# SPECIFIC AIMS

The Northridge earthquake of 1994 led to an abrupt 5-fold increase in cardiac deaths unaccounted for by physical stress,1 which highlights the importance of psychological distress in the natural history of coronary artery disease (CAD). Regardless of severity of disease, one-half of patients with CAD develop ischemia due to mental stress,2–4 which may be a result of abnormal vasomotor control from to 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 interventions that decrease mortality.10–12 Potential pathways to explore these pathways remains underway, exploring altered ANS functioning,13 coronary flow reserve,14 and mental-stress induced myocardial ischemia.15 A critical hurdle in understanding the mechanisms of depression in cardiovascular mortality is identifying the contributions of autonomic outflow to the heart. Low heart rate variability (HRV), a measurement of ANS dysfunction at the sinoatrial node, is strongly associated with both depressive symptoms and overall cardiovascular mortality.16–18 Low HRV is also suggestive of obstructive CAD independently and in depression, however studies are limited to time-independent measures, do not account for changes in the intrinsic cardiac nervous system, and do not assess the potential mediating effect of ANS dysfunction.19–22 The contribution of the ANS can be better characterized by studying the dose-dependent effect of both depression and CAD on ANS dysfunction using non-invasive markers of HRV and electrocardiographic (ECG) morphology.

This applicant, with the guidance of the mentoring team, is well-positioned to face this challenge. His mentors are renowned experts in psychological stress and cardiovascular disease (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 has 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.23 This suggests that coronary vasoreactivity may be mediated in part by the autonomic nervous system, however it remains unknown the contribution of obstructive CAD. In a subgroup analysis from the same cohort, it was found that non-linear HRV was also strongly associated with depressive symptoms. If the role of ANS dysfunction in the pathogenesis of depression and CAD was better characterized, therapies that focus on ANS recovery (e.g. biofeedback, vagal nerve stimulators) could be used in target patients to reduce both symptom burden and overall mortality.

We propose to study ANS dysfunction by measuring HRV and ECG morphology through ambulatory ECG patches (VivaLNK ECG recorder) in subjects with chronic stable angina undergoing evaluation in the Emory Cardiovascular Biobank (Arshed Quyyumi). The Biobank is an active prospective cohort study of individuals undergoing clinically indicated cardiac catherization, during which psychological profiling is also conducted. The applicant has training in digital signal processing using ECG patches, with close support from engineers in the department of biomedical informatics that developed the local HRV toolbox (Gari Clifford). This applicant has also enrolled over 80 patients at the time of writing from the Biobank, all with long-term ECG recordings. Preliminary analyses show prominent features of HRV and ECG morphology add predictive value to the finding of obstructive CAD over traditional risk factors. The data we collect from this proposal will allow us to assess the contributions and mechanisms of ANS dysfunction on depression and CAD. We hypothesize that ECG markers will reflect changes in sympathovagal balance in diseases states of both the brain and heart, which we will test with the following aims:

1. **Determine the relationship of neuropsychological distress, represented by depression, on ANS dysfunction:** We will A) assess psychological stress through depressive symptoms by questionnaires (Patient Health Questionnaire-9, PHQ-9), and B) test the relationship with changes in ECG. *Hypothesis: Increased depressive symptoms will associate with abnormal HRV findings, with non-linear HRV having the strongest association.*
2. **Evaluate the relationship of obstructive CAD with autonomic dysfunction:** We will A) measure the severity of CAD in patients undergoing cardiac catherization, B) analyze the effect of progressive CAD, including that of revascularization, on HRV, and C) measure the changes in ECG morphology in orthogonal leads. *Hypothesis: Abnormal HRV and decreased T-wave amplitude will associate with obstructive CAD (stenosis > 70%), and overall CAD plaque burden (Gensini score) in a dose-response relationship.*24
3. **Study clinical outcomes on individuals with ANS dysfunction (experimental):** We will A) obtain follow-up information on patients with ECG data over two years, and B) determine the effect of ECG abnormalities on morbidity and mortality. *Hypothesis: Abnormalities in ECG will associate with increased mortality, increased likelihood of revascularization, and increased hospitalization. Abnormalities in ECG will account for the increased morbidity in patients with depressive symptoms.*

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