# SPECIFIC AIMS

Depression, a form of chronic mental stress, affects up to 20% of patients with acute coronary syndrome and has been associated with a 3-fold increase in cardiovascular mortality.1–3 The evidence that treating depression can reduce this excess cardiovascular mortality is conflicting and limited,4–6 suggesting a key knowledge gap in the management of depression in cardiovascular disease. Developing interventions that target underlying potential pathways, such as low coronary flow reserve or mental-stress induced myocardial ischemia,7,8 instead of depressive symptoms will require a better understanding of the mechanisms by which depression leads to an increased mortality in coronary artery disease (CAD). Autonomic nervous system (ANS) dysfunction may play an important role in this pathway,9 as it occurs in both depression, from central neurological abnormalities,10,11 and in myocardial ischemia or infarction, from damage to the intrinsic cardiac nervous system.12 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.

To overcome this challenge, we will leverage the Emory Cardiovascular Biobank to enroll patients with chronic stable angina and use a novel heart rate variability (HRV) measure to quantify ANS dysfunction, collected by ambulatory ECG patches (VivaLNK ECG recorder). The Biobank, a multidisciplinary study led by Dr. Arshed Quyyumi (advisor), is an active prospective cohort of individuals undergoing clinically indicated cardiac catherization, during which depressive symptoms are also assessed using validated metrics.17,18 HRV is a measure of sinoatrial node function, which is altered in the setting of ANS dysfunction.13 Abnormal or low HRV, which can be measured non-invasively through electrocardiogram (ECG), is independently associated with depressive symptoms,14 cardiovascular mortality,15 and obstructive CAD.16 Our overall goal is to gain greater insight into the relationship of depression, CAD, and HRV and eventually translate these findings into targeted interventions.

using ambulatory ECG patches (VivaLNK ECG recorder) in subjects with chronic stable angina undergoing evaluation in the Emory Cardiovascular Biobank, 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:

**Aim 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 robust non-invasive marker for the effect of depression on the ANS. *Hypothesis: Elevated depressive symptoms will associate with low Dyx.*

**Aim 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 Findings will help clarify the role of ANS dysfunction in obstructive versus microvascular CAD. *Hypothesis: Low Dyx will be associated with obstructive CAD (stenosis > 70%) and plaque burden by CASS-50 in a dose-response relationship.*26

**Aim 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 partially mediated by low Dyx.*

This proposal will address a critical need in understanding the contributions and mechanisms of ANS dysfunction on depression and CAD, and may lead to potential therapies targeting ANS dysfunction, such as biofeedback and vagal nerve stimulation. With the support of my multidisciplinary mentoring team, and the training in quantitative epidemiology and autonomic physiology that results from this work, I will be well prepared to apply for a career development award evaluating more detailed mechanisms, outcomes, and interventions in neurocardiology and translational research.

# REFERENCES

1. Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW. Screening and Management of Depression in Patients With Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73(14):1827-1845. doi:10.1016/j.jacc.2019.01.041

2. Lichtman JH, Froelicher ES, Blumenthal JA, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: Systematic review and recommendations: A scientific statement from the american heart association. *Circulation*. 2014;129(12):1350-1369. doi:10.1161/CIR.0000000000000019

3. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011;33(3):203-216. doi:10.1016/j.genhosppsych.2011.02.007

4. Smolderen KG, Buchanan DM, Gosch K, et al. Depression Treatment and 1-Year Mortality after Acute Myocardial Infarction: Insights from the TRIUMPH Registry (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients’ Health Status). *Circulation*. 2017;135(18):1681-1689. doi:10.1161/CIRCULATIONAHA.116.025140

5. Van Melle JP, De Jonge P, Honig A, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry*. 2007;190(JUNE):460-466. doi:10.1192/bjp.bp.106.028647

6. Berkman LF, Blumenthal J, Burg M, et al. Effects of Treating Depression and Low Perceived Social Support on Clinical Events after Myocardial Infarction: The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *J Am Med Assoc*. 2003;289(23):3106-3116. doi:10.1001/jama.289.23.3106

7. Vaccarino V, Votaw J, Faber T, et al. Major depression and coronary flow reserve detected by positron emission tomography. *Arch Intern Med*. 2009;169(18):1668-1676. doi:10.1001/archinternmed.2009.330

8. Wei J, Pimple P, Shah AJ, et al. Depressive symptoms are associated with mental stress-induced myocardial ischemia after acute myocardial infarction. Hayley S, ed. *PLoS One*. 2014;9(7):e102986. doi:10.1371/journal.pone.0102986

9. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol*. 2017;14(3):145-155. doi:10.1038/nrcardio.2016.181

10. Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord*. 2000;61(3):201-216. doi:10.1016/S0165-0327(00)00338-4

11. Richard Jennings J, Allen B, Gianaros PJ, Thayer JF, Manuck SB. Focusing neurovisceral integration: Cognition, heart rate variability, and cerebral blood flow. *Psychophysiology*. 2015;52(2):214-224. doi:10.1111/psyp.12319

12. Armour JA. Myocardial ischaemia and the cardiac nervous system. *Eur Heart J*. 1999;16(12):1751-1752.

13. Task Force of the ESC and NAS. Heart Rate Variability. *Eur Heart J*. 1996;17(5):354-381. doi:10.1161/01.CIR.93.5.1043

14. Carney RM, Freedland KE. Depression and heart rate variability in patients with coronary heart disease. *Cleve Clin J Med*. 2009;76(SUPPL.2). doi:10.3949/ccjm.76.s2.03

15. Carney RM, Howells WB, Blumenthal JA, et al. Heart rate turbulence, depression, and survival after acute myocardial infarction. *Psychosom Med*. 2007;69(1):4-9. doi:10.1097/01.psy.0000249733.33811.00

16. Kotecha D, New G, Flather MD, Eccleston D, Pepper J, Krum H. Five-minute heart rate variability can predict obstructive angiographic coronary disease. *Heart*. 2012;98(5):395-401. doi:10.1136/heartjnl-2011-300033

17. Ko YA, Hayek S, Sandesara P, Samman Tahhan A, Quyyumi A. Cohort profile: The Emory Cardiovascular Biobank (EmCAB). *BMJ Open*. 2017;7(12):e018753. doi:10.1136/bmjopen-2017-018753

18. Shah AJ, Ghasemzadeh N, Zaragoza-Macias E, et al. Sex and age differences in the association of depression with obstructive coronary artery disease and adverse cardiovascular events. *J Am Heart Assoc*. 2014;3(3):e000741. doi:10.1161/JAHA.113.000741

19. Sacha J, Barabach S, Statkiewicz-Barabach G, et al. Gender differences in the interaction between heart rate and its variability - How to use it to improve the prognostic power of heart rate variability. *Int J Cardiol*. 2014;171(2):42-45. doi:10.1016/j.ijcard.2013.11.116

20. Olesen RM, Bloch Thomsen PE, Saermark K, et al. Statistical analysis of the DIAMOND MI study by the multipole method. *Physiol Meas*. 2005;26(5):591-598. doi:10.1088/0967-3334/26/5/002

21. Jørgensen RM, Abildstrøm SZ, Levitan J, et al. Heart Rate Variability Density Analysis (Dyx) and Prediction of Long-Term Mortality after Acute Myocardial Infarction. *Ann Noninvasive Electrocardiol*. 2016;21(1):60-68. doi:10.1111/anec.12297

22. Shah A, Lampert R, Goldberg J, Bremner JD, Vaccarino V, Shah A. Abstract 15216: Circadian Autonomic Inflexibility: A Marker of Ischemic Heart Disease. *Circulation*. 2018;138(Suppl\_1):A15216-A15216. doi:10.1161/circ.138.suppl\_1.15216

23. Vest AN, Da Poian G, Li Q, et al. An open source benchmarked toolbox for cardiovascular waveform and interval analysis. *Physiol Meas*. 2018;39(10):105004. doi:10.1088/1361-6579/aae021

24. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.

25. Ringqvist I, Fisher LD, Mock M, et al. Prognostic value of angiographic indices of coronary artery disease from the Coronary Artery Surgery Study (CASS). *J Clin Invest*. 1983;71(6):1854-1866. doi:10.1172/JCI110941

26. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol*. 1983;51(3):606. doi:10.1016/S0002-9149(83)80105-2