# 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 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.

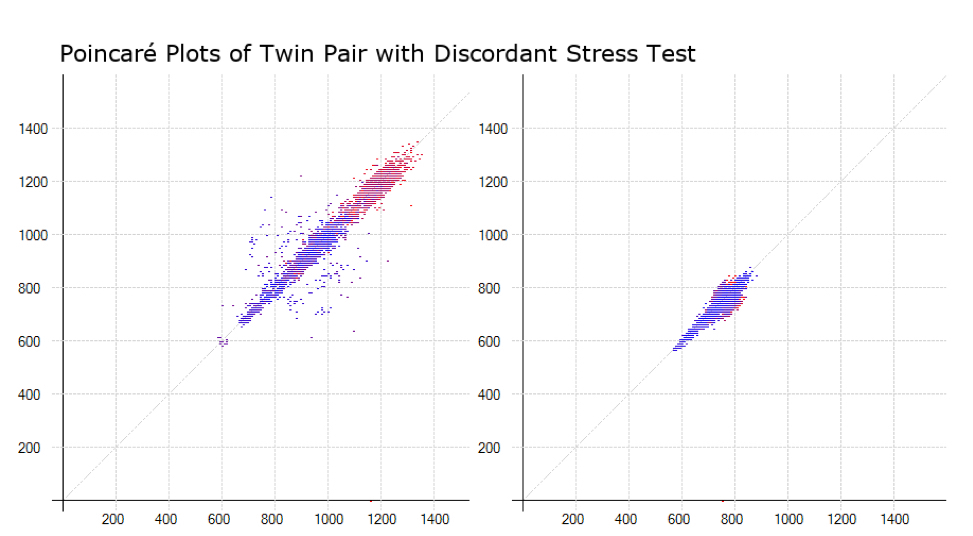


Figure 1. The two Poincaré plots represent ECG data at 7 AM for a twin pair that are discordant for stress test results. Both axes are RR interval lengths in milliseconds. The x-axis coordinate represents the RR interval for an initial beat, while the y-axis coordinate represents the RR interval for 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.

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 Vaccarino lab has pursued the influence of autonomic nervous system (ANS) dysfunction on these pathways as ANS dysfunction occurs in both depression and CAD.10,23,39,40 Understanding the mediating role of ANS dysfunction on the relationship between depression and CAD could eventually lead to potential future therapies that help reduce the risk for cardiovascular mortality in individuals with depression. ANS dysfunction occurs at multiple levels, from central neurological processes to peripheral cardiovascular reflexes, such as the vagal withdrawal in depression and increased sympathetic tone in hypertension. Heart rate variability (HRV) is an accepted measure of the integration of these multiple levels of autonomic outflow to the heart.30,31 Low HRV, a reflection of ANS dysfunction, is measured non-invasively through electrocardiogram (ECG) and is independently associated with depressive symptoms,41 cardiovascular mortality,42 and obstructive CAD.43 We propose to test a novel HRV measure to quantify ANS dysfunction. This novel measure, *Dyx*, derived from time series analysis,33 was found to be a more sensitive predictor of ventricular dysrhythmia and was associated with increased cardiovascular mortality.34,35 In our prior work, compared to traditional HRV, we found that 1) low *Dyx* in the early morning predicted abnormal coronary flow reserve,44 and 2) in preliminary analyses low *Dyx* strongly associated with depressive symptom burden. This makes *Dyx* a strong candidate for assessing ANS dysfunction in our proposal.

## 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.45 *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.46–48 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

Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Unless addressed separately in the Resource Sharing Plan attachment, include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.

Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.

If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.

Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised. If applicable, a full discussion on the use of select agents should appear in the Select Agent Research attachment below.

For new applications, include information on preliminary studies (including data collected by others in the lab), if any. Discuss the applicant's preliminary studies, data, and/or experience pertinent to this application.

### C1. Study Overview

This training grant proposes an ancillary study on an ongoing prospective registry of patients undergoing cardiac catherization, the Emory Cardiovascular Biobank (EmCAB, PI Quyyumi) ﻿which was established to identify novel factors associated with the pathobiological process and treatment of cardiovascular disease.49 The EmCAB 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 EmCAB 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 automatic and will be available from the Biostamp software suite.

### C2. Study Population

The EmCAB 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.49 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%). We will also exclude those with acute coronary syndrome.

### C3. Study Design

To examine patients with depression and stable CAD, we will leverage the Emory Cardiovascular Biobank (Dr. Arshed Quyyumi , PI (advisor)), a multidisciplinary ongoing prospective cohort of individuals undergoing clinically indicated cardiac catherization during which depressive symptoms are assessed using validated metrics.11,49 HRV will be generated for up to 72-hours of raw ECG data on 200 patients (expected: 34% women; 13% with severe depression),11 collected through ambulatory ECG patches (VivaLNK ECG recorder) on the day of catheterization. I will build upon existing skills in ECG analysis and signal processing using the pre-existing HRV toolbox, developed at Emory with the assistance of Dr. Amit Shah (mentor).50 *I hypothesize that ANS dysfunction, as measured by low Dyx, mediates the effect of depression on CAD*.

General Protocol: The enrollment, consent, and detailed phenotyping of the patients has been described in prior studies of the EmCAB.49 ﻿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 sample will be collected daily over the first several months, with an estimated 10-20 patients enrolled per week. 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.51

Heart Rate Variability: This study will add HRV to the data collected by the EmCAB. We will use non-invasive, continuous, ambulatory ECG patches (Biostamp®, MC10 Inc), which have already been acquired through my mentor Dr. Shah. I will assist with the consent and incorporation of ECG data collection into the larger study protocol. The consent will occur in the early morning (7 AM — 9 AM), after which the patch will be applied until their angiogram. 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.50 A materials transfer agreement with the company is already in place with HeartTrends.

Neuropsychological 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).52 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.53 Cognitive impairment will be measured by the Montreal cognitive assessment (MoCA), which is a measure of global cognitive function and is comprised of the sub-domains: memory, visuospatial function, executive function, sustained attention, language, and orientation. The MoCA has a sensitivity of 90% and specificity of 87% for detecting mild cognitive impairment with a score of 26 (out of 30).54

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).55

**C4. Specific Aim #1: Quantify the relationship between depressive symptoms and ANS dysfunction**.We will a) assess depressive symptoms using the Patient Health Questionnaire-9,53 and b) test the association of this score with ANS dysfunction as measured by *Dyx*. *We predict elevated depressive symptoms will associate with low Dyx,* thus generating a robust non-invasive marker for the effect of depression on the ANS.

Rationale: Depression and cognitive impairment are not only common is patients with CAD, but are also prognostic after MI, indepdent of traditional risk factors.15,56–58 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 a preliminary analysis from the Atherosclerotic Risk In Communities (ARIC) study, psychological life stressors such as exhaustion and anger are associated with abnormal HRV. Cognitive impairment also associates with decreases in HRV.59 We will look to elucidate the independent relationship Dyx, a marker of neuropsychiatric disturbance, with depression and cognitive impairment, which has not yet been studied.

Data Collection and Analysis: I will be directly involved with the study coordinators to enroll and consent patients for ambulatory ECG. I will be responsible for working with the BioStamp company to retrieve raw ECG data, and 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). I will communicate with the HeartTrends company to assist with the appropriate and timely generation of the *Dyx* index through Poincaré plot analysis.32,34 I will learn to use the HRV toolbox under the guidance of Dr. Shah to generate hourly frequency and geometric domain indices of HRV for additional HRV assessments.50 Familiarizing myself with the mathematical principles and technical skills underlying signal processing will be critical for my training. The primary exposures will be depressive symptoms (PHQ-9) and cognitive impairment (MoCA score). The exposures will be analyzed for correlation. The primary outcome will be autonomic function, measured by *Dyx* and other HRV indices. Each exposure will be included in individual regressions models for the continuous *Dyx* measure, and logistic regressions for *Dyx* using the clinical cutoff of <2 units.60 Secondary outcomes will adjust for sociodemographic and traditional cardiovascular risk factors. My training through the MSCR will provide me the necessary tools to conduct these analyses, with support from Dr. Alonso and Dr. Shah in evaluation and interpretation of the data.

Potential Problems and Solutions: The PHQ-9 is not validated in the setting of acute stress, for which we will exclude patients diagnosed with acute coronary syndrome. 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 patients with severe cognitive impairment may not be referred for catherization, and thus excluded from the study.

Anticipated Results: We expect to find an independent association of depression and cognitive impairment with autonomic dysfunction, measured by low *Dyx*.

**C5. Specific Aim #2: Examine the effect of obstructive CAD on ANS dysfunction.** We will a) assess the CAD burden with the CASS-50 score,61 an angiographic estimate of plaque burden, and b) test the association of plaque burden with ANS dysfunction, measured by *Dyx*, before, during, and after catherization and/or revascularization. Findings may help clarify the role of ANS dysfunction in obstructive versus microvascular CAD. *We predict low Dyx will associate with obstructive CAD (stenosis > 70%) and plaque burden by CASS-50 in a dose-response relationship,*51 *and Dyx will increase after revascularization.*

Rationale: Abnormal HRV indicates autonomic dysfunction and increases the risk of cardiovascular mortality. *Dyx* has been shown to predict myocardial perfusion defects during 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.

Data Collection and Analysis:I will compare the exposure of HRV to the outcome of coronary artery plaque burden, measured by the Gensini score, 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%).60 Secondary outcomes will evaluate the performance of HRV against traditional risk factors. I will perform these analyses independently to help apply the biostatistics skills strengthened by formal coursework during the MSCR.

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.62 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, which existing software techniques allow for the easy cleaning of raw RR interval data.

Anticipated Results: We expect to find an independent association with autonomic dysfunction in the morning hours, measured by low *Dyx*, with progressive coronary artery plaque burden.

### C6. Specific Aim #3: Study clinical outcomes of ANS dysfunction in patients with depression and CAD.

We will a) follow participants for adverse 1-year fatal and non-fatal outcomes, including all-cause mortality, myocardial infarction, revascularization, and development of CAD, and b) compare the differences in outcomes based on the presence of ANS dysfunction. *We predict depressive symptoms and low HRV together will synergistically be associated with an increased risk of fatal and non-fatal outcomes after 1 year of follow-up.*

Rationale: Abnormal HRV indicates autonomic dysfunction and increases the risk of cardiovascular mortality. *Dyx* has been shown to predict myocardial perfusion defects during 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.

Data Collection and Analysis:I will compare the exposure of HRV to the outcome of coronary artery plaque burden, measured by the Gensini score, 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%).60 Secondary outcomes will evaluate the performance of HRV against traditional risk factors. I will perform these analyses independently to help apply the biostatistics skills strengthened by formal coursework during the MSCR.

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Anticipated Results: We expect to find an independent association with autonomic dysfunction in the morning hours, measured by low *Dyx*, with progressive coronary artery plaque burden.

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