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Psychophysiological correlates of systemic inflammation in black and white men

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ABSTRACT

Inflammation plays a critical role in the pathophysiology of cardiovascular disease (CVD) and levels of circulating inflammatory markers are associated with future CVD risk. However, the physiological mechanisms that control systemic levels of circulating inflammatory markers are not well understood. Here, we explore possible autonomic nervous system mechanisms by testing whether resting and stressor-evoked cardiovascular responses are associated with two markers of systemic inflammation: interleukin (IL)-6 and C-reactive protein (CRP). Subjects were 159 black and 129 white men ($M = 33.0$ years) who completed a laboratory protocol including an anger recall speech task. Electrocardiography and impedance cardiography data were collected during a resting baseline, the speech task, and a final recovery period. Hierarchical regressions tested whether resting or stressor-evoked levels of heart rate (HR), high-frequency heart rate variability (HF-HRV), pre-ejection period (PEP), and pulse transit time (PTT) were associated with CRP or IL-6. Higher resting HR was associated with higher CRP ($\beta = 0.19$, $p = 0.003$) and IL-6 ($\beta = 0.13$, $p < 0.05$). Similarly, shorter resting PTT was associated with higher CRP ($\beta = -0.21$, $p < 0.001$) and IL-6 ($\beta = -0.14$, $p = 0.02$). In addition, greater stressor-evoked decreases in HF-HRV were associated with higher CRP ($\beta = -0.14$, $p = 0.01$). Associations were independent of age, race, body mass index (BMI), smoking behavior, and socioeconomic status. Resting HF-HRV and PEP were also associated with CRP and IL-6, but associations were not significant after controlling for BMI and smoking behavior. These findings indicate that resting HR and PTT, as well stressor-evoked HF-HRV reactivity, are associated with systemic inflammation. Our results suggest that both tonic and stressor-evoked sympathetic and parasympathetic nervous system activity may contribute to regulation of systemic inflammation.

1. Introduction

Inflammatory processes play a key role in cardiovascular disease (CVD) pathophysiology (Libby et al., 2002; Ross, 1999). In addition, basal levels of inflammatory markers in the peripheral circulation predict future CVD risk. Specifically, higher levels of inflammatory markers, such as C-reactive protein (CRP) or interleukin (IL)-6, are associated with greater likelihood of developing CVD (Danesh et al., 2008, 2000). These basal levels of circulating inflammatory markers are commonly referred to as "systemic inflammation", because they provide a non-specific indication of ongoing inflammatory processes in the body. Currently, the physiological mechanisms that drive and regulate systemic inflammation are not fully understood. The present study examined possible autonomic mechanisms underlying systemic inflammation by testing whether resting and stressor-evoked cardiovascular responses are associated with markers of systemic inflammation.

The autonomic nervous system (ANS) is one physiological system thought to regulate systemic inflammation. Two of the primary divisions of the ANS are the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS). Both divisions innervate multiple organs and regulate a wide variety of physiological functions outside of conscious control, including immune function (Kemeny, 2011). Animal and *in vitro* studies have provided evidence for associations between each division of the ANS and inflammation. Specifically, animal research indicates that tonic PNS input inhibits inflammation. This research is summarized by Tracey (2002, 2009) cholinergic anti-inflammatory pathway. According to this proposal, tonic stimulation of the vagus nerve promotes the release of acetylcholine (ACh), the primary neurotransmitter of the PNS. ACh acts on nicotinic, α-bungarotoxin-sensitive ACh receptors on macrophages, inhibiting

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macrophage production of proinflammatory cytokines. Through this mechanism, tonic PNS activity prevents the overproduction of cytokines and protects the body from the harmful effects of excessive inflammation (Tracey, 2002).

The role of the SNS in driving systemic inflammation is less clear. The SNS innervates a number of key immune organs, but sympathetic activation can both stimulate and inhibit production of inflammatory cytokines (Nance and Sanders, 2007). Rodent and *in vitro* evidence indicates that SNS activation drives short-term increases in IL-6, which may contribute to higher basal levels of systemic inflammation. Specifically, increases in sympathetic catecholamines (e.g., norepinephrine) lead to increased activation of cellular nuclear factor κB (NF-κB), a transcription factor that triggers IL-6 production (Bierhaus et al., 2003; Johnson et al., 2005; Tracey, 2009). Direct human evidence for this mechanism is limited. Preliminary work aligns with rodent findings, indicating that healthy adults show a positive association between stress-induced increases in norepinephrine and IL-6 (Kop et al., 2008). These results suggest it is theoretically plausible that increased SNS activation may trigger increases in systemic inflammation.

Similar to animal and *in vitro* models, human studies employing non-invasive psychophysiological methods to indirectly assess ANS activity also support regulation of systemic inflammation by the ANS. Such studies report positive correlations between resting HR and systemic inflammation (Piwońska et al., 2008; Rogowski et al., 2007; Whelton et al., 2014). Although the authors of these studies suggest that higher HR indicates greater sympathetic control over the cardiovascular system, HR is influenced by both the PNS and SNS (Cacioppo et al., 2007). Thus, it is unclear from this literature whether associations between HR and systemic inflammation in humans are driven primarily by the SNS.

Other psychophysiological measures of the distinct branches of the ANS may also be associated with systemic inflammation. Specifically, high frequency heart rate variability (HF-HRV), a marker of PNS input to the heart (Berntson et al., 1997), is negatively associated with circulating CRP and IL-6 (Cooper et al., 2015; Sajadieh et al., 2004; Singh et al., 2009; Sloan et al., 2007). Lower resting HF-HRV is also associated with greater stimulated production of cytokines, including IL-6, in response to an *in vitro* inflammatory challenge (Marsland et al., 2007). These findings are consistent with the existence of the cholinergic anti-inflammatory pathway (Tracey, 2009, 2002), indicating that lower levels of tonic PNS activity are associated with heightened systemic inflammation. SNS activity can also be assessed using cardiovascular measures, such as pre-ejection period (PEP). However, there is little human evidence linking SNS responses with systemic inflammation. Only one study has assessed this relationship, finding that PEP was not significantly associated with CRP (Singh et al., 2009). It is unknown whether PEP associates with IL-6.

It is important to note that current psychophysiological evidence linking ANS activity with inflammatory markers has largely focused on resting levels of these cardiovascular ANS indices. However, previous studies have shown that greater chronic and acute psychological stress are also associated with heightened systemic inflammation (Rohleder, 2014) and affect the ANS (Carter and Goldstein, 2015; Nater et al., 2013). Cardiovascular reactions to laboratory stressors have been found to be consistent within an individual over time (Debski et al., 1993; Kamarck et al., 1992), raising the possibility that these responses may influence chronic inflammation. Moreover, rodent and *in vitro* models indicate that the ANS regulates transient, stressor-evoked inflammatory responses (Johnson et al., 2005). These findings suggest that individual differences in ANS stress reactivity may also be associated with levels of systemic inflammation. This possibility remains largely unexplored in the existing literature.

Taken together, this evidence suggests that the ANS plays a role in stimulating and inhibiting systemic inflammation. There is, however, a paucity of studies examining (1) the association of systemic inflammation with concurrent psychophysiological measures of both SNS and PNS activity, and (2) the role of individual differences in ANS stress reactivity in relation to systemic inflammation. Thus, the first aim of the present study was to assess associations between systemic inflammation and resting psychophysiological measures of PNS and SNS activity. Specifically, we hypothesized that higher levels of systemic inflammation would be associated with (1) lower resting levels of PNS activity (HF-HRV), (2) higher SNS activity (PEP), and (3) higher HR, which reflects both PNS and SNS activity. Additionally, because previous studies have largely focused on resting levels of ANS activity, the second aim of the current study was to examine whether systemic inflammation is associated with individual differences in SNS and PNS reactivity to a stressful laboratory task. In particular, we hypothesized that higher levels of systemic inflammation would be associated with (1) greater stress-related decreases in PNS activity (HF-HRV), (2) larger increases in SNS activity (PEP), and (3) greater increases in combined SNS and PNS activity (HR), independent of resting SNS and PNS levels.

2. Methods

2.1. Sample

Participants were drawn from the Pittsburgh Youth Study (PYS). Initiated in 1987, PYS is an ongoing study of black and white men originally designed to examine the development of delinquency and antisocial behavior. Details of the original study and follow-up recruitment are published elsewhere (Loeber et al., 1998; Lynam et al., 2008). Briefly, a population-based sample of boys was drawn from Pittsburgh public school students enrolled in either first or seventh grade, with approximately 500 in each cohort. Recruitment involved an initial screening process to identify males at high risk for antisocial and delinquent behavior later in life. Risk status was classified as high if students in the younger cohort exhibited one of seven antisocial behaviors or those in the older cohort exhibited three antisocial behaviors. Approximately half of the original sample was classified as high risk. Participants have been followed since study initiation.

A subsample of adult participants from the original PYS study was recruited to participate in the laboratory-based Pathways to Healthy Hearts Study. Participants were excluded if they were incarcerated, lived more than 75 miles away from Pittsburgh and were not planning to return, were severely mentally disabled, had withdrawn from the original PYS study, or were deceased. Of the 322 eligible men in the original younger cohort, 267 participated in the laboratory study. Because the target sample size was 300 men, we then recruited 40 additional participants from eligible men in the older cohort. In total, 307 men participated in the laboratory protocol. This study was approved by the Institutional Review Board at the University of Pittsburgh and all participants provided informed consent.

Of the 307 men who participated in the laboratory protocol, 19 were excluded from the present analyses due to CRP values greater than 10 mg/dL. This resulted in an analytic sample of 288 men. Although most participants had complete data for all variables of interest, a small number had incomplete data for the psychophysiological variables due to data collection issues. For this reason, the N for each regression analysis varied slightly; the N for each set of regressions is noted in regression tables.