# RESEARCH STRATEGY

## SIGNIFICANCE

### A1. Burden of Depression in Coronary Artery Disease: An Untreated Epidemic

Depression is the leading cause of disability in the world,1 and CAD is the leading cause of death.2 Depression is estimated to occur in over 300 million people, which accounts for roughly 4% of the global population.1 The estimated yearly economic burden of depression in US is $210 billion dollars and the estimated direct and indirect costs of CAD is $204 billion, with the cost of both continuing to climb.3,4 In patients with CAD, the prevalence of depression is up to 20%.5 In comorbid depression and CAD, there is a 3-fold increase in cardiovascular,6 however only in the last several years has depression been recognized as an additional prognostic marker of mortality.7 The rate of increased mortality in CAD with depression has remained unchanged over the past 35 years.6 Although the American College of Cardiology recommends depression should be routinely screened for in patients with cardiovascular disease,5 there is limited evidence that this leads to an improvement in overall mortality.8

### A2. Mechanisms Involved in the Increased Mortality with Depression in Coronary Artery Disease

The treatment of depression through traditional interventions, such as cognitive behavioral therapy and antidepressants, have not shown an improvement in event-free survival.9 This underscores a critical knowledge gap in the understanding of the mechanisms underlying depression and CAD,10 which limit finding therapies that can actually decrease mortality. The potential mechanisms are complex – depressive symptoms can lead to changes in coronary vascular reactivity and cardiovascular mortality dependent on age, sex, and genetic differences, as we have seen in our lab. Dr. Vaccarino and Dr. Shah have shown that depressive symptoms are predictive of CAD, with the finding being most prevalent in younger women (age < 55 years) as compared to older women or men.11 In twins discordant for depression, only dizygotic twins show a decrease in coronary flow reserve, a marker of CAD, as compared to monozygotic twins, suggesting a shared genetic pathways between depression and microvascular dysfunction.12 Depression also leads to an increased propensity to develop myocardial ischemia due to mental stress,13 which in turn is more likely to develop in young women but not men.14 However, the type of depressive symptoms are also predictive of mortality. Recent literature suggests that increased mortality may be confined to patients with untreated depression,15 but only somatic depressive symptoms (versus cognitive symptoms) lead to the increased mortality.16 In a manuscript under review, we found that somatic depressive symptoms were strongly associated with persistent electrocardiographic changes, a marker of autonomic dysfunction.

### A3. Autonomic Nervous System Plays a Critical Role in both Depression and Coronary Artery Disease

The ANS plays an important role in the manifestations of disease in both the brain and heart.17 Autonomic dysfunction occurs at multiple levels, from central neurological processes to peripheral cardiovascular reflexes,18 such as the vagal withdrawal in depression or heightened sympathetic tone in cardiovascular disease. Depression has been linked to dysregulation of the ANS though increased levels of catecholamines,19 increased cardiovascular reactivity to stress,20 and decreased baroreflex sensitivity.21 This includes an increase in the frequency of premature ventricular contractions and QT variability.22 The heart itself boasts an intrinsic cardiac nervous system that shows a profound response to injury and ischemia.23,24 As strong biological pathways exist, treatments that target the ANS are a promising area for further research.25 For example, the vagal nerve is known to be protective against ventricular fibrillation,26 and vagal nerve stimulation has been shown to relieve angina pectoris and cardiac arrhythmias.27,28 Vagal nerve stimulation is also effective in treatment-resistant depression.29 The ANS is thus of physiological importance in both diseases, and ANS dysfunction may be a shared target for intervention.

### A4. Advances in Electrocardiography can Assess Autonomic Dysfunction

The multiple levels of sympathetic and parasympathetic efferent input are integrated at the level of the sinoatrial node. HRV is an accepted measure of this cardiac autonomic outflow.30,31 A novel HRV method, *Dyx*, has surfaced as a promising ECG biomarker of ANS dysfunction. *Dyx* is derived from heart rate time series analysis that measures the non-linear variability of the heart rhythm. *Dyx* is generated through the multipole method analysis of Poincaré plot, in which beat-to-beat (RR) interval lengths are plotted as a function of prior RR intervals to form an ellipse, as seen in our prior work (**Figure 1**).32 *Dyx* is novel in that it is generated as the ratio of the kurtosis along the y-axis and the x-axis of the, better capturing the density of heart beats and thus including non-linear features of heart rate dynamics.33,34 Other studies have found that low Dyx predicts ventricular dysrhythmia and cardiovascular mortality after myocardial infarction, with a hazard ratio of 2.4 (95% CI 1.5 – 3.8).34,35 In addition, individuals with chest pain and low Dyx had an odds ratio of 8 for having abnormal exercise stress test results.36,37 This makes *Dyx* a strong candidate for assessing ANS dysfunction in our proposal.

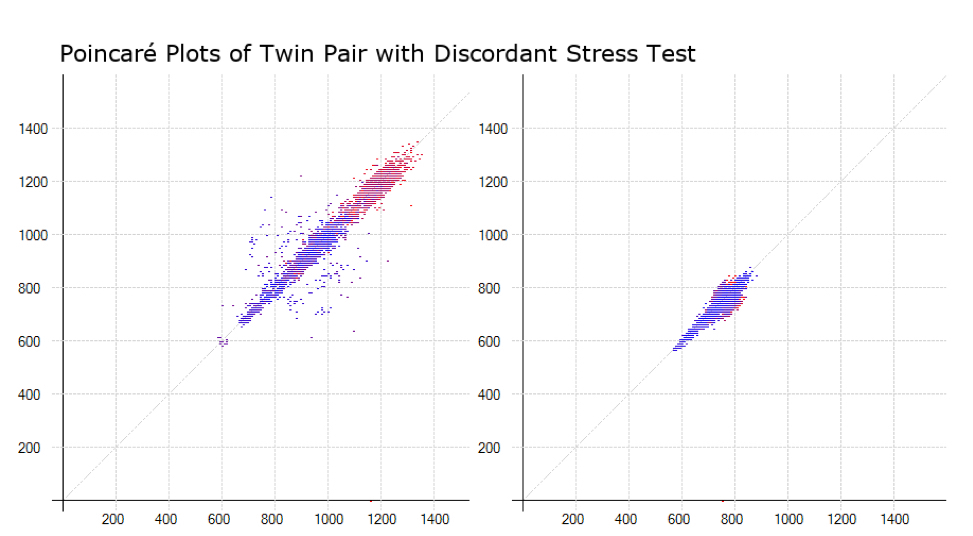


Figure 1. The two Poincaré plots represent ECG data at 7 AM for a twin pair that are discordant for stress test results. Both axes are RR interval lengths in milliseconds. The x-axis coordinate represents the RR interval for an initial beat, while the y-axis coordinate represents the RR interval for the following beat, such that the (x, y) coordinate represents (RRn, RRn+1). Each subsequent coordinate is plotted in this way. The red points are beats that were slower than the previous beat, while the blue points were faster than the previous beat. The shape of the resulting plot is abstracted into a single descriptive index called *Dyx*. The first twin (left) had no myocardial perfusion deficits on stress testing with a *Dyx* = 3.7. The second twin (right) had an abnormal stress test with a *Dyx* = 1.7.

## PRELIMINARY DATA

We demonstrated recently that in a cohort of 276 individuals without known CAD, low *Dyx* in the morning hours had a 12-fold increase in the odds of abnormal MPI and a decrease coronary flow reserve (**Table 1**).38 In the same cohort, preliminary analysis also showed *Dyx* was predictive of depressive symptoms.

Table 1. Regression models for both regional and global CFR with *Dyx*. Adjusted models accounted for twin pairs, and multivariate models also included traditional covariates. The regional territories are defined as LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery.



The relationship between HRV, depression, and CAD is supported by data from our pilot study of 30 participants from the Emory Cardiovascular Biobank. The methods and analysis are described in more detail below. Of the participants that completed the psychological profiling, 25% (n=7) had high depressive symptoms (PHQ-9 > 10), and 75% (n=21) had low depressive symptoms. Based on coronary angiography, 73% (n=22) had stenosis of the coronary arteries, while 27% (n=8) had mild to no angiographic disease. Long-term HRV was collected on all patients, ECG signal was collected on all patients, ranging from 4 to 25 hours, with only 26% data loss due to low-quality signal for HRV analysis. For the preliminary analysis, HRV was compared by the first hour of ECG after recording began, which occurred before anesthesia, sedation, or cardiac catherization occurred. When comparing HRV recordings in patients with and without depression (PHQ-9), there was a difference in overall distribution by Kolmogorov-Smirnov test (p < 0.05), and two-sample t-test (p < 0.05). When comparing long-term HRV recordings in patients with >70% stenosis of any major coronary artery (CASS-70 > 1), HRV was different in overall distribution (p < 0.05) and by population means (p < 0.05). This data provides evidence that HRV is the appropriate tool for further analyzing the relationship between depression and CAD. The proposed research plan will allow us to improve the power of our study to analyze hourly effects, adjust for multiple covariates (such as clinical indications for catherization), and study the effect of age and sex.

## INNOVATION

Innovation is central to this proposal, which seeks to validate a new, low-cost ECG-based measure (*Dyx*) as a tool to measure disturbances of the neurocardiac axis that has additional relevance to depression and ischemic heart disease. This is a paradigm shift towards metrics that have a focus on the brain-heart connection, as opposed to focused tests on anatomy or self-reported symptoms. This new way of seeing depression and CAD as connected to the neurocardiac axis may lead to clinical practice changes in disease management as well. For example, it may promote stress management, exercise therapy, and biofeedback in the management of these conditions.39 *Dyx* is relatively new and unexplored compared to other HRV indices. For the first time, we are taking into close consideration the time of day when measuring HRV.40–42 Most previous studies, on the other hand, do not evaluate this at all, or average all of the HRV metrics over and entire 24 hour period.36,37 The technology utilized for this study is also cutting edge and more easily collected in clinical settings than previous methods. We will utilize the VivaLNK patch (**Figure 2**), which has a much lower patient burden than traditional Holter monitoring (smaller than a credit card). Our study design also allows us to achieve a breakthrough in the assessment of *Dyx*; as opposed to previous studies,36 we can now evaluate its predictive potential with coronary angiography findings. Further studies (included a future K23) may also evaluate the relationship of *Dyx* with secondary clinical outcomes. Additional evaluation of *Dyx* with depression will be the first study of their kind. It will lead to better a mechanistic understanding of the neurocardiac axis, and future work may help to evaluate how interventions can target autonomic dysfunction. Overall, our rigorous, holistic evaluation of HRV will help provide critical assessment of its value in measuring autonomic dysfunction in the evaluation of depression and CAD.

Figure 2. The VivaLNK ECG patch is a small, wireless device, roughly 2” by 0.5” that will be placed in the mid-axillary line at the level of the heart. It has been approved for use for heart rate monitoring and recording of raw ECG signal.



## APPROACH

### C1. Study Overview

This training grant proposes an ancillary study on an ongoing prospective registry of patients undergoing cardiac catherization, the Emory Cardiovascular Biobank (Biobank, PI Quyyumi) ﻿which was established to identify novel factors associated with the pathobiological process and treatment of cardiovascular disease.43 The Biobank is enriched for patients with high suspicion for obstructive CAD, which provides ample statistical power for studies of risk prediction. The registry has over 7,000 unique patients from three Atlanta-based sites in the Emory University Hospital system. The Biobank has ongoing enrollment (10-20 patients per week), with established facilities, staff, and data collection mechanisms in place, and has IRB approval for future research that includes analysis of de-identified data. **Figure 3** shows an overview of the scientific basis of the proposed aims. The ECG data needed to calculate *Dyx* will be added as an ancillary study using the existing study team. The current coordinator will apply the patch and retrieve the data. Processing of HRV is automated as detailed below, with raw signal available from the VivaLNK software suite.

### C2. Study Population

The Biobank has assessed approximately 3,000 major cardiovascular events thus far.11 It also evaluates additional biomarkers for inflammation, cardiac injury, and genetics, with the goal of predicting CVD outcomes.43 All patients aged 18 years and older undergoing cardiac catherization are recruited to participate by a full-time study coordinator. After informed consent, they are interviewed for health behaviors and neuropsychological functioning the same day, prior to cardiac catherization. They are excluded if they have congenital heart disease, severe valvular heart disease, severe anemia, a recent blood transfusion, myocarditis, history of active inflammatory disease, cancer or are unable or not willing to provide consent (approximately 5%).

### C3. Study Design

General Protocol: The enrollment, consent, and detailed phenotyping of the patients has been described in prior studies of the Biobank.43 ﻿Additional measures, including lifestyle factors, medical comorbidities, revascularization during the index cardiac catheterization, and previous revascularization procedures are ascertained via patient interview and chart review. The study will enroll participants daily from October 2019 until December 2020. The Biobank enrolls on average 10-20 patients per week, and we estimate from our pilot study that up to half will agree to further ECG analysis.

Heart Rate Variability: This study will add HRV to the data collected by the Biobank. We will use non-invasive, continuous, ambulatory ECG patches (VivaLNK ECG Monitor), which have already been acquired through my mentor Dr. Shah. I will continue to teach and assist the study staff on the incorporation of ECG data collection into the larger study protocol. The consent will occur in the evening before or morning of the catherization, after which the patch will be applied and remain on through angiogram, for up to 72 hours. Our recent findings demonstrate that the most important time for detecting autonomic dysfunction is between 7 AM and 10 AM.38 If possible, the ECG duration will be extended. We will use the commercial HeartTrends algorithm (Lev-El Diagnostics Ltd., Israel) to generate the *Dyx* measure, as well as an internally developed HRV toolbox to generate additional indices for comparison.44 A materials transfer agreement with the company is already in place with HeartTrends.

Psychological Measures: The enrollment protocol includes patient interviews by study staff. Depressive symptoms will be assessed via the 9-question Primary Care Evaluation of Mental Disorders Brief Patient Health Questionnaire (PHQ-9).45 Moderate depression is seen at a cutoff of 10 points or higher (out of 27), with a sensitivity and specificity of 88% for major depression.46

Cardiac Measures: Coronary angiography will be evaluated by the Gensini score, which is a visual estimation of luminal narrowing in multiple segments based on a modified form of the American Heart Association classification of the coronary tree by trained cardiologists.47 Coronary angiography will also be evaluated using the Coronary Artery Surgery Study (CASS), which evaluates the number of major epicardial vessels that have a certain percent stenosis, e.g. the CASS-50 score determines the number of vessels with > 50% stenosis. Additionally, during catherization additional values of end-diastolic pressure and estimated ejection fraction are collected. Through the standardized clinical chart review done for each participant, prior cardiac stress testing data will also be available.

Power Calculation: In this exploratory pilot study, the expected cohort size is 150 patients, collected over the first 6 months. We anticipate a maximum of 20% loss of data due to poor ECG quality (>20% artifact), missing data, or other exclusion criteria as above. We do not expect attrition as this is a cross-sectional study. After these reductions, we expect a sample size of 120 patients. We expect a rate of 70% of CAD, and 15-20% of neuropsychiatric disease. After biostatistician consultation, we will use α=0.05, and 1-β=0.80. We would be adequately powered to detect a large effect size in for the primary outcomes for both specific aims (Cohen’s d = 0.5).48

**C4. Specific Aim #1: Quantify the relationship between depressive symptoms and ANS dysfunction.**

Rationale: Depression is not only common is patients with CAD, but is also prognostic after myocardial infarction, independent of traditional risk factors.15,49–51 Our preliminary analyses from the Emory Twin Study found *Dyx* to be a significant determinant of depressive symptoms (r= 0.14, p<0.001 in 276 individuals). Also, in aanalysis from the Atherosclerotic Risk In Communities (ARIC) study, somatic depressive symptoms were associated with abnormal HRV. We will look for the first time to elucidate the independent relationship of *Dyx*, a potent marker of autonomic dysfunction, with depression.

Data Collection and Analysis: I will be directly involved with the study coordinators to enroll and consent patients for ambulatory ECG. The VivaLNK software allows for the import of raw data. We have prepared additional programs that allow for extraction of the raw ECG signal. We will use the HRV toolbox to automatically extract and convert it into usable RR intervals and evaluate for arrhythmia (which would be excluded from analysis). We will communicate with the HeartTrends company to assist with the appropriate and timely generation of the *Dyx* index through Poincaré plot analysis.32,34 Under the guidance of Dr. Shah, I will continue to learn how to use the HRV toolbox to generate hourly frequency and geometric domain indices of HRV for additional assessments.44 The primary outcome will be depressive symptoms (PHQ-9). The primary exposure will be autonomic function, measured by *Dyx* and other HRV indices. We will create individual regressions models for the continuous *Dyx* measure, and logistic regressions for *Dyx* using the clinical cutoff of <2 units.52 Secondary outcomes will include adjustment for age and sex to study the potential interaction effect that may be present. My training through additional biostatistical and epidemiology courses will provide me the necessary tools to conduct these analyses, with support from Dr. Vaccarino and Dr. Shah in evaluation and interpretation of the data. Familiarizing myself with the mathematical principles and technical skills underlying signal processing and time-series analysis will be critical for my training, allowing me to translate our findings into clinically meaningful assessments.

Power calculations: In this exploratory study, the expected cohort size is 200 participants collected over 10-12 months. We anticipate a maximum of 20% data loss due to poor ECG quality (>20% artifact) or missing psychological data. We do not expect attrition as this is a cross-sectional study. After these reductions we expect a sample size of 160 participants. We expect 25% of participants to have major depression, as our pilot study suggests. We will use α = 0.05, and 1 – β = 0.80. We would be adequately powered to detect an medium effect size (Cohen’s d = 0.45).53

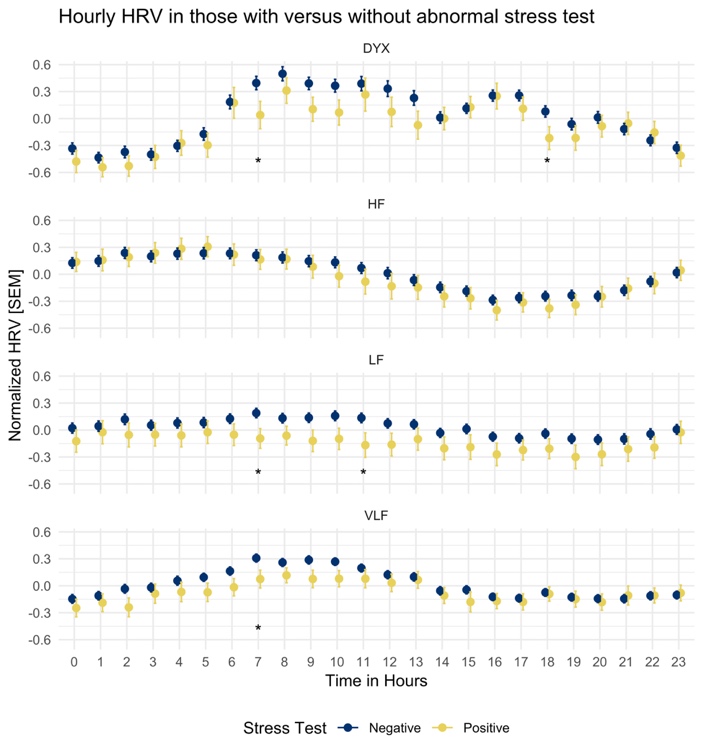
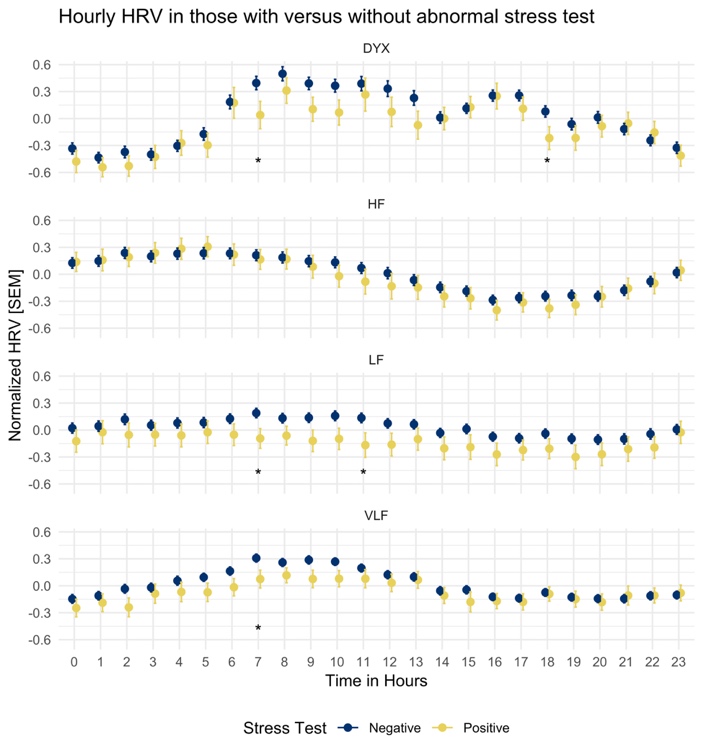
Potential Problems and Solutions: The PHQ-9 is not validated in the setting of acute stress, which certain patients may present for in the setting of acute coronary syndromes. We will attempt to assess participants that are clinically stable by excluding those admitted to the intensive care unit. Treatment of depression may lead to favorable changes in HRV. We will control for antidepressant use through additional subgroup analysis. The generalizability of this data is difficult, as depression leads to changes in health behaviors. There are additional socioeconomic and health literacy data that may help control for health behavior changes.

Anticipated Results: We expect to find an independent association between increased depressive symptoms and autonomic dysfunction, measured by low HRV and most robustly seen with *Dyx*. We expect that this finding of depression and low HRV will be most strongly associated in women and in younger participants (age < 65 years).

**C5. Specific Aim #2: Examine the relationship of obstructive CAD with ANS dysfunction and its potential dose-response relationship.**

Rationale: Abnormal HRV indicates autonomic dysfunction and increases the risk of cardiovascular mortality. *Dyx* has been shown to predict myocardial perfusion defects during pharmacological stress test. Our previous work suggests this finding is most robust during morning hours, as in **Figure 4**.38 We are looking to, for the first time, evaluate *Dyx* during morning hours and the relationship with obstructive CAD and overall plaque burden. Our prior work was conducted in middle-aged, male veterans and can be expanded by including women.

Figure 4. The non-linear HRV metric, *Dyx*, was found to be significantly lower in the early morning hours in patients with abnormal myocardial perfusion deficits.



Data Collection and Analysis: I will compare the exposure of HRV to the outcome of coronary artery plaque burden, measured by the Gensini and CASS scores, from cardiac catherization using linear regression models. Logistic regression models will be fit using a clinical cutoff point of *Dyx* (< 2.0 units)against obstructive CAD (stenosis > 70%).52 Additional analysis will be performed to test the interaction of age and sex on HRV and CAD. Secondary outcomes will evaluate the performance of HRV against traditional risk factors. I will perform these analyses independently to help apply the biostatistical skills already gained from the MSCR and expand upon them by formal coursework in advanced biostatistics. This is particularly crucial to future training as time-series analyses require familiarity with repeat measure analysis and imputation. Dr. Shah will help supervise me in these analyses, along with support from the Biostatistics, Epidemiology, & Research Design program that provides services to Emory clinical investigators. Dr. Vaccarino will help in the interpretation of this work due to her expertise and prior work in coronary vasoreactivity.12

Power calculations: As above, we expect an initial cohort size of 200 patients, with 160 patients with non-missing data. We expect that 75% of patients will have obstructive CAD, similar to the rate seen in our pilot study. With an α = 0.05, and 1 – β = 0.80, we will be adequately powered to detect an medium effect size (Cohen’s d = 0.46).53

Potential Problems and Solutions: This patient population is likely to have a high proportion of patients on beta-blockers, which has a known effect on heart rate and spectral HRV.54 For patients on beta-blocker therapy we will perform an additional subgroup analysis to prevent confounding. Continuous ECG data are susceptible to artifact, which may lead to erroneous data. Such data can be edited to remove noise and ectopy, and interpolated to fill gaps. Existing software techniques allow for the easy cleaning of raw RR interval data. As our prior work suggests a circadian variability to autonomic dysfunction, continuous time-series analysis is an important component of analysis, but can lead to issues of repeat measures and adjustments for circadian rhythm. We have developed experience with cosinor analysis to overcome this challenge.55,56

Anticipated Results: We expect to find an independent association with autonomic dysfunction, measured by low Dyx, with progressive coronary artery plaque burden. As seen in our prior work, we expect this finding to be most prominent during the morning hours. We expect that the relationship of low Dyx and CAD will be stronger in women and in younger participants (age < 65 years).

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