**SPECIFIC AIMS**

Sudden cardiac death (SCD) has less than a 10% hospital survival rate and account for 15-20% of all deaths,1 yet risk stratification is limited until after the development of major adverse cardiovascular events. The theoretical model suggests that a trigger event (psychological distress) in a damaged cardiac substrate (ischemic heart disease) can lead to SCD. The autonomic nervous system, heavily implicated in SCD, also plays an important role in the mechanisms behind several component causes, but studies that look at risk prediction are limited by the invasive nature of autonomic testing.3 However, there is a growing interest however in using electrocardiographic (ECG) features to study autonomic dysfunction with population level outcomes.2

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.*4

**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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