Depression, HRV, and CAD Pilot Study

Southeast Regional CTSA Conference

Anish Shah, MD[1] Amit Shah, MD/MSCR[2] Alvaro Alonso, MD/PhD[3]

February 28, 2020

[1]Department of Medicine, School of Medicine, Emory University

[2]Divison of Cardiology, Department of Medicine, Emory University

[3]Department of Epidemiology, Rollins School of Public Health, Emory University

Introduction

Background

- Depression is the leading cause of disability in the world [Friedrich, 2017]
- CAD remains leading cause of death [McAloon et al., 2016]
- Up to 20% of patients with CAD have depression, and cardiovascular mortality is 3 times higher in patients with comorbid CAD and depression. [Meijer et al., 2011, Lichtman et al., 2014, Jha et al., 2019]
- No current interventions, such as treating depression, impact mortality or CAD outcomes [Kronish et al., 2019]

The autonomic nervous system connects the brain and the heart and is a common mechanistic pathway in both depression and CAD. [Taggart et al., 2011, Carney and Freedland, 2017] [1]

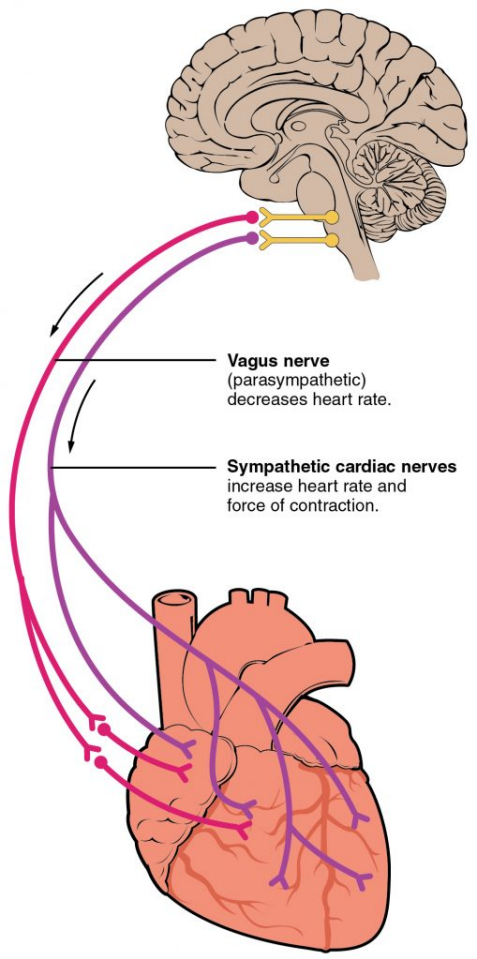


Figure 1: Representation of the brain-heart connection

[1] Figure by OpenStax College

Heart Rate Variability (HRV)

Heart rate variability can represent the current state of the ANS.

Heart Rate Fluctuations

- Fluctuations in the HR are mediated by sympathetic (SNS) and parasympathetic (PNS) inputs to the sinoatrial node
- Rapid fluctuations in HR reflect vagal/PNS control
- Slower fluctuations in HR reflect SNS and PNS integartion, along with other influences

HRV

- External influences such as activity, mental stress, etc
- Internal period rhythms also exist: RSA, baroreceptor reflexes, circadian rhythm, RAAS/neuroendocrine secretions, etc

There are multiple methods of describing HRV: geometric, frequency, and non-linear.[2]

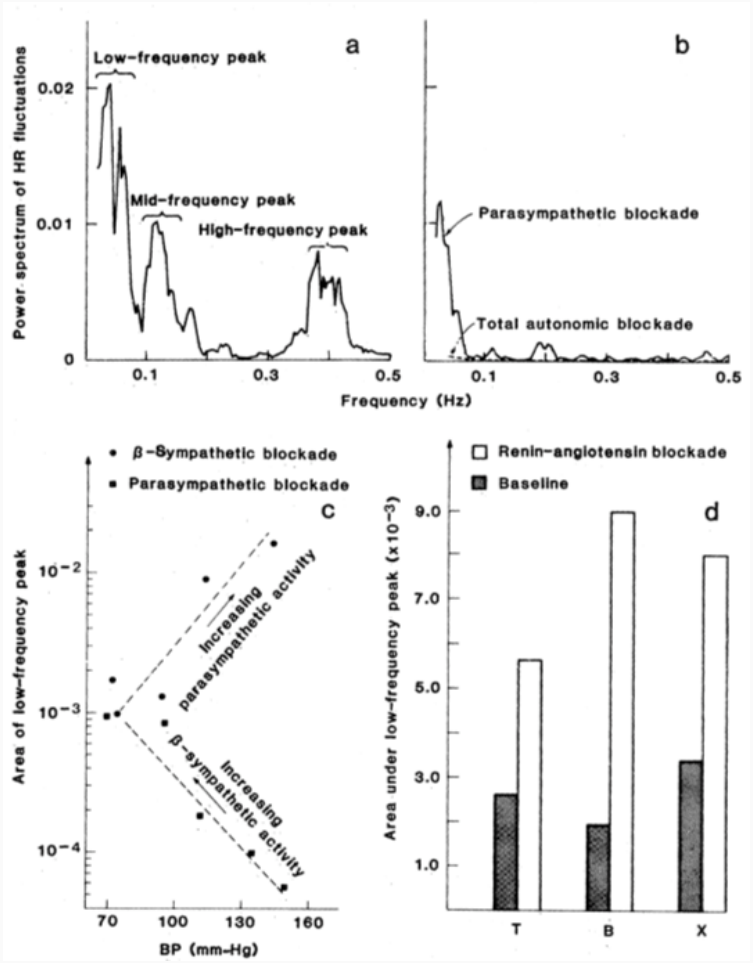


Figure 2: Power spectral density measurements of HRV in experimental settings

[2] Akselrod S. et al. [1981]

We are studying the novel non-linear HRV metric, **Dyx**, in both CAD and depression. **Dyx** is generated from the Poincare plot using the multipole method, calculated from the ratio of the kurtoses of the y-axis and x-axis.[3]

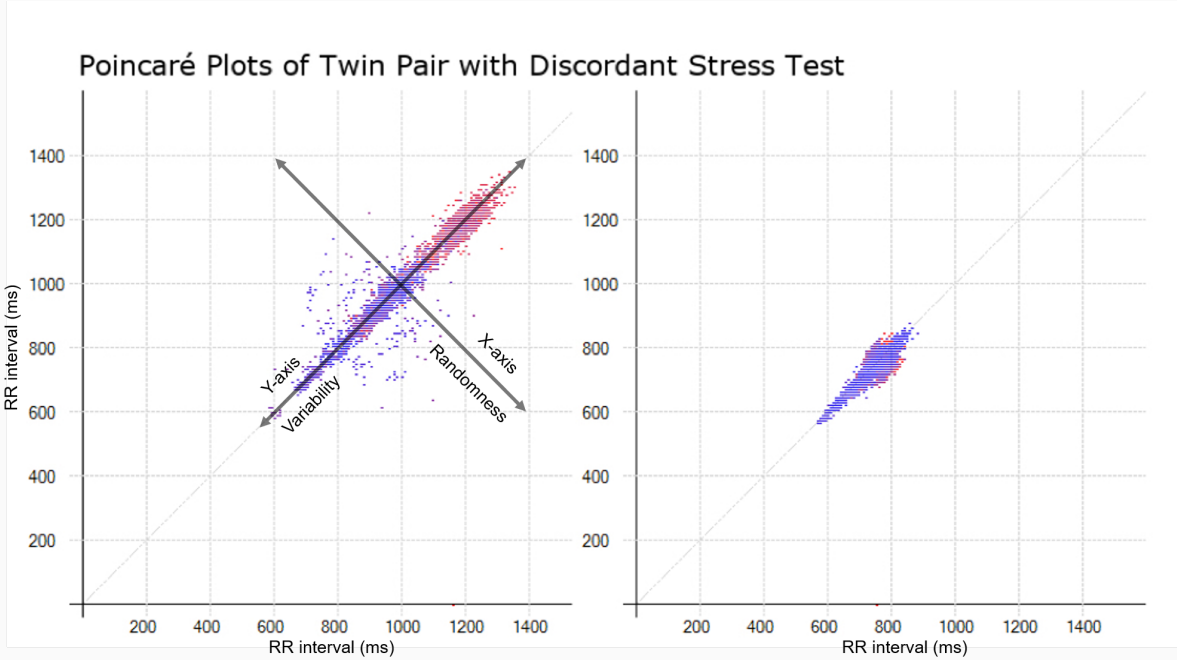


Figure 3: Poincare plot of normal MPI (left) and abnormal MPI (right)

[3] Lewkowicz et al. [2002]; Shah et al. [2020]

We have shown using the non-linear HRV metric, Dyx, is a powerful predictor of CAD,[4] and can also be a useful marker for depression.

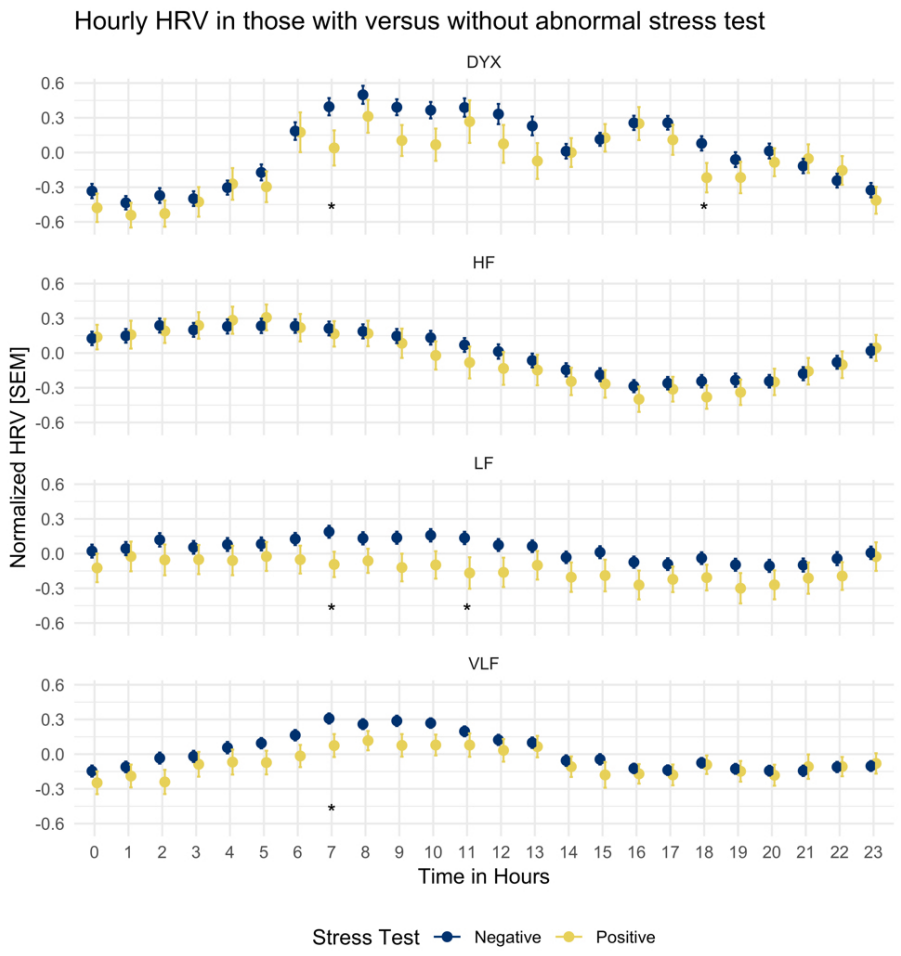


Figure 4: Differences in diurnal HRV with abnormal MPI

[4] Shah et al. [2020]

Study Aims

This is a pilot study examining the relationship between depression and CAD using HRV metrics

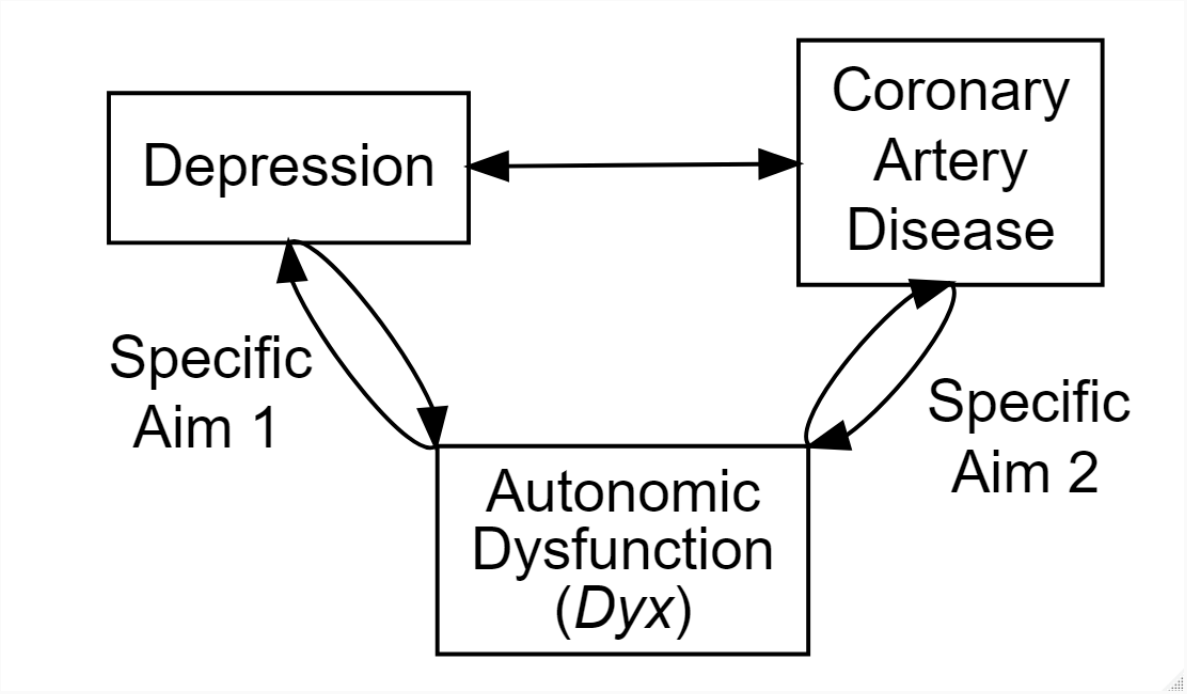


Figure 5: Overview of relationship to ANS dysfunction

Hypothesis

1. We hypothesize that elevated PHQ-9 scores will associate with abnormal HRV
2. We hypothesize that abnormal HRV will associate with obstructive CAD (stenosis > 70%), and that abnormal HRV will associate with a greater number of obstructed vessels in a dose-response manner

Methods

Study overview

- Using the Emory Cardiovascular Biobank, we have an ongoing recruitment of a prospective cohort undergoing cardiac catherization [Ko et al., 2017]
- Patients included have non-STEMI presentations, and preferentially those with no known CAD prior
- Clinical history and biomarkers are generated (including blood samples)
- Psychological questionnaires are performed, including depression by PHQ9
- ECG data is collected on all patients

Depression scoring

- Each patient is given a questionnaire, the PHQ9
- The scores are validated and suggest severity/category of depression
- Scores >= 10 are considered moderate to severe depression, and accepted cut-off

Cardiac catherization

- Every patient presents for cardiac catherization to be enrolled
- Are either inpatient or outpatient
- Etiology: pre-op, heart transplant, UA, NSTEMI, STEMI, positive stress test
- Scored by angiographic severity indices - CASS and Gensini scores [Gensini, 1983]

ECG and HRV collection

- ECG data is collected using the VivaLNK patch (6-24 hours of data per patient)
- ECG was started the AM of LHC, and continued for several hours after event
- HRV was generated through signal processing in Matlab (PhysioNet Cardiovascular Signal Toolbox)
- HRV was blocked into averaged 1-hour segments for analysis
- **Dyx** was also generated, which summarizes a Poincare plot by the ratio of the kurtoses of the y-axis and x-axis

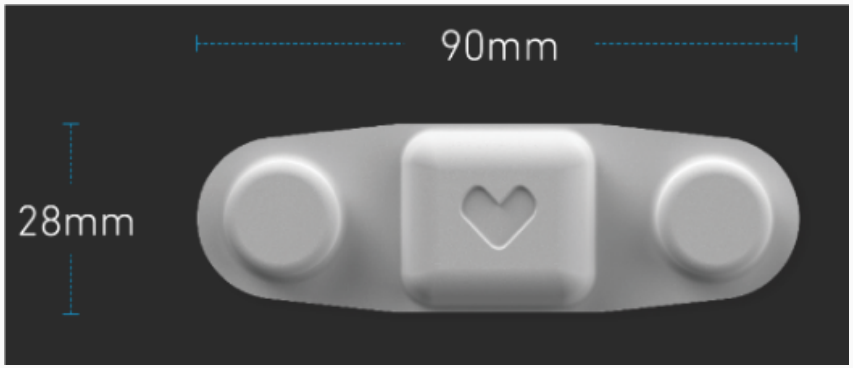


Figure 6: VivaLNK ECG Patch

Statistical analysis

- For this pilot study, the first hour of HRV was used (to control for procedural sedation, the effects of catherization, etc)
- Linear/logistic regression models were used to predict depression by HRV
- Linear/logistic regression models were used to predict CAD plaque burden by HRV

Results

Study Population

Table 1: Population

	[ALL] N=31	N
age	62.4 (13.2)	30
Gender: Male	28 (93.3%)	30
race:		30
African American Black	5 (16.7%)	
Asian	2 (6.67%)	
Caucasian White	23 (76.7%)	
Body Mass Index	30.4 (6.96)	30
setting:		31
Inpatient	11 (35.5%)	
Outpatient	20 (64.5%)	
PHQ > 9:		28
0	21 (75.0%)	
1	7 (25.0%)	
CASS-70 >= 1:		27
0	10 (37.0%)	
1	17 (63.0%)	

Quality of HRV data

- Arrhythmia, artifact were excluded from analysis
- Approximately 25% of the HRV data was considered unusable and discarded

Table 2: HRV quality

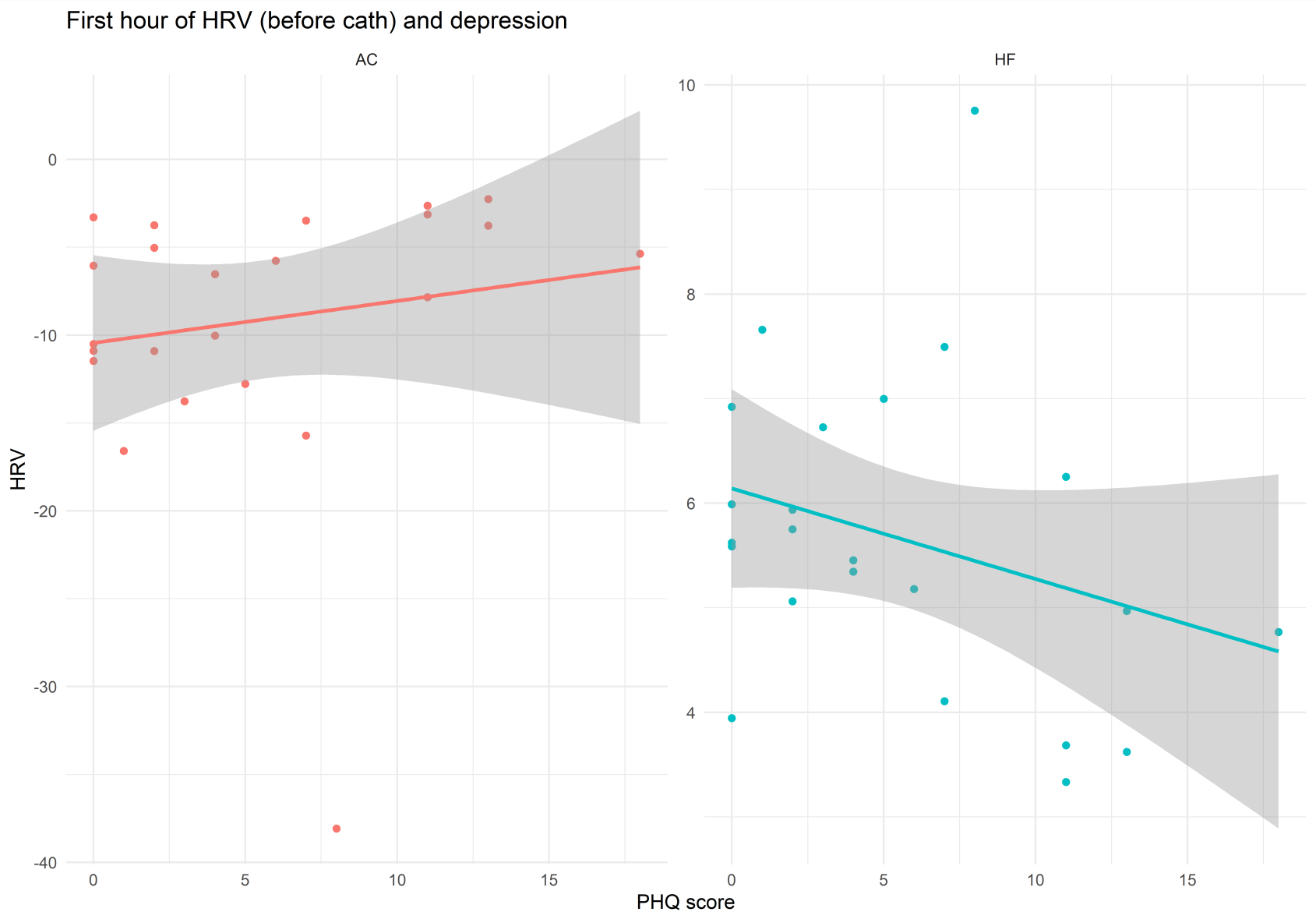
	[ALL] N=28	N
Duration	12.9 (9.35)	28
PercentNotAnalyzed	26.8 (31.2)	28
PercentLowQualityWind	26.8 (31.2)	28

HRV by Depressive Sx Burden Status

Table 3: HRV by Depressive Sx Burden

	PHQ <= 9 N=17	PHQ > 9 N=6	p.overall
Mean HF (SD)	6.09 (1.41)	4.44 (1.11)	0.014
Mean LF (SD)	6.13 (1.24)	4.47 (1.49)	0.041
Mean VLF (SD)	6.63 (0.99)	5.47 (1.35)	0.093
Mean SDNN (SD)	55.3 (33.0)	27.0 (12.9)	0.008
Mean RMSSD (SD)	51.2 (46.9)	21.7 (12.4)	0.027
Mean PNN50 (SD)	15.2 (22.0)	3.12 (4.44)	0.045
Mean AC (SD)	-10.86 (8.20)	-4.17 (2.11)	0.006
Mean DC (SD)	9.34 (5.35)	4.74 (2.16)	0.008
Mean SampEn (SD)	1.56 (0.35)	1.39 (0.34)	0.323
Mean ApEn (SD)	0.91 (0.11)	1.03 (0.15)	0.109
Mean DYX (SD)	2.55 (0.75)	2.16 (0.83)	0.344

Visualizing impact of HRV on depression score



Depression ~ HRV Regression Models

Table 4: First hour of HRV and depression

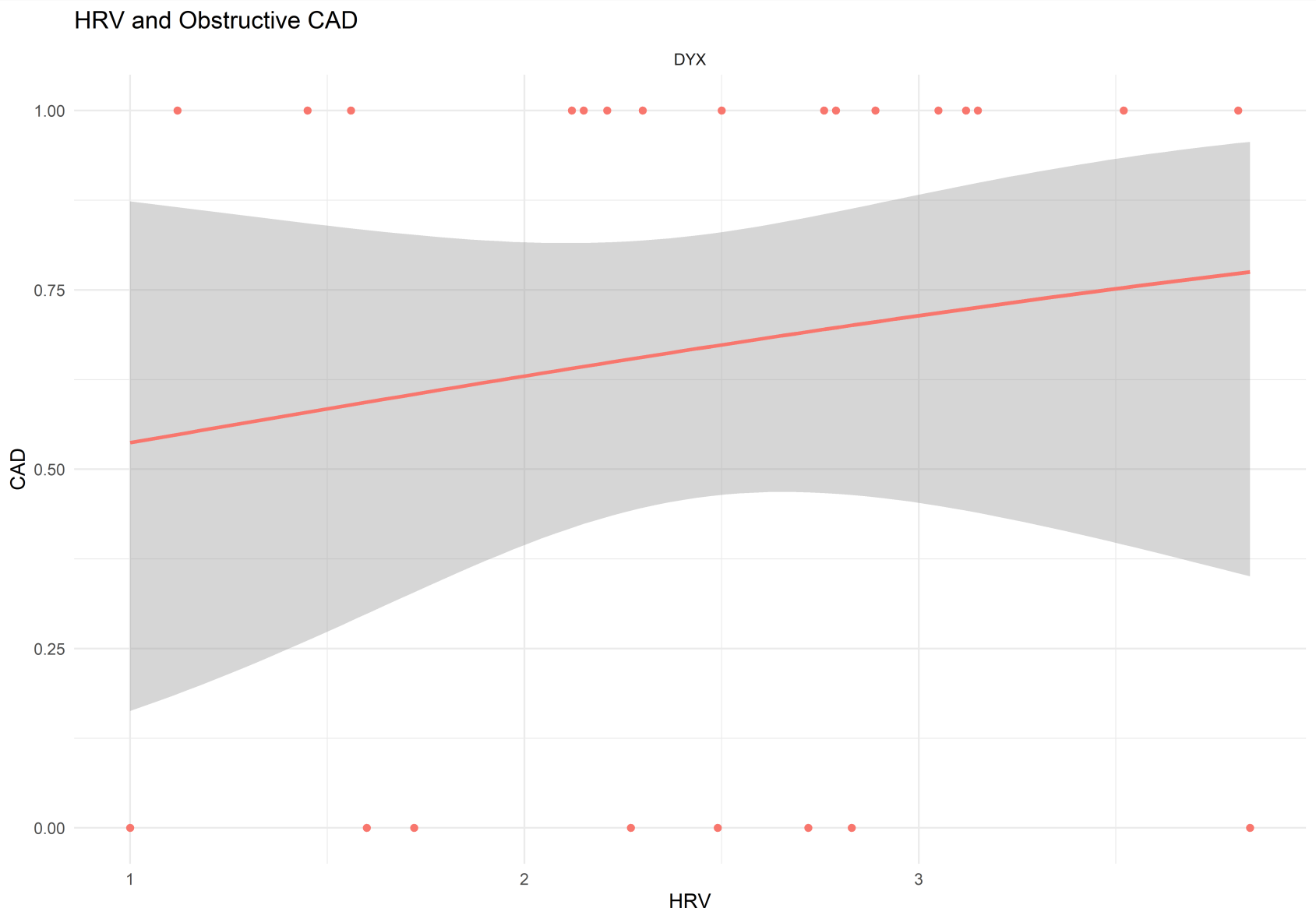
	Dependent variable:		
	PHQ > 9		
HF	0.14** (0.01, 0.61)		
LF		0.34* (0.07, 0.89)	
AC			2.47 (1.18, 11.50)
Observations	22	22	22
Log Likelihood	−6.25	−7.91	−6.22
Akaike Inf. Crit.	20.50	23.80	20.40
Note:			*p<0.1; **p<0.05; ***p<0.01

HRV by Obstructive Coronary Artery Disease

Table 5: HRV by Obstructive CAD by CASS-70

	Nonobstructive N=8	Obstructive > 70% N=16	p.overall
Mean HF (SD)	5.79 (1.99)	5.95 (1.48)	0.840
Mean LF (SD)	5.42 (1.94)	6.10 (1.40)	0.395
Mean VLF (SD)	6.14 (1.47)	6.55 (1.21)	0.504
Mean SDNN (SD)	51.3 (45.2)	54.1 (30.2)	0.878
Mean RMSSD (SD)	55.7 (69.3)	46.9 (26.7)	0.738
Mean PNN50 (SD)	17.2 (30.3)	12.9 (13.2)	0.715
Mean AC (SD)	-10.48 (11.6)	-9.04 (4.93)	0.744
Mean DC (SD)	8.36 (6.85)	8.44 (4.49)	0.975
Mean SampEn (SD)	1.28 (0.24)	1.51 (0.34)	0.070
Mean ApEn (SD)	0.96 (0.13)	0.95 (0.12)	0.783
Mean DYX (SD)	2.31 (0.88)	2.53 (0.75)	0.550

Visualizing effect of HRV on CAD



Discussion

Interpretion of Findings

- Depression is associated with ANS dysfunction, particularly decreases in HF HRV
- CAD may have associations with ANS dysfunction that can be measured, but may require more complex analyses and adjustments
- HRV may serve as a marker for ANS dysfunction, and may be the mediating factor in patients with comorbid depression and CAD

Future Directions and Limitations

- Larger sample size
- Identify times of catherization to control for sedation
- Consider stratifying effects of medications (e.g. beta blockers)
- Subset of patients with first-time angina (versus known CAD)
- Cosinor/complex time series analyses
- Circadian / time-of-day adjustment
- Adjustment for risk factors
- **Interaction between CAD and depression**

Conclusion

Conclusion

The ANS is a target that should be studied for potential interventions to reduce the excess cardiovascular risk in those with depression and coronary artery disease.

Thank you!

Questions?

References

Akselrod S., Gordon D., Ubel A., Shannon D., Barger C., and Cohen R. Power Spectrum Analysis of Heart Rate Fluctuation: A Quantitative Probe of Beat-To-Beat Cardiovascular Control. Technical Report 4504, 1981.

Robert M. Carney and Kenneth E. Freedland. Depression and coronary heart disease, mar 2017. ISSN 17595010. URL http://www.ncbi.nlm.nih.gov/pubmed/27853162http://www.nature.com/articles/nrcardio.2016.181.

M. J. Friedrich. Depression Is the Leading Cause of Disability Around the World. *JAMA*, 317(15):1517, apr 2017. ISSN 15383598. doi: 10.1001/jama.2017.3826.

References ii

Goffredo G Gensini. A more meaningful scoring system for determining the severity of coronary heart disease, feb 1983. ISSN 00029149. URL http://www.ncbi.nlm.nih.gov/pubmed/6823874.

Manish K Jha, Arman Qamar, Muthiah Vaduganathan, Dennis S Charney, and James W Murrough. Screening and Management of Depression in Patients With Cardiovascular Disease: JACC State-of-the-Art Review, apr 2019. ISSN 15583597. URL http://www.ncbi.nlm.nih.gov/pubmed/30975301.

Yi An Ko, Salim Hayek, Pratik Sandesara, Ayman Samman Tahhan, and Arshed Quyyumi. Cohort profile: The Emory Cardiovascular Biobank (EmCAB). *BMJ Open*, 7(12):e018753, 2017. ISSN 20446055. doi: 10.1136/bmjopen-2017-018753. URL http://www.ncbi.nlm.nih.gov/pubmed/29288185http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5778297.

References iii

Ian M. Kronish, Nathalie Moise, Ying Kuen Cheung, Gregory N. Clarke, Rowena J. Dolor, Joan Duer-Hefele, Karen L. Margolis, Tara St Onge, Faith Parsons, Jessica Retuerto, Anusorn Thanataveerat, and Karina W. Davidson. Effect of Depression Screening after Acute Coronary Syndromes on Quality of Life: The CODIACS-QoL Randomized Clinical Trial. *JAMA Internal Medicine*, 2019. ISSN 21686106. doi: 10.1001/jamainternmed.2019.4518.

M. Lewkowicz, J. Levitan, N. Puzanov, N. Shnerb, and K. Saermark. Description of complex time series by multipoles. *Physica A: Statistical Mechanics and its Applications*, 311(1-2):260–274, 2002. ISSN 03784371. doi: 10.1016/S0378-4371(02)00831-2.

References iv

Judith H. Lichtman, Erika S. Froelicher, James A. Blumenthal, Robert M. Carney, Lynn V. Doering, Nancy Frasure-Smith, Kenneth E. Freedland, Allan S. Jaffe, Erica C. Leifheit-Limson, David S. Sheps, Viola Vaccarino, and Lawson Wulsin. 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, mar 2014. ISSN 15244539.

Christopher J. McAloon, Luke M. Boylan, Thomas Hamborg, Nigel Stallard, Faizel Osman, Phang B. Lim, and Sajad A. Hayat. The changing face of cardiovascular disease 2000–2012: An analysis of the world health organisation global health estimates data, dec 2016. ISSN 18741754.

Anna Meijer, Henk Jan Conradi, Elisabeth H. Bos, Brett D. Thombs, Joost P. van Melle, and Peter de Jonge. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. *General Hospital Psychiatry*, 33(3):203–216, may 2011. ISSN 01638343. doi: 10.1016/j.genhosppsych.2011.02.007.

References v

Anish S. Shah, Rachel Lampert, Jack Goldberg, J. Douglas Bremner, Lian Li, Marc D. Thames, Viola Vaccarino, and Amit J. Shah. Alterations in heart rate variability are associated with abnormal myocardial perfusion. *International Journal of Cardiology*, XXX(XXX):XXX, jan 2020. ISSN 01675273. doi: 10.1016/j.ijcard.2020.01.069. URL https://linkinghub.elsevier.com/retrieve/pii/S0167527319355214.

P Taggart, H Critchley, and P D Lambiase. Heart-brain interactions in cardiac arrhythmia. *Heart*, 97(9):698–708, may 2011. ISSN 1355-6037. doi: 10.1136/hrt.2010.209304. URL http://heart.bmj.com/http://heart.bmj.com/cgi/doi/10.1136/hrt.2010.209304.