# SPECIFIC AIMS

The Northridge earthquake of 1994 led to an abrupt 5-fold increase in cardiac deaths unaccounted for by physical stress,1 highlighting the importance of psychological distress in the natural history of coronary artery disease (CAD). Regardless of the severity of disease, up to one-half of patients with CAD develop ischemia due to mental stress,2–4 which may be mediated by abnormal vasomotor control from autonomic nervous system (ANS) dysfunction.5,6 Depression, a form of chronic mental stress, affects 20% of patients with acute coronary syndrome and leads to a 3-fold increase in cardiovascular mortality,7–9 yet there remains contrasting evidence on whether interventions for depression can reduce this excess risk.10–12 These interventions target depressive symptoms and not the underlying potential pathways, including sympathovagal imbalance,13 low coronary flow reserve,14 and mental-stress induced myocardial ischemia.15 A potentially important mechanism of depression in CAD is abnormal autonomic regulation of the heart, which may arise from central neurological abnormalities.16,17 Abnormal autonomic regulation of the heart may also occur during myocardial ischemia or infarction due to dysfunction of the intrinsic cardiac nervous system.18 The abnormalities are known to change the fundamental functioning of the sinoatrial node, resulting in altered heart rate patterns and subsequently lowered heart rate variability (HRV).19 Low HRV serves as electrocardiographic (ECG) measurement of ANS dysfunction and is strongly associated with both depressive symptoms and overall cardiovascular mortality.20–22 Low HRV is also suggestive of obstructive CAD, and therefore a potentially useful autonomic measure of cardiotoxicity in depression.23–26 Few studies have examined these pathways, which may have important diagnostic and therapeutic implications.

This applicant, with the support of the mentoring team, is well-positioned to face this challenge. His mentors are renowned experts in depression and cardiovascular pathophysiology (Amit Shah), mental stress-induced myocardial ischemia (Viola Vaccarino), cardiovascular epidemiology (Alvaro Alonso), and neural control of cardiac physiology (Marc Thames). In published work, this applicant found that decreased early morning non-linear HRV was strongly predictive of abnormal coronary flow reserve in a cohort of 276 veteran twins without known CAD,27 suggesting that coronary vasoreactivity may be driven by the ANS. Additionally, non-linear HRV was found to be strongly associated with depressive symptoms. In a recent analysis, the applicant found a strong association between somatic depressive symptoms and HRV. By elucidating the role of ANS dysfunction in the pathogenesis of depression and CAD, we can better assess the potential benefit of interventions that target the ANS such as biofeedback and vagal nerve stimulation.

We propose to study ANS dysfunction by measuring HRV through ambulatory ECG patches (VivaLNK ECG recorder) in subjects with chronic stable angina undergoing evaluation in the Emory Cardiovascular Biobank,28 a multidisciplinary study led by Dr. Arshed Quyyumi (advisor). The Biobank is an active prospective cohort of individuals undergoing clinically indicated cardiac catherization, during which depressive symptoms are also assessed using validated metrics.29 They enroll approximately 15 participants per week, and the mentoring team has a long history of collaboration with the study. The applicant has been trained in ECG analysis using the pre-existing HRV toolbox, developed at Emory.30 This applicant, who is currently a postdoctoral epidemiology fellow and Emory TL1 scholar, has already enrolled 32 patients from the Biobank with long-term ECG recordings. The data we collect from this proposal will allow us to assess the contributions and mechanisms of ANS dysfunction on depression and CAD, and prepare the applicant for future career development awards that evaluate more detailed mechanisms, outcomes, and/or interventions. We hypothesize that ECG markers will reflect both cardiac autonomic dysregulation and psychological stress, which we will test with the following aims:

1. **Examine the relationship between psychological distress and cardiac autonomic dysregulation:** We will A) measure psychological stress through depressive symptoms by validated questionnaires (Patient Health Questionnaire-9, PHQ-9),31 and B) measure cardiac autonomic dysregulation with non-linear HRV. Non-linear techniques allows for the measurement of the complexity and unpredictability of heart rate. *Hypothesis: Elevated depressive symptoms will associate with abnormally low non-linear HRV.*
2. **Evaluate the relationship of obstructive CAD with cardiac autonomic dysregulation:** We will A) assess the CAD burden with the CASS-50 score.32 *Hypothesis: Abnormal HRV will associate with obstructive CAD (stenosis > 70%), and CAD plaque burden by CASS-50 score in a dose-response relationship.*33
3. **[Exploratory] Study clinical outcomes of individuals with ANS dysfunction:** We will leverage ongoing efforts from the Biobank to follow participants for adverse 1-year fatal and non-fatal outcomes. *Hypothesis: Depressive symptoms and low non-linear HRV will associate with an increased risk of composite myocardial infarction and cardiovascular death after 1 year of follow-up.*

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