SPECIFIC AIMS

Hook | Known Information | Gap in Knowledge | Critical Need

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 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.

Long-term Goal | Proposal Objective | Rationale | Hypothesis

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. All analyses will be stratified by sex, due to the important effect of sex on HRV, depression, and CAD.[18,19] The novel non-linear HRV measure, *Dyx*, represents the ratio of the kurtosis along the y-axis and x-axis of the elliptical Poincaré plot of RR intervals.[20] Compared to traditional HRV, we found that 1) low *Dyx* in the early morning predicted abnormal coronary flow reserve,[21] 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 proposed study. 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 also been trained in ECG analysis using the pre-existing HRV toolbox, developed at Emory with the assistance of Dr. Amit Shah (mentor).[22] 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 Title | Experimental Strategy | Outcome or Impact

1. Establish the relationship between depression and ANS dysfunction: We will (A) assess depressive symptoms by validated questionnaires (Patient Health Questionnaire-9, PHQ-9),[23] and (B) measure the association of depressive symptoms with ANS dysfunction, measured by *Dyx*, generating a novel and more robust non-invasive marker of the effect of depression on the ANS. *Hypothesis: Elevated depressive symptoms will associate with low Dyx.*
2. Examine the effect of obstructive CAD with 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,[24] which will clarify the role of obstructive versus microvascular CAD in ANS dysfunction. *Hypothesis: Low Dyx will associate with obstructive CAD (stenosis ≥ 70%) and plaque burden by CASS-50 in a dose-response relationship.*[25]
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 mediated by low Dyx.*

Innovation | Expected Outcomes | Impact/Pay-off

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/or 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. 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
22. 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
23. 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.
24. 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
25. 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
26. Leor J, Poole WK, Kloner RA. Sudden Cardiac Death Triggered by an Earthquake. *N Engl J Med*. 1996;334(7):413-419. doi:10.1056/NEJM199602153340701
27. Wei J, Rooks C, Ramadan R, et al. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. In: *American Journal of Cardiology*. Vol 114. ; 2014:187-192. doi:10.1016/j.amjcard.2014.04.022
28. Jain D. Mental stress, a powerful provocateur of myocardial ischemia: Diagnostic, prognostic, and therapeutic implications. *J Nucl Cardiol*. 2008;15(4):491-493. doi:10.1016/j.nuclcard.2008.05.003
29. Strike PC, Steptoe A. Systematic review of mental stress-induced myocardial ischaemia. *Eur Heart J*. 2003;24(8):690-703. doi:10.1016/S0195-668X(02)00615-2
30. Hammadah M, Kim JH, Al Mheid I, et al. Coronary and peripheral vasomotor responses to mental stress. *J Am Heart Assoc*. 2018;7(10). doi:10.1161/JAHA.118.008532
31. Ramadan R, Sheps D, Esteves F, et al. Myocardial ischemia during mental stress: Role of coronary artery disease burden and vasomotion. *J Am Heart Assoc*. 2013;2(5). doi:10.1161/JAHA.113.000321
32. Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Association of depression witk reduced heart rate variability in coronary artery disease. *Am J Cardiol*. 1995;76(8):562-564. doi:10.1016/S0002-9149(99)80155-6
33. Carney RM, Rich MW, TeVelde A, Saini J, Clark K, Freedland KE. *The Relationship between Heart Rate, Heart Rate Variability and Depression in Patients with Coronary Artery Disease*. Vol 32.; 1988. doi:10.1016/0022-3999(88)90050-5