SPECIFIC AIMS

There is a key knowledge gap in the understanding of the mechanisms underlying depression and coronary artery disease (CAD).[1] This is a major public health issue, considering that depression is the leading cause of disability in the world,[2] and CAD is the leading cause of death.[3] They are also comorbid and likely share common mechanisms: depression affects up to 20% of patients with coronary artery disease (CAD) and is associated with a 3-fold increase in cardiovascular mortality.[4–6] Despite these associations, treatments for depression in CAD patients have only modest effects in reducing depressive symptoms, and furthermore have no impact on CAD outcomes.[7,8] *Therefore, more research is needed to develop more effective interventions that address shared mechanisms*. A common mechanistic pathway for depression and CAD is dysfunction of the autonomic nervous system (ANS). Although current treatment strategies do not specifically target the ANS, research into such therapies may be promising, given the strong biological relationships that exist.[9,10] Vagal nerve stimulation, for example, may be effective in treatment-resistant depression,[11] angina pectoris,[12] and cardiac arrhythmias.[13] We seek to gain a better understanding of relationship of ANS biomarkers that can help elucidate the heart-brain relationship and uncover effective therapies for both.

We have recently investigated a novel electrocardiographic (ECG) biomarker of ANS dysfunction, *Dyx*, that was predictive of abnormal myocardial perfusion and coronary flow reserve,[14] as well as depressive symptoms. Encouraged by these findings, we seek to further explore its potential as a means of investigating dysfunction in both central neurological processes (depression) as well as peripheral cardiovascular reflexes as they relate to obstructive CAD. Both mechanisms can influence the adaptability/flexibility of the ANS, which can be measured by heart rate variability (HRV).[15,16] We have found that *Dyx* is a particularly promising HRV metric, and measured in a low cost/burden manner with ambulatory ECG. *Dyx* is derived from an algorithm of the heart rate time series that measures the unpredictability and variability of the heart rhythm.[17] Other studies have also found low *Dyx* to predict ventricular dysrhythmia and cardiovascular mortality;[18,19] in addition, individuals with chest pain who had low *Dyx* values were found to have an odds ratio of 8 for having positive stress test results.[20,21] Overall, *Dyx* may serve as an important clinical biomarker, but more studies are needed before it can be translated into clinical practice.

To best study these ANS pathways, we would test HRV metrics in a target a population that has both depression and CAD, either disease, or neither. To do so, we will leverage the Emory Cardiovascular Biobank (Dr. Arshed Quyyumi, PI (advisor),[22,23] a prospective, well-characterized cohort of high-risk symptomatic patients referred for angiography. We will examine depressive symptoms (via Patient Health Questionnaire-9 or PHQ-9)[24] and HRV using a newly developed ECG patch in 200 patients prior to catheterization,[25] and examine the shared ANS mechanism between depression and CAD. Our preliminary analysis suggests a strong relationship with abnormal HRV and both CAD and depression. Furthermore, the autonomic pathways that underlie depression and CAD are heavily influenced by age and sex. My mentors, Drs. Shah and Vaccarino, have found that depressive symptoms and CAD are most strongly associated in women less than 60 years of age;[22] in addition, young women are twice as likely to have depression and myocardial ischemia with mental stress.[26] HRV is strongly affected by both age and sex,[27] and in preliminary work we found that abnormal HRV was most strongly associated with depressive symptoms in younger women. By studying how *Dyx* and its relationships with depression and CAD may differ by age and sex, we can better understand mechanisms that may be potentially specific to a high-risk group.[28] Our aims are:

Aim 1. Quantify the relationship between depressive symptoms and ANS dysfunction. *We hypothesize A) elevated PHQ-9 scores will associate with low Dyx, and B) that this association will be stronger in women and in younger participants (age ≤ 65 years) than men and older participants of age > 65 years.*

Aim 2. Examine the relationship of obstructive CAD with ANS dysfunction and its potential dose-response relationship. *We hypothesize that A) low Dyx will associate with obstructive CAD (stenosis ≥ 70%), B) that lower Dyx will associate with a greater number of obstructed vessels in a dose-response manner,[29] and C) that the association with Dyx and CAD will be stronger in women and in younger participants (age ≤ 65 years) than men and older participants of age > 65 years.*

This project will allow me to expand on my TL1 award to work with experts in mental health and cardiovascular pathophysiology (Drs. Viola Vaccarino, Amit Shah) and cardiovascular epidemiology (Dr. Alvaro Alonso), and prepare me for an early career development award that also includes examination of long-term cardiovascular outcomes. This multidisciplinary, collaborative team has shown evidence of effective collaborations as well.[1,30–32] Collectively, our work can help lay the groundwork for future clinical trials on ANS therapies such as vagal nerve stimulation, and also help bridge the gap in gender disparities in both depression and CAD.[33]

REFERENCES

1. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol*. 2017;14(3):145-155. doi:10.1038/nrcardio.2016.181
2. Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. *JAMA*. 2017;317(15):1517. doi:10.1001/jama.2017.3826
3. McAloon CJ, Boylan LM, Hamborg T, et al. The changing face of cardiovascular disease 2000–2012: An analysis of the world health organisation global health estimates data. *Int J Cardiol*. 2016;224:256-264. doi:10.1016/j.ijcard.2016.09.026
4. 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
5. 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
6. 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
7. 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
8. Kronish IM, Moise N, Cheung YK, et al. Effect of Depression Screening after Acute Coronary Syndromes on Quality of Life: The CODIACS-QoL Randomized Clinical Trial. *JAMA Intern Med*. 2019. doi:10.1001/jamainternmed.2019.4518
9. Carney RM, Blumenthal JA, Freedland KE, et al. *Low Heart Rate Variability and the Effect of Depression on Post-Myocardial Infarction Mortality*. Vol 165.; 2005. doi:10.1001/archinte.165.13.1486
10. Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev*. 2017;74:277-286. doi:10.1016/j.neubiorev.2016.07.003
11. Carreno FR, Frazer A. Vagal Nerve Stimulation for Treatment-Resistant Depression. *Neurotherapeutics*. 2017;14(3):716-727. doi:10.1007/s13311-017-0537-8
12. Zamotrinsky A V., Kondratiev B, De Jong JW. Vagal neurostimulation in patients with coronary artery disease. *Auton Neurosci Basic Clin*. 2001;88(1-2):109-116. doi:10.1016/S1566-0702(01)00227-2
13. Zhang Y, Mazgalev TN. Arrhythmias and vagus nerve stimulation. *Heart Fail Rev*. 2011;16(2):147-161. doi:10.1007/s10741-010-9178-2
14. 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
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. Saul J. Beat-To-Beat Variations of Heart Rate Reflect Modulation of Cardiac Autonomic Outflow. *Physiology*. 1990;5(1):32-37. doi:10.1152/physiologyonline.1990.5.1.32
17. Lewkowicz M, Levitan J, Puzanov N, Shnerb N, Saermark K. Description of complex time series by multipoles. *Phys A Stat Mech its Appl*. 2002;311(1-2):260-274. doi:10.1016/S0378-4371(02)00831-2
18. 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
19. 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
20. Goldkorn R, Naimushin A, Shlomo N, et al. Comparison of the usefulness of heart rate variability versus exercise stress testing for the detection of myocardial ischemia in patients without known coronary artery disease. *Am J Cardiol*. 2015;115(11):1518-1522. doi:10.1016/j.amjcard.2015.02.054
21. Oieru D, Moalem I, Rozen E, et al. A novel heart rate variability algorithm for the detection of myocardial ischemia: pilot data from a prospective clinical trial. *Isr Med Assoc J*. 2015;17(3):161-165.

http://www.ncbi.nlm.nih.gov/pubmed/25946767.
22. 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
23. 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
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. http://www.ncbi.nlm.nih.gov/pubmed/11556941. Accessed March 3, 2019.
25. 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
26. Vaccarino V, Wilmot K, Mheid I Al, et al. Sex differences in mental stress-induced myocardial ischemia in patients with coronary heart disease. *J Am Heart Assoc*. 2016;5(9). doi:10.1161/JAHA.116.003630
27. 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
28. Vaccarino V, Sullivan S, Hammadah M, et al. Mental stress-induced-myocardial ischemia in young patients with recent myocardial infarction: Sex differences and mechanisms. *Circulation*. 2018;137(8):794-805. doi:10.1161/CIRCULATIONAHA.117.030849
29. 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
30. 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
31. 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
32. Armour JA. Myocardial ischaemia and the cardiac nervous system. *Eur Heart J*. 1999;16(12):1751-1752. https://academic.oup.com/cardiovascres/article-abstract/41/1/41/317013. Accessed September 27, 2018.
33. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. *J Inflamm Res*. 2018;11:203-213. doi:10.2147/JIR.S163248