1. **SPECIFIC AIMS**

Four out of five patients with ischemic heart disease (IHD) are unrecognized by electrocardiography (ECG) and clinical exam.1 The majority of sudden cardiac death (SCD) still occurs in those without diagnosed IHD,2 and although the overall rate of cardiovascular mortality is declining, the rate of community events has not declined proportionally.3 A growing body of literature suggests that autonomic dysfunction is not only of prognostic value in cardiovascular mortality,4 but may serve as a novel risk factor for IHD. Recently, a new ECG-based biomarker of autonomic dysfunction based on heart rate variability (HRV), named *Dyx*, was found to be an important predictor of myocardial ischemia.5 *Dyx* is calculated from an hour-long recording of ambulatory ECG, and low values (< 2.0 units) are associated with an 8-fold increased odds of positive nuclear stress test findings (suggesting IHD).5 While promising, the study was limited by a small sample size, it did not assess for relationship with angiographic findings, and the outcome used, single photon emission tomography (SPECT), is only 80% sensitive and specific for obstructive coronary artery disease (CAD).6 In an analysis I independently conducted that was highlighted at the 2018 American Heart Association Scientific Sessions, we found that that low *Dyx* in the early morning was predictive of myocardial perfusion imaging (MPI) deficits in a cohort of 276 veteran twins without known CAD.7 We found for the first time that the time of day in which HRV is measured is a critical step in measuring heart disease risk. Nonetheless, we were unable to differentiate whether this relationship is due to obstructive CAD (requiring revascularization) and/or abnormal vascular reactivity (likely microvascular). This is important when considering the clinical implications of low *Dyx*.

Low *Dyx*, as with other HRV metrics, is influenced by central neurologic mechanisms, and in an unpublished analysis in our twins dataset, we found a robust association between depressive symptoms and Dyx. This relationship is consistent with the neurovisceral integration theory, which describes a network of brain regions that influence cognitive function, mood, and autonomic regulation.8 Neurovisceral dysfunction occurs in the setting of neuropsychological pathology, such as in depression and cognitive impairment, which have well-known effects on autonomic regulation,9,10 confer a worse prognosis in coronary artery disease (CAD),11,12 and increase the risk of SCD.13,14 One remaining question is to what extent low Dyx values are due to brain-related factors, rather than (or in addition to) obstructive CAD.8,15 By evaluating the relationship of brain-based metrics and CAD with Dyx in the same population, we can better evaluate the best intervention for this important prognostic marker.

I hypothesize that disturbances of the neurocardiac axis, assessed by both heart and brain metrics, result in autonomic dysfunction, which can be measured by *Dyx*. As such, Dyx is a useful metric in both efforts to risk stratify for CAD, as well as detect neurovisceral dysfunction. We propose to study *Dyx* by measuring HRV through ambulatory ECG patches (BioStamp®, MC10 Inc.) in the Emory Cardiovascular Biobank. The Biobank is a prospective cohort study of individuals undergoing cardiac catherization, and records data on angiographic outcomes, and conducts validated neuropsychological assessments.16 The data we collect from this proposal will allow the assessment of autonomic function prior to the heart catheterization and its relationship to IHD and its relationship to neurovisceral dysfunction. We will test the central hypotheses through two proposed aims:

1. **To evaluate the relationship of autonomic dysfunction, measured by abnormal HRV, on the spectrum of progressive CAD.** *Hypothesis:* *Lower Dyx in the morning hours will be predictive of increasing CAD plaque burden (Syntax score), independent of traditional risk factors.* Coronary artery stenosis will be measured visually at time of cardiac catherization. We will also test if specific cutoff points of *Dyx* are predictive for obstructive CAD (stenosis >= 70%).
2. **To determine the effect of neurovisceral dysfunction on autonomic dysfunction.***Hypothesis: Neurovisceral dysfunction, as measured through depression, stress, and cognitive impairment, will be independent predictors of lower Dyx.* Cognitive impairment, depression, and perceived stress will be measured by the Montreal Cognitive Assessment (MoCA), Patient Health Questionnaire-9, and a stress questionnaire.

The mentored research and structured didactics of the MSCR will prepare me for my goal of becoming a physician-scientist. My future goals include the pursuit of a K grant focusing on translational studies in neurocardiology, risk stratification, and prevention. Under the guidance of my mentorship team (Amit Shah, MD, MSCR; Alvaro Alonso, MD, PhD; Marc Thames, MD; Viola Vaccarino, MD, PhD; Arshed Quyyumi, MD) I will gain invaluable training in study design, primary data collection and analysis, and be well-prepared for a career as a clinical investigator in cardiovascular epidemiology.