# C. SPECIFIC AIMS

There is a key knowledge gap in the understanding of the mechanisms underlying depression and coronary artery disease (CAD).1 This is a major public health issue, considering that depression is the leading cause of disability in the world,2 and CAD is the leading cause of death.3 They are also comorbid and likely share common mechanisms: depression affects up to 20% of patients with coronary artery disease (CAD) and is associated with a 3-fold increase in cardiovascular mortality.4–6 Despite these associations, treatments for depression in CAD patients have only modest effects in reducing depressive symptoms, and furthermore have no impact on CAD outcomes.7,8 *Therefore, more research is needed to develop more effective interventions that address shared mechanisms*. A common mechanistic pathway for depression and CAD is dysfunction of the autonomic nervous system (ANS). Although current treatment strategies do not specifically target the ANS, research into such therapies may be promising, given the strong biological relationships that exist.9,10 Vagal nerve stimulation, for example, may be effective in treatment-resistant depression,11 angina pectoris,12 and cardiac arrhythmias.13 We seek to discover potential ANS biomarkers that can help elucidate heart-brain relationships and help develop effective therapies for both.

We have recently investigated a novel electrocardiographic (ECG) biomarker of ANS dysfunction, *Dyx*, that was predictive of abnormal myocardial perfusion and coronary flow reserve,14 as well as depressive symptoms (preliminary analysis). Encouraged by these findings, we seek to further explore its potential as a means of investigating dysfunction in both central neurological processes (depression) as well as peripheral cardiovascular reflexes as they relate to obstructive CAD. Both mechanisms can influence the adaptability/flexibility of the ANS, which can be measured by heart rate variability (HRV).15,16 We have found that *Dyx* is a particularly promising HRV metric, which can be measured in a low cost/burden manner with ambulatory ECG. *Dyx* is derived from an algorithm of the heart rate time series that measures the unpredictability and variability of the heart rhythm.17 Other studies have also found low *Dyx* to predict ventricular dysrhythmia and cardiovascular mortality;18,19 in addition, individuals with chest pain who had low *Dyx* values were found to have an odds ratio of 8 for having positive stress test results.20,21 *Dyx* may serve as an important clinical biomarker, but more studies are needed before it can be translated into clinical practice.

To best study these ANS pathways, we would test HRV metrics in a target a population that has both depression and CAD, either disease, or neither. To do so, we will leverage the Emory Cardiovascular Biobank (Dr. Arshed Quyyumi, PI (advisor),22,23 a prospective, well-characterized cohort including thousands of patients referred for coronary angiography. We will examine depressive symptoms (using the Patient Health Questionnaire-9 or PHQ-9)24and HRV using a newly developed ECG patch in 200 patients selected for having angina but without known CAD prior to catheterization,25 and examine the shared ANS mechanism between depression and CAD. Our preliminary analysis suggests a strong relationship with abnormal HRV and both CAD and depression. Furthermore, the autonomic pathways that underlie depression and CAD are heavily influenced by age and sex. My mentors, Drs. Shah and Vaccarino, have found that depressive symptoms and CAD are most strongly associated in women less than 60 years of age;22 in addition, young women are twice as likely to have depression and myocardial ischemia with mental stress.26 HRV is strongly affected by both age and sex,27 and in preliminary work we found that abnormal HRV was most associated with depressive symptoms in younger women. By studying how *Dyx* and its relationships with depression and CAD may differ by age and sex, we can better understand mechanisms that may be potentially specific to a high-risk group.28

**Aim 1. Quantify the relationship between depressive symptoms and ANS dysfunction.** *We hypothesize that A) elevated PHQ-9 scores will associate with low Dyx, and B) this association will be stronger in women and in younger participants (age < 65 years) than men and older participants of age > 65 years.*

**Aim 2. Examine the relationship of obstructive CAD with ANS dysfunction and its potential dose-response relationship.** *We hypothesize that A) low Dyx will associate with obstructive CAD (stenosis > 70%), B) lower Dyx will associate with a greater number of obstructed vessels in a dose-response manner,*29 *and C) the association between Dyx and CAD will be stronger in women and in younger participants (age < 65 years) than men and older participants of age > 65 years.*

This project 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 that also includes examination of long-term cardiovascular outcomes. This multidisciplinary, collaborative team has shown evidence of effective collaborations as well.1,30–32 Collectively, our work can help lay the groundwork for future clinical trials on ANS therapies such as vagal nerve stimulation, and also help bridge the gap in sex-related disparities in both depression and CAD.33