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The relation between hostility and concurrent levels of inflammation is sex, age, and measure dependent

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ABSTRACT

Background and objective: Hostility may be associated with greater systemic inflammation. However, contradictory evidence exists. Certain individuals or dimensions of hostility may be more susceptible to these effects. Main and interactive effects of hostility with sex and/or age were evaluated on markers of inflammation, independently of traditional risk factors for coronary artery disease.
Methods: 199 healthy men (81) and women (118), aged 20–64 years (M = 41 ± 11 years) were recruited. Hostility was assessed using the Cook–Medley Hostility Inventory (CMHo) and ecological momentary assessments (EMA) of quarrelsome behavior and angry affect in daily living. Blood samples were drawn to measure inflammatory activity (Il-6, TNF-α, hsCRP, Il-8, Il-10, Il-18, MCP-1) and lipid oxidation (Myeloperoxidase; MPO). Correlations and hierarchical regression analyses were performed controlling for pertinent behavioral, psychological, medical, and socio-demographic factors.
Results: Significant univariate associations emerged between CMHo and Il-6, TNF-α, MCP-1 ($p < .05$). Hierarchical regressions showed interactions of hostility with sex (Il-6, TNF-α; $p < .05$) and age (hsCRP, Il-6, TNF-α; $p < .05$). For example, in simple slope analyses, hostility was positively related to TNF-α in women ($b = 0.009$, $p = 0.006$) but not men. Greater hostility was also related to greater Il-6 levels among younger women ($b = .027$, $p = 0.000$).
Conclusion: Hostility, particularly cynical hostility, may be detrimental to (younger) women. The TNF-α, Il-6, CRP triad appears vulnerable to psychological and behavioral factors, and may be one mechanism by which cynical hostility (CMHo) contributes to increased cardiovascular risk in women. Prospective research is needed to verify this.

Introduction

Hostility is a multidimensional, trait-like personality characteristic comprised of cognitive (cynicism, hostile attributions), affective (anger), and behavioral (aggression, antagonism) components [1]. Considerable research has implicated hostility in the development and progression of coronary artery disease (CAD) [2–5]. However, the mechanisms by which hostility confers risk remain to be established.

Hostility may increase risk of CAD through its association with or impact on other risk factors for CAD. CAD is now understood to be an inflammatory disease [6,7]. Proinflammatory cytokines, such as interleukin-6 (Il-6) and tumor necrosis factor-alpha (TNF-∝) and chemokines, such as monocyte chemotactic protein 1(MCP-1), play a central role in the formation and progression of atherosclerotic plaque in the arterial wall [7–9]. TNF-α is a major regulator of the cytokine cascade involving both pro and anti-inflammatory mediators [7]. Inflammatory processes involving TNF-α trigger the induction of Il-6, promoting the production of acute-phase proteins like C-reactive protein (CRP) [8,9]. CRP predicts CAD independently of traditional risk factors [10–13] and predicts more cardiovascular events in women compared to men [14].

There is evidence for a positive association of hostility with various markers of inflammation [15–20]. For example, in a study involving 6814 healthy men and women, cynical hostility was associated with higher circulating levels of Il-6 and CRP [16]. Nonetheless, conflicting results do exist both across and within studies. Graham & al. [21] observed a significant association between cynical hostility and CRP among older adults, but no association was found for Il-6. Another study, reported lower (rather than higher) levels of Il-6 in more hostile men working

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in the military [22]. In several studies, the relation between hostility and inflammatory markers depended on the presence of depressive symptoms [21,23–27]. In contrast, Miller & al. [24] found that cynical hostility was associated with higher Il-6 and TNF-α concentrations among individuals with low, rather than high, depressive scores.

Discrepancies in results among studies may reflect methodological differences, such as sample characteristics (we will focus here on sex and age) and the measure of hostility used. Sex differences exist in the degree of risk for CAD [28], in the prevalence or meaning of hostility [29–31], and in the importance of inflammatory markers like CRP to the development of CAD [32]. Hostility may predict future elevations in CRP levels principally in women [31]. Factors relating to age may also be important. Increasing age is associated with increased CAD risk [33] and inflammatory activity, but with decreased hostility [22,29,30]. An overview of the literature suggests that age may moderate the relation between hostility and inflammatory activity, with less consistent associations observed in studies using older individuals [16,21,26].

Hostility has been examined using a variety of self-report questionnaires administered once. These questionnaires measure overlapping but distinct constructs that may show different associations with inflammatory markers [19,25]. Self-report questionnaires require participants to report on typical behaviors, thoughts, and/or feelings, and hence rely on autobiographic memory [34]. Intensive repeated assessments of individuals' behaviors, thoughts, and/or emotions as they occur in moment-to-moment interactions in the participant's natural setting [34] may provide more reliable and ecologically valid measures of hostility.

Measures of CRP, TNF-α and/or Il-6 have been extensively examined in the literature, but few studies have investigated other inflammatory markers known to contribute to the development or progression of CAD. Only one study examined the association of hostility with the chemokines, MCP-1 and Il-8 in healthy premenopausal women [25]. MCP-1 is a protein synthesized by arterial smooth muscle cells and endothelial cells during inflammation [35] and is involved in the movement of monocytes and T-cells into the vessel wall during the formation of atherosclerosis [36]. Il-8 is secreted by endothelial and smooth muscle cells as well as by peripheral blood monocytes [37–39] and has been shown to increase with acute stress [40]. Only two studies examined Il-10, an anti-inflammatory cytokine that modulates immune responses [41], with mixed results [20,22]. Further research on these and other biomarkers could illuminate mechanisms through which hostility may impact CV risk.

The purpose of the present study is to examine the relation of hostility with inflammatory markers in healthy adult men and women of varying age. In addition to TNF-α, Il-6, and CRP, myeloperoxidase (MPO), MCP-1 and interleukins 8, 10, and 18 are also explored. MPO is a hemoprotein secreted during inflammation and is involved in lipid oxidation [42]. Il-8 and MPO predict an increased risk of CAD in healthy adults [42–44]. Il-18, another pro-inflammatory cytokine [37–39], is produced by both immune and non-immune cells and has been found to have pathophysiological roles in several inflammatory conditions [45]. It polarizes Th-1 cytokines such as TNF-α [46]. While these various biomarkers of inflammation may interact, they impact CAD development and progression in different ways. Differential associations of these markers with hostility may provide indices as to the mechanisms through which hostility may increase risk of disease. Three measures of hostility were obtained to capture the cognitive, behavioral, and affective dimensions of the construct, using questionnaire and ecological momentary assessments (EMA) over a 21-day period. An important goal of the study is to determine whether observed relations between hostility and inflammatory activity differ as a function of sex and/or age. We hypothesized that more hostile individuals would show greater inflammatory activity compared to those who are less hostile. Based on the limited data available, these relations may be stronger in women compared to men, and among younger versus older individuals.

Methods

Participants

Participants were recruited for a broader study examining the psychophysiological and psychological correlates of various CAD risk factors (for published articles [47–51]).

One hundred and ninety nine healthy working men (n = 81) and women (n = 118) aged 20–64 years (M_{age} = 41 ± 11 years) were recruited via community and newspaper advertisements within the greater Montreal area from 2005–2007. Subjects were excluded from the study if they: (a) received mental health services within the past year; (b) were suffering from a current or known health problem (asthma, hypertension, diabetes, hypercholesterolemia, heart disease, cancer, auto-immune disorders, disorders of the adrenal gland, etc.) or used medication (statins, beta-blockers, anti-inflammatory agents, etc.) capable of affecting cardiovascular, immune, or neuroendocrine functions; (c) learning or cognitive disabilities that could impair their comprehension ability; (d) were currently on hormone replacement therapy. Subjects meeting eligibility criteria were then selected from three groups (18–34 years, 35–44 years, and 45–65 years) to obtain an equal age distribution within our sample. Women were oversampled to ensure a substantial number of post-menopausal women for a separate component of the main study, not addressed here.

Procedure

Laboratory appointments took place at the Montreal Heart Institute (MHI) at 8:00 a.m. on weekdays to control for circadian rhythms. Participants were asked to abstain from drinking (other than water), smoking, and strenuous exercise for 12 h prior to testing, and to refrain from alcohol or drug use for 24 h. Subjects were rescheduled for another appointment when these guidelines were not adhered to or if participants presented physical symptoms such as a cough, cold, or a headache on the day of testing. Participants with hsCRP values >10 mg/L indicative of potential acute infections or other inflammatory conditions were excluded post-hoc.

Participants were tested by a research assistant of the same sex, who was trained to maintain a neutral tone and expression throughout the laboratory session. After reading and signing the consent form, anthropomorphic data were obtained. Individuals completed demographic, medical, and psychological questionnaires. Following a resting period of 10 min, blood was drawn. A stress protocol was then initiated for a separate component of the study not addressed here (see [48,51]). Afterwards, participants were equipped with ambulatory blood pressure (BP) and ECG monitoring devices, and measurements were obtained during the 24-h period following the laboratory session. Subjects were also asked to complete a log on their verbal and nonverbal behavior and affects following each significant interpersonal interaction lasting at least 5 min for the next 21 days. The log was completed on a palm pilot handheld computer as soon as possible after each social interaction.

Participants received 200 dollars compensation for time and travel. The Research and Ethics Board of the Montreal Heart Institute approved this study.

Measurement

Socio-demographic and anthropomorphic variables

Data on sex, age in years, body mass index (BMI), waist circumference, marital status, annual personal and family income, and years of schooling were collected, as was information on behavioral risk factors relating to tobacco and alcohol intake, as well as physical activity.

Psychological variables

Hostile cognitive trait was assessed using the Cook–Medley Hostility Inventory (CMHo; [52]); a widely used self-report measure on cynical

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