# 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 There is conflicting and limited evidence that treating depression, through standard measures including counseling or antidepressants, reduces the excess risk of cardiovascular mortality,4–6 suggesting a key knowledge gap in how to prevent the cardiovascular complications of depression.

An alternative to targeting depressive symptoms in CAD is to target underlying potential pathways, such as low coronary flow reserve or mental-stress induced myocardial ischemia,7,8 that may mediate the increased cardiovascular risk in depression. To do so will require a better understanding of the mechanisms by which depression leads to 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 better understand the relationship of ANS dysfunction with 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 cardiovascular mortality in depression.

To address these critical knowledge gaps, we will use a novel heart rate variability (HRV) measure to quantify ANS dysfunction. To examine patients with depression and stable CAD, we will leverage the Emory Cardiovascular Biobank, a multidisciplinary study led by Dr. Arshed Quyyumi (advisor) of an ongoing prospective cohort of individuals undergoing clinically indicated cardiac catherization, during which depressive symptoms are assessed using validated metrics.13,14 ANS dysfunction occurs at multiple levels, from central neurological processes to peripheral cardiovascular reflexes, such as the vagal withdrawal in depression and increased sympathetic tone in hypertension. HRV is an accepted measure of the integration of these multiple levels of autonomic outflow to the heart.15,16 Low HRV, a reflection of ANS dysfunction, is measured non-invasively through electrocardiogram (ECG) and is independently associated with depressive symptoms,17 cardiovascular mortality,18 and obstructive CAD.19 Our overall goal is to gain greater insight into the relationship of depression, CAD, and HRV, and eventually translate these findings into targeted interventions. The novel HRV measure, *Dyx*, derived from time series analysis,20 was found to be associated with increased cardiovascular mortality.21,22 In our 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. HRV will be generated for up to 72-hours of raw ECG data on 200 patients, collected through ambulatory ECG patches (VivaLNK ECG recorder) on the 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,14,24 and the circadian rhythm of the heart.25 I will build upon existing skills in ECG analysis and signal processing using the pre-existing HRV toolbox, developed at Emory with the assistance of Dr. Amit Shah (mentor).26 *I hypothesize that ANS dysfunction, as measured by low Dyx, 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-9,27 and b) test the association of the depressive symptom score 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 Dyx.*

**Aim 2. Examine the effect of obstructive CAD on ANS dysfunction.** We will a) assess the CAD burden with the CASS-50 score,28 an angiographic estimate of plaque burden, b) test the association of plaque burden with ANS dysfunction, measured by *Dyx*, before, during, and after catherization and/or revascularization. Findings may help clarify the role of ANS dysfunction in obstructive versus microvascular CAD. *Hypothesis: Low Dyx will associate with obstructive CAD (stenosis > 70%) and plaque burden by CASS-50 in a dose-response relationship,*29 *and Dyx will increase 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 synergistically 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 as a link between depression and CAD, we can assess the potential 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 (Drs. Viola Vaccarino, Amit Shah) and cardiovascular epidemiology (Dr. Alvaro Alonso). Their mentorship, the training in computational methods, quantitative epidemiology, and autonomic physiology, and this research experience will help me establish expertise in the area of neurocardiology and prepare me for an independent career as a physician scientist dedicated to improving the cardiovascular outcomes in patients with psychological disorders.

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