SPECIFIC AIMS

Depression affects up to 20% of patients with coronary artery disease (CAD) and has been associated with a 3-fold increase in cardiovascular mortality.[1–3] The evidence that treating depression with counseling or antidepressants 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. Instead of treating depressive symptoms, developing interventions that target underlying potential pathways, such as low coronary flow reserve or mental-stress induced myocardial ischemia,[7,8] will require a better understanding of the mechanisms by which depression leads to an increased mortality in CAD. Autonomic nervous system (ANS) dysfunction may play an important role in these pathways,[9] as it occurs in both depression and CAD.[10–12] 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 examine patients with stable CAD using a novel heart rate variability (HRV) measure to quantify ANS dysfunction. The Biobank, a multidisciplinary study led by Dr. Arshed Quyyumi (advisor), is an ongoing prospective cohort of individuals undergoing clinically indicated cardiac catherization, during which depressive symptoms are also assessed using validated metrics.[13,14] HRV measures the integration of multiple levels of autonomic outflow to the heart.[15] This integration incorporates both central neurological processes and peripheral reflexes, such as the vagal withdrawal in depression and increased sympathetic tone in hypertension. Low HRV, which can be measured non-invasively through electrocardiogram (ECG), is independently associated with depressive symptoms,[16] cardiovascular mortality,[17] and obstructive CAD.[18] Our overall goal is to gain greater insight into the relationship of depression, CAD, and HRV, and eventually translate these findings into targeted interventions. HRV will be generated from up to 72-hours of raw ECG data on 200 patients, collected by ambulatory ECG patches (VivaLNK ECG recorder) on day of catheterization. We will use adjusted linear regression models for analysis with special consideration given to sex, which has a known effect on depression, CAD, and HRV,[14,19] and the circadian rhythm of the heart.[20] The novel HRV measure, *Dyx*, is a non-linear measure of the complexity and unpredictability of heart rate and is associated with increased cardiovascular mortality.[21,22] In prior work, compared to traditional HRV, we found that 1) low *Dyx* in the early morning predicted abnormal coronary flow reserve,[23] 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. I will build upon existing skills in ECG analysis signal processing using the pre-existing HRV toolbox, developed at Emory with the assistance of Dr. Amit Shah (mentor).[24] *I hypothesize that ANS dysfunction, as measured by non-linear HRV, mediates the effect of depression on CAD*.

Aim 1. Establish the relationship between depressive symptoms and ANS dysfunction. We will a) assess depressive symptoms with the Patient Health Questionnaire-9,[25] and b) test the association of depressive symptoms with ANS dysfunction, measured by *Dyx*. This may generate a novel and robust non-invasive marker for the effect of depression on the ANS. *Hypothesis: Elevated depressive symptoms will associate with low HRV.*

Aim 2. Examine the effect of obstructive CAD on ANS dysfunction. We will a) assess the CAD burden with the CASS-50 score, an angiographic estimate of plaque burden, and b) measure HRV before, during, and after catherization and/or revascularization.[26] Findings will help clarify the role of ANS dysfunction in obstructive versus microvascular CAD. *Hypothesis: Low HRV will be associated with obstructive CAD (stenosis ≥ 70%) and plaque burden by CASS-50 in a dose-response relationship,[27] and HRV will improve after revascularization.*

Aim 3. Study clinical outcomes of ANS dysfunction in 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. *Hypothesis: Depressive symptoms and low HRV together will be associated with an increased risk of fatal and non-fatal outcomes after 1 year of follow-up.*

By elucidating the role of ANS dysfunction in the link between depression and CAD, we can better assess the potential benefit of interventions that target the ANS, such as biofeedback or vagal nerve stimulation. The F32 will allow me to work with experts in mental health and cardiovascular pathophysiology (Viola Vaccarino, Amit Shah) and cardiovascular epidemiology (Alvaro Alonso). With their support and additional training in computational methods, quantitative epidemiology, and autonomic physiology from this work, I will be well

prepared to apply for a career development award to evaluate 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. 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
14. 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
15. 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
16. 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
17. 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
18. 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
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. Guo YF, Stein PK. Circadian rhythm in the cardiovascular system: Chronocardiology. *Am Heart J*.

2003;145(5):779-786. doi:10.1016/S0002-8703(02)94797-6
21. 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
22. 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
23. 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
24. 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
25. 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.
26. 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
27. 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