# C. SPECIFIC AIMS

There is a key knowledge gap in the pathological mechanisms underlying depression and coronary artery disease (CAD) that may lead to suboptimal clinical outcomes for both.1 Depression affects up to 20% of patients with coronary artery disease (CAD) and is associated with a 3-fold increase in cardiovascular mortality,2–4 however treating depression does not decrease the risk of cardiovascular complications.5,6 An alternative pathway for the cardiotoxicity seen in depression may stem from dysfunction of the autonomic nervous system (ANS).7,8 Therapies targeting the ANS, such as vagal nerve stimulation, show efficacy in treatment-resistant depression,9 angina pectoris,10 and cardiac arrythmias,11 implicating a potential target for focused interventions. We seek to gain a better understanding of the autonomic mechanisms in depression and coronary artery disease, which may lead to improved, targeted interventions to decrease adverse outcomes in both conditions.

We have recently discovered a novel electrocardiographic (ECG) biomarker of ANS dysfunction that we found to be predictive of abnormal myocardial perfusion and coronary flow reserve,12 and in preliminary analyses showed a strong association with depressive symptom burden. 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. Heart rate variability (HRV), measured non-invasively through ECG, is an accepted measure of the integration of these multiple levels of autonomic outflow to the heart.13,14 Low HRV, a reflection of ANS dysfunction is independently associated with depressive symptoms,15 cardiovascular mortality,16 and obstructive CAD.17 Our novel HRV measure, *Dyx*, outperformed traditional HRV measures.12 *Dyx* is derived from time-series analysis and captures the unpredictability of the heart.18 *Dyx* was recently shown to be a sensitive marker of ventricular dysrhythmia and cardiovascular mortality,19,20 and was found to be predictive of cardiac stress tests.21,22 We have also shown that depressive symptoms in CAD most prominently increase the risk of death in young women, suggesting that sex and age play a strong role in the underlying pathways.23 HRV is strongly affected by both age and sex,23,24 and in preliminary work we found that abnormal HRV was most strongly associated with depressive symptoms in younger women. Our goal is to study how ANS dysfunction may mediate the sex differences in the pathology of depression and CAD.

To examine the ANS in patients with symptoms concerning for CAD, we will leverage the Emory Cardiovascular Biobank (Dr. Arshed Quyyumi , PI (advisor)), a multidisciplinary ongoing prospective cohort of individuals undergoing clinically indicated cardiac catherization during which depressive symptoms are assessed using validated metrics.23,25 HRV will be generated from raw ECG data on 200 collected through ambulatory ECG patches (VivaLNK ECG recorder) on the day of catheterization. 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

**Aim 1. Quantify the relationship between depressive symptoms and ANS dysfunction (low Dyx).** We will a) measure depressive symptoms via thePatient Health Questionnaire-9,27and b) test the association with low Dyx. *We hypothesize 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, and b) test the association of plaque burden with ANS dysfunction, measured by *Dyx*, *We hypothesize that low Dyx will associate with obstructive CAD (stenosis > 70%) and plaque burden by CASS-50 in a dose-response relationship.*29

**Exploratory Aim 3. Study the differences in ANS dysfunction in patients with depression and CAD by sex**. We will a) collect sex-specific data on participants (including menopausal status, hormone therapy, pregnancy, etc.), and b) perform sex-stratified analyses on patients with depression and CAD. *We hypothesize that in patients with depression and CAD, Dyx will be lower in women than in men.*

Our lab has investigated the influence of autonomic nervous system (ANS) dysfunction on these pathways as ANS dysfunction occurs in both depression and CAD.1,30–32 By elucidating the role of ANS dysfunction as the mechanistic link underlying depression and CAD, we can assess the potential of interventions that target the ANS, such as vagal nerve stimulation.33 The F32 will allow me to expand on my TL1 award to work with experts in mental health and cardiovascular pathophysiology (Drs. Viola Vaccarino, Amit Shah) and cardiovascular epidemiology (Dr. Alvaro Alonso), and prepare me for an early career development award on improving cardiovascular outcomes in patients with psychological disorders.**REFERENCES**

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