# SPECIFIC AIMS

The day of the Northridge earthquake of 1994, there was a 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 overall severity of atherosclerosis, up to one-half of patients with CAD develop ischemia due to mental stress,2–4 which may in part be a result of abnormal vasomotor control secondary 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 Current efforts are being made to understand potential pathways, including altered ANS functioning.13

A critical hurdle in understanding the mechanism of depression in cardiovascular mortality is a lack of understanding of the contributions of ANS dysfunction. 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.14–16 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 mediating effect of ANS dysfunction.17–20 Studying the dose-dependent effect of both depression and CAD on ANS dysfunction, using non-invasive markers of HRV and electrocardiographic (ECG) morphology, the contribution of the ANS can be better characterized.

The most critical hurdle in Identifying at-risk individuals before major adverse cardiovascular events occur is the lack of non-invasive markers of sympathovagal balance. The ideal candidate disorders to study would be both component causes of SCD, and have known associations with autonomic dysfunction. Coronary artery disease (CAD), the predominant substrate found in SCD, leads to increased cardiac sympathetic outflow and may cause changes in coronary vasoreactivity. Depression, a potential trigger of SCD, associates with increased mortality in coronary artery disease (CAD) and leads to autonomic dysfunction, likely through vagal withdrawal. ECG techniques, such as heart rate variability (HRV) or morphology analysis, offer a non-invasive means to measure these disorders.

The major limitations in the non-invasive quantification of autonomic dysfunction stems from limited interdisciplinary teams (physicians, engineers, epidemiologists, and physiologists), the computational power required for long-term ECG analyses, and well-characterized population-based cohorts.

We are very well positioned to face this problem because of the interdisciplinary team we have created, including computer scientists (Gari Clifford), cardiovascular epidemiologists (Amit Shah, Alvaro Alonso), applied physiologists (Jeanie Park), and experts in the field of neurocardiology (Marc Thames) and mental stress (Viola Vaccarino, Arshed Quyyumi). With their support, I have been able to publish data that supports the role of HRV in coronary vasoreactivity, and the importance of psychosomatic symptoms in abnormal HRV. In addition, I have worked with this mentorship team to receive a TL1 award that has allowed me to enroll patients undergoing cardiac catherization with the addition of long-term ECG recordings using the VivaLNK ECG patch. As of December 2019, we have enrolled over 80 patients, with the expectation to have enrolled over 200 patients by June 2020. My preliminary analysis suggests that there are certain ECG features that add predictive value to the likelihood of obstructive CAD. These analyses require not only clinical understanding of cardiac physiology, but also experience with programming and computer science and the HRV toolbox. Determining clinically relevant, non-invasive markers of autonomic dysfunction will allow us to identify patients at risk, and study autonomic dysfunction at the population level, which will help us identify the mechanism by which neuropsychological and cardiovascular factors may lead to pathology. We are proposing to test the hypothesis that ECG markers will reflect changes in sympathovagal balance in disease states — of both the brain and heart — with the following aims.

**Aim #1: Evaluate the relationship of CAD with autonomic dysfunction:** We will A) measure cardiac sympathetic outflow through ECG in patients undergoing cardiac catherization, B) analyze the effect of progressive CAD on HRV, and C) describe the effect of revascularization on autonomic recovery. As an exploratory sub-aim, we will also measure spatial vector gradient variability using orthogonal three-lead ECG patches. *Hypothesis: Abnormal HRV and decreased T-wave amplitude will associate with obstructive CAD (stenosis > 70%), and will associate with CAD plaque burden (Gensini score) in a dose-response relationship.*

**Aim #2:** **Determine the effect of neuropsychological disturbances on autonomic dysfunction:** We will A) measure neuropsychological profiles, measured by depressed mood, through 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 being the strongest association.*

**Aim #3: Study clinical outcomes on individuals with increased autonomic dysfunction:** We will A) obtain follow-up information on patients over three years, and B) determine the effect of ECG abnormalities on morbidity and mortality. *Hypothesis: Abnormalities in ECG will associate with increased mortality, increased visit frequency, and increased chance of future chest pain workups.* *Abnormalities in ECG will also account for the increased morbidity of patients with depressive symptoms.*

By establishing the predictive utility of non-invasive correlates of autonomic dysfunction in diseases of both the heart and brain, we can begin to understand how sympathovagal balance plays an important role in as SCD. The mentored research will let me collect data that can serve as part of a larger, longitudinal study for a future K award focusing on translational studies in neurocardiology, risk stratification, and prevention.

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