely associated with fibrinogen and CRP. We did not observe consistent sex differences. These results support the existence of the vagal anti-inflammatory pathway and suggest that it has similar effects in men and women.

1. Introduction

The vagus nerve plays an important role in regulating inflammation and preventing tissue damage from excessive inflammatory responses. Vagal activity decreases production of pro-inflammatory cytokines such as TNF (Bernik et al., 2002) and inhibits the migration of leukocytes to sites of inflammation (Saeed et al., 2005), in part by its action on the reticuloendothelial system of the liver and spleen where cytokines are produced, and may function to dampen systemic inflammatory processes (Tracey et al., 2007). Data from numerous animal studies support this anti-inflammatory pathway. For example, administration of endotoxin in mice following vagotomy or in mice possessing knockout of the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR) expressed in macrophages causes an unrestrained cytokine response (Borovikova et al., 2000; Wang et al., 2003). On the other hand, stimulation of the vagus nerve or administration of α7nAChR agonists has been found to decrease cytokine release (Wang et al., 2004).

Because heart rate variability (HRV) is a well-established and reliable index of cardiac vagal regulation, it should be inversely related to levels of inflammatory markers. Many studies show this predicted inverse relationship. For example, decreased low frequency HRV (LF-HRV) was found to be associated with increased levels of C-reactive protein (CRP) in a study of 1601 healthy young people (Haarala et al., 2011). A prospective cohort study of 188 middle-aged and older adults found an inverse relationship between high frequency HRV (HF-HRV) and CRP ($p < 0.01$) (Singh et al., 2009). A study of 264 middle-aged male twins found that ultra low frequency HRV and very low frequency HRV were inversely related to CRP and IL-6 after controlling for a host of factors ($p < 0.01$) (Lampert et al., 2008). IL-6 levels were shown to have an inverse relationship with HF-HRV and LF-HRV in a study of 682 patients after cardiac catheterization for acute myocardial infarction (MI) or unstable angina with elevated Troponin-T levels (Frasure-Smith et al., 2009). Inverse relationships between IL-6 and HRV have also been observed in patients with sepsis, type 1 diabetes and type 2 diabetes (Tateishi et al., 2007; Gonzalez-Clemente et al., 2007; Stuckey and Petrella, 2013).

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Inflammatory processes are also influenced by the sympathetic nervous system (SNS), but its role is less well understood. The SNS possesses both pro- and anti-inflammatory properties and has been implicated in the production of cytokines (Koopman et al., 2011). Adrenergic signaling may activate or suppress macrophages depending on the subtype of adrenergic receptor they express (Bellinger et al., 2008). SNS activity can reduce Th1 response in favor of Th2 (Elenkov et al., 2000). Sympathetic activity has also been found to enhance leukocyte attraction (Viswanathan et al., 2005) and alter expression of cell adhesion markers (Redwine et al., 2003).

A thorough examination of the inflammatory role of the autonomic nervous system thus requires consideration of both vagally-mediated and sympathetically-mediated effects. With only a single exception, studies linking HRV and inflammation fail to control for levels of SNS activity. In that study, Thayer and Fischer found that even after controlling for SNS effects, measured by urinary epinephrine, the inverse relationships between HRV and CRP and between HRV and WBC count remained significant (Thayer and Fischer, 2009). In addition, they observed interesting sex differences in these relationships. For example, an increase of 1 SD in HRV measured as root mean square of successive interval differences was associated with a 48% decrease in CRP in men ($p = 0.05$), whereas in women, an increase of 1 SD in HRV was associated with a 104% decrease in CRP ($p = 0.008$). Larger differences in WBC count, another marker of inflammation, were also seen in women. This study suggests that there may be important sex differences in the relationship between parasympathetic activity and inflammatory markers. However, the study was limited by a small number of women ($n = 66$) relative to men ($n = 545$) and a relatively homogeneous sample of factory workers.

In the current study, we sought to replicate these findings on the relationship between HF-HRV and inflammatory markers using a larger, more diverse, and more representative sample. We tested the hypothesis that HF-HRV, as an index of cardiac vagal regulation, would be inversely related to inflammatory markers even after control for sympathetic effects. Because many studies also examine the relationship between LF-HRV and inflammatory markers, we also tested this relationship.

2. Methods

2.1. Participants

The data were collected from 1255 participants in Midlife Development in the U.S. (MIDUS), a study of the behavioral, psychological and social factors accounting for age-related variation in health and well-being in a national sample of middle-aged and older Americans (Brim et al., 2004). Data for the current study are from MIDUS II, a 9-year follow-up of the MIDUS I cohort, conducted between 2004 and 2006. MIDUS II consisted of five projects, including a self-administered survey of a wide array of behavioral, social and psychological factors and a Biomarker Project, with data collection conducted during a 1.5-day visit to a clinical research center (CRC) at the University of Wisconsin, UCLA, or Georgetown University. Biomarker data were collected from mid-2004 to mid-2009 (Ryff et al., 2012). IRB approval was obtained for data collection at the three sites, and written consent was obtained from all study participants.

2.2. Physical exam

Clinicians or trained staff evaluated vital signs, morphology, functional capacities, bone densitometry and medication usage and performed a physical exam. Medical history was obtained from participants.

2.3. Biomarker data

Subjects underwent fasting blood draws prior to breakfast. Samples were sent to the MIDUS Biocore Lab for analysis. Additionally, glycated hemoglobin and cholesterol panel assays were analyzed at Meriter Labs (Madison, WI) using a Cobas Integra® analyzer (Roche Diagnostics, Indianapolis, IN). IL-6 was measured using Quantikine® High-sensitivity ELISA kit #HS600B (R&D Systems, Minneapolis, MN). Soluble IL-6 receptor levels were measured using Quantikine® ELISA kit #DR600 (R&D Systems, Minneapolis, MN). Human soluble intercellular adhesion molecule-1 was measured by Parameter Human sICAM-1 Immunoassay (R&D Systems, Minneapolis MN). Soluble E-selectin was measured by Parameter Human sE-selectin Immunoassay (R&D Systems, Minneapolis, MN). Fibrinogen and CRP were measured by BNII nephelometer (Dade Behring Inc., Deerfield, IL). 12-h urine samples were collected overnight (7:00 PM–7:00 AM). Urinary catecholamine assays were performed using high-pressure liquid chromatography at the Mayo Medical Laboratory (Rochester, MN). Urinary norepinephrine levels were corrected for creatinine levels.

2.4. HRV assessment

After an overnight stay at the CRC, participants were provided with a light breakfast, but no caffeine consumption was permitted. Following breakfast, they began the HRV psychophysiology protocol.

ECG electrodes were placed on the left and right shoulders as well as in the left lower quadrant. Respiration bands were placed around the chest and abdomen, and the finger cuff of a Finometer beat-to-beat blood pressure monitor was placed around the middle finger of the non-dominant hand. Respiration was calibrated using an 800 cc spirobag. While participants were in the seated position, data were recorded during an 11-min baseline as part of a more extensive psychophysiology protocol with exposure to challenging stimuli and recovery periods. Here we report HRV data from this resting baseline.

Analog ECG signals were digitized at 500 Hz by a 16-bit A/D conversion board (National Instruments, Austin, TX) and passed to a microcomputer. The ECG waveform was submitted to an R-wave detection routine implemented by custom-written software, resulting in an RR interval series. Errors in marking R waves were corrected by visual inspection. Ectopic beats were corrected by interpolation.

HF-HRV (0.15–0.40 Hz) was computed based on 300-s epochs, using an interval method for computing Fourier transforms similar to that described by (DeBoer et al., (1984). The mean value of HF-HRV from the two baseline 300-s epochs was computed. The process was repeated for LF-HRV (0.04–0.15 Hz).

2.5. Respiration

Respiratory rate was measured using an Inductotrace respiration monitor (Ambulatory Monitoring Systems, Ardsley, NY). Signals from thoracic and abdominal stretch bands were collected by the A/D board at 20 Hz and submitted to a custom-written program that computed respiratory rate on a minute-by-minute basis. The mean respiratory rate for the baseline period was computed.

2.6. Statistical analysis

All analyses were carried out in SAS 9.3. The distributions of variables were examined and the right-skewed variables

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