SPECIFIC AIMS

Depression, a form of chronic mental stress, affects 20% of patients with acute coronary syndrome and leads to a 3-fold increase in cardiovascular mortality,[1–3] yet there remains contrasting evidence on whether interventions for depression can reduce this excess risk.[4–6] These interventions target depressive symptoms and not the potential underlying pathways, including low coronary flow reserve or mental-stress induced myocardial ischemia,[7,8] because the mechanism by which depression leads to increased mortality in coronary artery disease (CAD) is not well understood. Autonomic nervous system (ANS) dysfunction may play an important role in this pathway.[9] ANS dysfunction can occur in both depression, arising from central neurological abnormalities,[10,11] and myocardial ischemia or infarction, arising from disease of the intrinsic cardiac nervous system.[12] ANS dysfunction leads to abnormalities in sinoatrial node function, which results in altered heart rate patterns and subsequently lowered heart rate variability (HRV).[13] Abnormal or low HRV serves as an electrocardiographic (ECG) measurement of ANS dysfunction and is independently associated with depressive symptoms,[14] cardiovascular mortality,[15] and obstructive CAD.[16] There is a critical need to understand how ANS dysfunction may mediate the effect of depression on CAD, which would allow identification of at-risk individuals and provide a target for potential future therapies that can actually reduce the risk for mortality. This has been historically challenging due to limitations in quantifying ANS dysfunction in depression and CAD, and the lack of ECG data during cardiac events and interventions.

To overcome this challenge, we will use a novel HRV measure to quantify ANS dysfunction in depression and CAD using ambulatory ECG patches (VivaLNK ECG recorder) in subjects with chronic stable angina undergoing evaluation in the Emory Cardiovascular Biobank,[17] a multidisciplinary study led by Dr. Arshed Quyyumi (advisor). The Biobank is an active prospective cohort of individuals undergoing clinically indicated cardiac catherization, during which depressive symptoms are also assessed using validated metrics.[18] They enroll approximately 15 participants per week, and the mentoring team has a long history of collaboration with the study. We will test the relationship of depression, CAD, and HRV, with additional stratification by sex due to its known effect on these variables.[18,19] The novel HRV measure, *Dyx*, is a non-linear measure that represents the ratio of the kurtosis along the y-axis and x-axis of the elliptical Poincaré plot of RR intervals, and is associated with increased cardiovascular mortality.[20,21] Compared to traditional HRV, we found that 1) low *Dyx* in the early morning predicted abnormal coronary flow reserve,[22] 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. As a postdoctoral epidemiology fellow and Emory TL1 scholar, I have already enrolled 32 out of a target of 200 patients from the Biobank with long-term ECG recordings. I have been trained in ECG analysis using the pre-existing HRV toolbox, developed at Emory with the assistance of Dr. Amit Shah (mentor).[23] I hypothesize that ANS dysfunction, as measured by non-linear HRV, mediates the effect of depression on CAD, which we will test with the following aims:

1. **Establish the relationship between depression and ANS dysfunction:** We will (A) assess depressive symptoms by validated questionnaires (Patient Health Questionnaire-9, PHQ-9),[24] and (B) test the association of depressive symptoms with ANS dysfunction, measured by *Dyx*, generating a novel and more robust non-invasive marker for the effect of depression on the ANS. *Hypothesis: Elevated depressive symptoms will associate with low Dyx.*
2. **Examine the effect of obstructive CAD on ANS dysfunction:** We will (A) assess the CAD burden with the CASS-50 score, and (B) measure HRV before, during, and after catherization and/or intervention.[25] This may also help clarify the role of ANS dysfunction in obstructive versus microvascular CAD. *Hypothesis: Low Dyx will associate with obstructive CAD (stenosis ≥ 70%) and plaque burden by CASS-50 in a dose-response relationship.*[26]
3. **Determine how much ANS dysfunction mediates the relationship between depression and obstructive CAD:** Preliminary data suggests a strong relationship between ANS dysfunction and both depression and CAD respectively. We will analyze the association between depression and CAD with ANS dysfunction as a potential mediator variable. *Hypothesis: The relationship between depression and CAD will be fully mediated by low Dyx.*

This proposal will help overcome current limitations in assessing the contributions and mechanisms of ANS dysfunction on depression and CAD, and in the future may lead to potential therapies that target ANS dysfunction, such as biofeedback and vagal nerve stimulation. With the support of my mentoring team and additional training in quantitative epidemiology and autonomic physiology, I will be prepared for future career development awards that evaluate more detailed mechanisms, outcomes, and interventions in neurocardiology and translational research.

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