# SPECIFIC AIMS

Depression affects up to 20% of patients with coronary artery disease (CAD) and has been associated with a 3-fold increase in cardiovascular mortality.1–3 The evidence that treating depression with counseling or antidepressants 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. Instead of treating depressive symptoms, developing interventions that target underlying potential pathways, such as low coronary flow reserve or mental-stress induced myocardial ischemia,7,8 will require a better understanding of the mechanisms by which depression leads to an increased mortality in CAD. Autonomic nervous system (ANS) dysfunction may play an important role in these pathways,9 as it occurs in both depression and CAD.10–12 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 examine patients with stable CAD using a novel heart rate variability (HRV) measure to quantify ANS dysfunction. The Biobank, a multidisciplinary study led by Dr. Arshed Quyyumi (advisor), is an ongoing 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 known 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 of the complexity and unpredictability of heart rate 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 depressive symptoms and ANS dysfunction**. We will a) assess depressive symptoms with the Patient Health Questionnaire-9,25 and b) test the association of depressive symptoms with ANS dysfunction, measured by *Dyx*. 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. Study clinical outcomes of ANS dysfunction in depression and CAD**. We will a) follow participants for adverse 1-year fatal and non-fatal outcomes, including all-cause mortality, myocardial infarction, revascularization, and development of CAD, and b) compare the differences in outcomes based on the presence of ANS dysfunction. *Hypothesis: Depressive symptoms and low HRV together will be associated with an increased risk of fatal and non-fatal outcomes after 1 year of follow-up.*

By elucidating the role of ANS dysfunction in the link between depression and CAD, we can better assess the potential benefit of interventions that target the ANS, such as biofeedback or vagal nerve stimulation. The F32 will allow me to work with experts in mental health and cardiovascular pathophysiology (Viola Vaccarino, Amit Shah) and cardiovascular epidemiology (Alvaro Alonso). With their support and additional training in computational methods, quantitative epidemiology, and autonomic physiology from this work, I will be well prepared to apply for a career development award to evaluate more detailed mechanisms, outcomes, and interventions in neurocardiology and translational research.

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