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# Neighborhood poverty and hemodynamic, neuroendocrine, and immune response to acute stress among patients with coronary artery disease

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ABSTRACT

Living in neighborhoods characterized by poverty may act as a chronic stressor that results in physiological dysregulation of the sympathetic nervous system. No previous study has assessed neighborhood poverty with hemodynamic, neuroendocrine, and immune reactivity to stress. We used data from 632 patients with coronary artery disease. Patients' residential addresses were geocoded and merged with poverty data from the 2010 American Community Survey at the census-tract level. A z-transformation was calculated to classify census tracts (neighborhoods) as either having 'high' or 'low' poverty. Systolic blood pressure, diastolic blood pressure, heart rate, rate-pressure product, epinephrine, interleukin-6, and high-sensitivity C-reactive protein were measured before and after a public speaking stress task. Multilevel models were used for repeated measures and accounting for individuals nested within census tracts. Adjusted models included demographics, lifestyle and medical risk factors, and medication use. Another set of models included propensity scores weighted by the inverse probability of neighborhood status for sex, age, race, and individual-level income. The mean age was 63 years and 173 were women. After adjusting for potential confounders, participants living in high (vs. low) poverty neighborhoods had similar hemodynamic values at rest and lower values during mental stress for systolic blood pressure (157 mmHg vs. 161 mmHg; $p = 0.07$), heart rate (75 beats/min vs. 78 beats/min; $p = 0.02$) and rate-pressure product (11839 mmHg x beat/min vs 12579 mmHg x beat/min; $p = 0.01$). P-values for neighborhood poverty-by-time interactions were $< 0.05$. Results were similar in the propensity weighted models. There were no significant differences in inflammatory and epinephrine responses to mental stress based on neighborhood poverty status. A blunted hemodynamic response to mental stress was observed among participants living in high poverty neighborhoods. Future studies should explore whether neighborhood poverty and blunted hemodynamic response to stress translate into differences in long-term cardiovascular outcomes.

## 1. Introduction

Living in low-income neighborhoods characterized by poverty and socioeconomic disadvantage is an important predictor for developing coronary artery disease (CAD) (Diez Roux et al., 2001; Nordstrom et al., 2004; Sundquist et al., 2004) as well as poorer prognosis and decreased

*Abbreviations:* BDI-II, Beck depression inventory second edition; BMI, body mass index; CAD, coronary artery disease; DASI, Duke activity status instrument; DBP, diastolic blood pressure; HR, heart rate; HsCRP, high-sensitivity C-reactive protein; HPA, hypothalamic-pituitary-adrenal axis; IL-6, interleukin-6; MIPS, Mental Stress Ischemia Mechanisms and Prognosis Study; RPP, rate pressure product; SBP, systolic blood pressure; SNS, sympathetic nervous system

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survival among patients with CAD (Engstrom et al., 2000; Tonne et al., 2005). There is growing interest in disentangling the physiological pathways through which the neighborhood environment, such as living in low income neighborhoods, may affect cardiovascular outcomes. However, the underlying mechanisms are not well understood.

One hypothesis is that living in socially- and physically-disordered neighborhood environments characterized by poverty may act as a chronic stressor that results in physiological dysregulation of the body's reactivity to stress, such as through the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) (Augustin et al., 2008; Broyles et al., 2012; Dulin-Keita et al., 2012; Hajat et al., 2015; Le-Scherban et al., 2018). Exposure to acute emotional stress, and stress-induced physiological perturbations are associated with cardiometabolic risk and events (Chida and Steptoe, 2010). An altered reactivity to stress, either in the direction of exaggerated reactivity or diminished reactivity, may signal a dysregulation of systems intended to maintain homeostasis (Phillips et al., 2013). Enhanced responsivity to stress provocation such as through hemodynamic, immune, and neuroendocrine responses regulated by the SNS, may serve as mechanisms for the development or exacerbation of CAD (Hammadah et al., 2017b; Ramadan et al., 2013; Vaccarino, 2016). However, there is growing recognition that even low cardiovascular reactivity to stress, as well as low cortisol reactivity, may index a dysregulation of the stress response systems and may have adverse consequences for health and behavior including obesity, depression, poorer cognitive function, and poor lung function (de Rooij, 2013; Lovallo, 2013; Phillips et al., 2013).

To date, limited research has assessed the association between neighborhood poverty with hemodynamic, neuroendocrine, and immune reactivity to stress. Furthermore, most research in this area has focused on hemodynamic response to stress among children with chronic stressors or measures of disadvantage other than the neighborhood environment (Brenner et al., 2013; Evans et al., 2013; Hackman et al., 2012; Lovallo, 2013; Lovallo et al., 2012). Virtually no data have been published on individuals with CAD, a group at high risk for subsequent adverse events. Thus, the objective of the current study was to comprehensively assess SNS reactivity to acute mental stress, including hemodynamic, neuroendocrine, and immune responses, among patients with CAD living in high (vs. low) poverty neighborhoods. To provide further validation of the phenomena of mental stress and SNS reactivity among patients living in high poverty neighborhoods, we contrasted results to hemodynamic reactivity during exercise stress testing. We hypothesized that patients in high poverty neighborhoods would have an abnormal (either enhanced or blunted) SNS response to acute mental stress but not to exercise stress.

## 2. Materials and methods

### 2.1. Study design and participants

The Mental Stress Ischemia Mechanisms and Prognosis Study (MIPS) is a prospective study designed to investigate mechanisms and prognosis of mental stress-induced ischemia among patients with stable coronary artery disease (CAD) (Hammadah et al., 2017a). Patients from Emory University-affiliated hospitals and clinics with documented CAD were eligible for the study if they were between 30-79 years of age. Criteria for documented CAD included at least one of the following: 1) abnormal coronary angiography or intravascular ultrasound demonstrating atherosclerosis with at least luminal irregularities; 2) previous percutaneous or surgical coronary revascularization; 3) documented myocardial infarction; or 4) positive exercise or pharmacological nuclear stress test or electrocardiographic exercise stress test. Patients were excluded from the study if they were pregnant; if they were hospitalized in the previous week for unstable angina, decompensated heart failure, or myocardial infarction; if they had severe psychiatric conditions such as schizophrenia or a history of alcohol or substance abuse; or if they had active malignancy, end stage renal disease, or other severe medical problems expected to shorten life expectancy to less than 5 years.

Between June 2011 and August 2014, 695 patients were enrolled in MIPS. Baseline studies were performed during two visits within a week. At the initial visit (visit 1), patients were consented and underwent a medical history and psychosocial/psychiatric assessments, blood draw, baseline vascular function testing, and either a conventional (exercise or pharmacological) stress test or a mental stress test as described below. During visit 2, they had the other stress test performed. The sequence of the two stressors was randomly assigned. The present analysis was restricted to 632 patients with available geocoded addresses. The Institutional Review Board at Emory University approved the MIPS research protocol. Written informed consent was obtained from all patients enrolled in the study. More detailed information on the MIPS objectives and study design has been described elsewhere (Hammadah et al., 2017a; Vaccarino et al., 2016).

### 2.2. Measurements

#### 2.2.1. Mental stress testing procedure

Mental stress testing in the laboratory setting is an established experimental approach to elicit sympathetic nervous system responses to emotional challenges and evaluate disturbances of stress mechanisms including cardiac and hemodynamic functions, especially in relation to myocardial ischemia and cardiovascular disorders (Steptoe and Vogele, 1991; Ramachandruni et al., 2006; Strike and Steptoe, 2003; Vaccarino, 2016). The mental stress protocol we used has been validated and widely used in CAD patients (Goldberg et al., 1996; Kim et al., 2003; Ramachandruni et al., 2006; Sheps et al., 2002), and has been found to be highly reproducible and predictive of mental stress induced myocardial-ischemia and of hemodynamic and vascular responses to stress in our laboratory (Hammadah et al., 2017b; Sullivan et al., 2018).

Patients were tested using a standardized public speaking task after a 30-minute rest period, in a temperature controlled, quiet, and dimly lit room, as previously described (Goldberg et al., 1996; Kim et al., 2003; Sullivan et al., 2018; Vaccarino et al., 2014, 2016). Cardiovascular medications, including beta-blockers, calcium-channel blockers, long-acting nitrates, and other anti-ischemic medications, as well as xanthine derivatives and caffeine-containing products were withheld for approximately 24 hours prior to stress testing. Briefly, patients were asked to imagine a real-life stressful situation, in which a close relative had been mistreated in a nursing home and asked to make up a realistic story around this scenario. Patients were given two minutes to prepare a statement and then three minutes to present it in front of a video camera and an audience wearing white coats. Participants were told that their speech would be evaluated by the laboratory staff for content, quality, and duration. We recorded blood pressure and heart rate at five-minute intervals during the resting phase and at one-minute intervals during the mental stress task, and calculated the rate-pressure product.

#### 2.2.2. Conventional stress testing

On a separate day, and within one week of the mental stress test, patients underwent treadmill exercise stress testing using the standard Bruce Protocol (Bruce, 1971; Fletcher et al., 2001; Gibbons et al., 2002), or, when contraindicated, pharmacologic testing with regadenoson (Lexiscan; Astellas Pharma US, Inc., Northbrook, IL). The treadmill test is clinically used in patients with CAD to detect myocardial ischemia due to supply-demand mismatch. According to the Bruce protocol, the test is administered in three-minute stages with gradual increases in treadmill speed and incline until the participant reaches 85% of their predicted heart rate according to sex and age. As exercise gradually increases, cardiac output is increased and the blocked arteries are not able to supply enough blood to the heart resulting in a mismatch in demand and supply leading to myocardial ischemia. Heart rate and blood pressure normally increase rapidly in