# SPECIFIC AIMS

Depression, a form of chronic mental stress, affects up to 20% of patients with acute coronary syndrome and has been associated with a 3-fold increase in cardiovascular mortality.1–3 The evidence that treating depression can reduce this excess cardiovascular mortality is conflicting and limited,4–6 suggesting a key knowledge gap in the management of depression in cardiovascular disease. Developing interventions that target underlying potential pathways, such as low coronary flow reserve or mental-stress induced myocardial ischemia,7,8 instead of depressive symptoms will require a better understanding of the mechanisms by which depression leads to an increased mortality in coronary artery disease (CAD). Autonomic nervous system (ANS) dysfunction may play an important role in this pathway,9 as it occurs in both depression, from central neurological abnormalities,10,11 and in myocardial ischemia or infarction, from damage to the intrinsic cardiac nervous system.12 There is a critical need to understand how ANS dysfunction may mediate the effect of depression on CAD, which would allow identification of at-risk individuals and provide a target for potential future therapies that can actually reduce the risk for mortality.

To overcome this challenge, we will leverage the Emory Cardiovascular Biobank to enroll patients with chronic stable angina and use a novel heart rate variability (HRV) measure to quantify ANS dysfunction. The Biobank, a multidisciplinary study led by Dr. Arshed Quyyumi (advisor), is an active prospective cohort of individuals undergoing clinically indicated cardiac catherization, during which depressive symptoms are also assessed using validated metrics.13,14 HRV is a measure of sinoatrial node function, which is altered in the setting of ANS dysfunction.15 Abnormal or low HRV, which can be measured non-invasively through electrocardiogram (ECG), is independently associated with depressive symptoms,16 cardiovascular mortality,17 and obstructive CAD.18 Our overall goal is to gain greater insight into the relationship of depression, CAD, and HRV, and eventually translate these findings into targeted interventions. HRV will be generated from up to 72-hours of raw ECG data on 200 patients, collected by ambulatory ECG patches (VivaLNK ECG recorder) on day of catheterization. We will use adjusted linear regression models for analysis with special consideration given to sex, which has a strong effect on depression, CAD, and HRV,14,19 and the circadian rhythm of the heart.20 The novel HRV measure, *Dyx*, is a non-linear measure that represents the ratio of the kurtosis along the y-axis and x-axis of the elliptical Poincaré plot of RR intervals, and is associated with increased cardiovascular mortality.21,22 In prior work, compared to traditional HRV, we found that 1) low *Dyx* in the early morning predicted abnormal coronary flow reserve,23 and 2) in preliminary analyses low Dyx strongly associated with depressive symptom burden. This makes *Dyx* a strong candidate for assessing ANS dysfunction in our proposal. I will build upon existing skills in ECG analysis signal processing using the pre-existing HRV toolbox, developed at Emory with the assistance of Dr. Amit Shah (mentor).24 *I hypothesize that ANS dysfunction, as measured by non-linear HRV, mediates the effect of depression on CAD*.

**Aim 1. Establish the relationship between depression and ANS dysfunction**. We will (A) assess depressive symptoms by validated questionnaires (Patient Health Questionnaire-9, PHQ-9),25 and (B) test the association of depressive symptoms with ANS dysfunction, measured by *Dyx*, using adjusted linear regression models. This may generate a novel and robust non-invasive marker for the effect of depression on the ANS. *Hypothesis: Elevated depressive symptoms will associate with low HRV.*

**Aim 2. Examine the effect of obstructive CAD on ANS dysfunction:** We will (A) assess the CAD burden with the CASS-50 score, an angiographic estimate of plaque burden, and (B) measure HRV before, during, and after catherization and/or revascularization.26 Findings will help clarify the role of ANS dysfunction in obstructive versus microvascular CAD. *Hypothesis: Low HRV will be associated with obstructive CAD (stenosis > 70%) and plaque burden by CASS-50 in a dose-response relationship,*27 *and HRV will improve after revascularization.*

**Aim 3. Determine how much ANS dysfunction mediates the relationship between depression and obstructive CAD:** Preliminary data suggests a strong relationship between ANS dysfunction and both depression and CAD respectively. We will analyze the association between depression and CAD with ANS dysfunction as a potential mediator variable. *Hypothesis: The relationship between depression and CAD will be partially mediated by low HRV after adjustment for confounders.*

This proposal will address a critical need in understanding the contributions and mechanisms of ANS dysfunction on depression and CAD, and may lead to potential therapies targeting ANS dysfunction, such as biofeedback and vagal nerve stimulation. My mentors are renowned experts in mental-stress induced myocardial ischemia (Viola Vaccarino), cardiovascular epidemiology (Alvaro Alonso), and depression in cardiovascular pathophysiology (Amit Shah). With their support and the additional training in computational biology, quantitative epidemiology, and autonomic physiology that results from this work, I will be well prepared to apply for a career development award evaluating more detailed mechanisms, outcomes, and interventions in neurocardiology and translational research.

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