# RESEARCH STRATEGY (six page limit)

## Significance

Explain the importance of the problem or critical barrier to progress that the proposed project addresses.

Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields. Describe how the concepts, methods, technologies, treatments, services, or preventative

### A1. The 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 However, in patients with CAD, the prevalence of depression is up to 20%.3 In comorbid depression and CAD, there is a 3-fold increase in cardiovascular,4 however only in the last several years has depression been recognized as an additional prognostic marker of mortality.5 The rate of increased mortality in CAD with depression has remained unchanged over the past 35 years.4 The treatment of depression through traditional interventions, such as cognitive behavioral therapy and antidepressants, has not shown an improvement in event-free survival.6 Although the American College of Cardiology recommends depression should be routinely screened for in patients with cardiovascular disease,3 there has been no evidence that screening and/or treatment improves overall mortality.7 There is a critical knowledge gap in the understanding of the mechanisms underlying depression and CAD,8 which limit the potential targets for therapy that can actually decrease mortality.

### A2. Understanding the Mechanisms of Depression and Increased Mortality in Coronary Artery Disease

The pathogenesis of increased mortality in CAD and depression is not fully understood.9

Recent literature suggests that increased mortality may be confined to patients with untreated depression,10 but only somatic depressive symptom burden leads to increased mortality.11 In a manuscript under review, we found that somatic depressive symptoms were strongly associated with persistent autonomic dysfunction. Dr. Vaccarino and Dr. Shah have shown that depressive symptoms

The ANS is a common mechanistic pathway in both depression and CAD.12 Current treatment strategies do not specifically target ANS dysfunction in comorbid depression and CAD, however this is a promising area of research as strong biological pathways exist.13 The vagal nerve is known to be protective against ventricular fibrillation,14 and vagal nerve stimulation has been shown to relieve angina pectoris and cardiac arrhythmias.15,16 Vagal nerve stimulation is also effective in treatment-resistant depression.17 The ANS is thus of physiological importance in both diseases, and ANS dysfunction may be a shared target for intervention.

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.8,18–20 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.21,22 Low HRV, a reflection of ANS dysfunction, is measured non-invasively through electrocardiogram (ECG) and is independently associated with depressive symptoms,23 cardiovascular mortality,24 and obstructive CAD.25 We propose to test a novel HRV measure to quantify ANS dysfunction. This novel measure, *Dyx*, derived from time series analysis,26 was found to be a more sensitive predictor of ventricular dysrhythmia and was associated with increased cardiovascular mortality.27,28 In our prior work, compared to traditional HRV, we found that 1) low *Dyx* in the early morning predicted abnormal coronary flow reserve,29 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.

There is a key knowledge gap in how to prevent the cardiovascular complications of depression. An alternative to targeting the depressive symptoms per se is to target the underlying potential pathways that may mediate the increased cardiovascular risk in depression in CAD, such as low coronary flow reserve or mental-stress induced myocardial ischemia.30,31 Depression affects up to 20% of patients with coronary artery disease (CAD) and is associated with a 3-fold increase in cardiovascular mortality.3–5 We seek to gain a better understanding of the mechanisms by which depression leads to increased mortality in CAD as treatment for depression is complex and often not successful. Moreover, there is conflicting and limited evidence that treating depression using counseling or antidepressants reduces the excess risk of cardiovascular mortality.6,10,32

### A3. Autonomic Nervous System Activity along the Neurocardiac Axis

Heart rate variability (HRV) is an inexpensive biomarker derived from ambulatory electrocardiographic monitoring.33 It allows for continuous, non-invasive assessment of autonomic function, which is influenced by neuropsychological factors, such as mental stress, and heart disease.23,34 The neurovisceral integration theory provides the anatomical basis for this relationship. This theory links cognitive and affective networks to autonomic regulation by identifying the differential activation of important brain structures (prefrontal cortex, cingulate cortex, and insula).18,19 Psychological stress, including depression, leads to changes in autonomic function that are historically known to increase to the risk of ventricular ectopy, SCD, and cardiovascular disease.8,13,35–38 Cognitive impairment, particularly as it relates to executive function, also is related to abnormal HRV, and leads to an increased odds of IHD independent of other cardiovascular risk factors.39,40 These interesting findings suggest that neurovisceral dysfunction may contribute greatly to autonomic dysfunction as measured by HRV. Exploring this relationship may provide important insight into why those with dysautonomia have worse psychological, neurological, and cardiovascular outcomes.

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

Advanced ECG analysis conveys information about autonomic function that is an independent marker for cardiovascular mortality.33,41,42 Traditional methods including exercise stress testing have limited sensitivity,43 but HRV analysis has led to novel risk markers for IHD that need further investigation.44,45 Information within traditional HRV indices was thought to be explained by heart rate itself,46 but newer indices capture additional information.47 A novel method for HRV analysis is througha non-linear method named *Dyx*, which uses the multipole method in Poincaré plots where RR intervals are plotted as a function of prior RR intervals (**Figure 1)**.26,27,48 *Dyx* measures overall variability in heart rate, but also indicates how erratic and non-linear the heart rate trends are as well. After MI, low *Dyx* has an independent hazard ratio of 2.4 (CI 1.5 to 3.8) for mortality in a recent study.28 Very few studies however have studied the prospective value of autonomic dysfunction in predicting obstructive CAD as measured by coronary angiography. A single, recent study examined *Dyx* with no known IHD and found that low *Dyx* predicted abnormal MPI with an improved sensitivity and specificity to exercise stress test.44 We demonstrated in a cohort of 276 individuals with no known IHD from the Emory Twin Study, low *Dyx* in morning hours had a 12-fold increase in the odds of abnormal MPI. 49 These findings validate the prior work on *Dyx* but also contextualize autonomic balance within the circadian rhythm.50,51 These important findings have helped to place measures of autonomic dysfunction in a potentially clinically useful role. Given the low costs and risks associated with this measure (requires only ambulatory ECG), there is a pressing need for more translational research in the area. Such technologies may ultimately reduce the need for invasive testing with coronary angiography as well as identify asymptomatic, high-risk individuals.

Our research program will pursue clinical relevance for an HRV-based biomarker, and potentially help to fill an important gap that has prevented HRV from becoming a mainstream clinical test for cardiovascular disease diagnosis.33 This potential is gaining momentum. Based on recent research findings,44 HeartTrends was recently established as a company to offer *Dyx* as a clinical tool to risk-stratify individuals for CAD. Their work is only supported by small, industry-sponsored studies of non-invasive cardiac imaging however, and therefore not currently being utilized in most clinics. Our project will provide an independent evaluation of their metrix, *Dyx*, as a potentially measure of *obstructive CAD* as measured by *coronary angiography*. This additional test of its clinical relevance may help evaluate its clinical potential; if we find that it is predictive, this may have widespread clinical implications when deciding who to send for coronary angiography. *Dyx* is not solely a metric of obstructive CAD risk, however. It may also help measure the complex relationship between the heart and the brain, and explain stress-related microvascular disease dysfunction as well.30 This is important because studies showing low *Dyx* as predictive of abnormal myocardial perfusion imaging (MPI), including our own, are inherently limited: abnormal MPI findings cannot distinguish between the larger epicardial coronary arteries and smaller myocardial resistance vessels.45,49 *Dyx*, as a marker for neurovisceral dysfunction, may also shed light into the mechanism of increased non-cardiac risk. As such, it may have potential in predicting psychiatric outcomes such as future depression,52 as well as future cognitive decline.53

Ischemic heart disease (IHD) accounts for in 1 in every 7 deaths in the United States, with a prevalence of 3% or 7.9 million US adults.54 Over 700,000 new heart attacks occur annually, with annual costs of heart attacks ($12.1 billion). The estimated direct and indirect costs of IHD were $204 billion, and these medical costs are projected to double by the year 2030.54 However up to 20% of MIs are silent and up to 80% of IHD is unrecognized by standard ECG and clinical parameters.55 Although there has been a decline in cardiovascular mortality overall, the rate of out-of-hospital events has not decreased in proportion to the rate of in-hospital events.56 Mental stress plays a role in the complications of IHD, and is an under-recognized and important risk factor. More research on the brain-heart connection may help unlock some of the difficult roadblocks in reducing IHD in the community.57 New integrative and/or holistic strategies to approach IHD and prevent its associated complications may help lead to a downward frameshift in event rates.

## Innovation

Innovation is central to this proposal, which seeks to validate a new, low-cost ECG-based measure (*Dyx*) as an alternative diagnostic test for obstructive CAD. It may also provide a robust measure of autonomic regulation in disturbances of the neurocardiac axis that has additional relevance to psychiatric and neurologic diseases. 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 IHD as connected to the neurocardiac axis may lead to clinical practice changes in disease management as well. For example, it may promote stress management and exercise therapy in management of IHD.58 *Dyx* is relatively new and unexplored compared to other HRV indices. For the first time, we are also taking into close consideration the time of day when measuring HRV. 50,59 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.45,60,61

The technology utilized for this study is also cutting edge and more easily collected in clinical settings than previous methods. We will utilize the BioStamp 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 achive breakthrough in the assessment of Dyx; as opposed to previous studies, we can now evaluate its predictive potential with with coronary angiography findings. Future studies (may be included in K23) may also evaluate the relationship of *Dyx* with secondary clinical outcomes. Additional evaluation of *Dyx* with depression and cognitive function will be the first studies of their kind. It will lead to better a mechanistic understanding of the neurocardiac axis, and future work may help to evaluate non-cardiac outcomes such as depression. Overall, our rigorous, holistic evaluation of *Dyx* will help provide critical assessment of its value in IHD risk prediction and evaluation of neuropsychological pathology.

## 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.62 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.63 It also evaluates additional biomarkers for inflammation, cardiac injury, and genetics, with the goal of predicting CVD outcomes.62 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.62,63 HRV will be generated for up to 72-hours of raw ECG data on 200 patients (expected: 34% women; 13% with severe depression),63 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).64 *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.62 ﻿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.65

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.49 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.64 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).66 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.67 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).68

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).69

**C4. Specific Aim #1: Quantify the relationship between depressive symptoms and ANS dysfunction**.We will a) assess depressive symptoms using the Patient Health Questionnaire-9,67 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.10,39,70,71 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.72 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.27,48 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.64 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.33 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,73 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,*65 *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**.49 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%).33 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.74 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**.49 We are looking to, for the first time, evaluate *Dyx* during morning hours and the relationship with obstructive CAD and overall plaque burden.

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