Stress Reactivity
Disturbances of the Neurocardiac Axis

Anish Sanjay Shah

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Preface

Acknowledgements

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Finally, I would like to thank my family for their patience and support.

Abbreviations

There are several key abbreviations that will be used throughout. They have been outlined here for reference.

Term	Abbreviation
Biobank	Emory Cardiovascular Biobank
CAD	Coronary Artery Disease
HRV	Heart Rate Variability
MACE	Major Adverse Cardiovascular Events
MIMS	Myocardial Infraction and Mental Stress
MIPS	Mental Stress Ischemia Mechanisms and Prognosis Study
Twins	Emory Twins Study

INTRODUCTION

1 Overview

1.0.1 Research Problem

- Mental stress can cause changes in the brain
- These changes can lead to depression and psych disease
- Those changes lead to increased cardiovascular disease
- Patients that are comorbid with psych and CAD do worse clinically

The relationship between the autonomic nervous system, stress reactivity, cardiovascular disease, and overall outcomes is outlined in Figure 15.1.1.

2 Outline

1. Research problem
2. Purpose of research
3. Underlying causal mechanisms
4. Overview of how to address problem

> "Why did he die on Tuesday and not on Monday?"
>
> — Douglas Zipes

BACKGROUND

3 Review of the Literature

4 Clinical Relevance

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5 Specific Aims

The response to both physiological and psychological stress can be markers of overall cardiovascular adaptability. The following aims help to assess the clinical importance of stress reactivity as measured by disturbances to the neurocardiac axis.

1. To assess the association between myocardial ischemia and coronary perfusion on cardiac autonomic activity.
2. To determine if cardiac autonomic activity modifies the relationship between acute and chronic psychological stress and myocardial ischemia.
3. To explore the association of cardiac autonomic activity with future major adverse cardiovascular events.

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Here are my thoughts.

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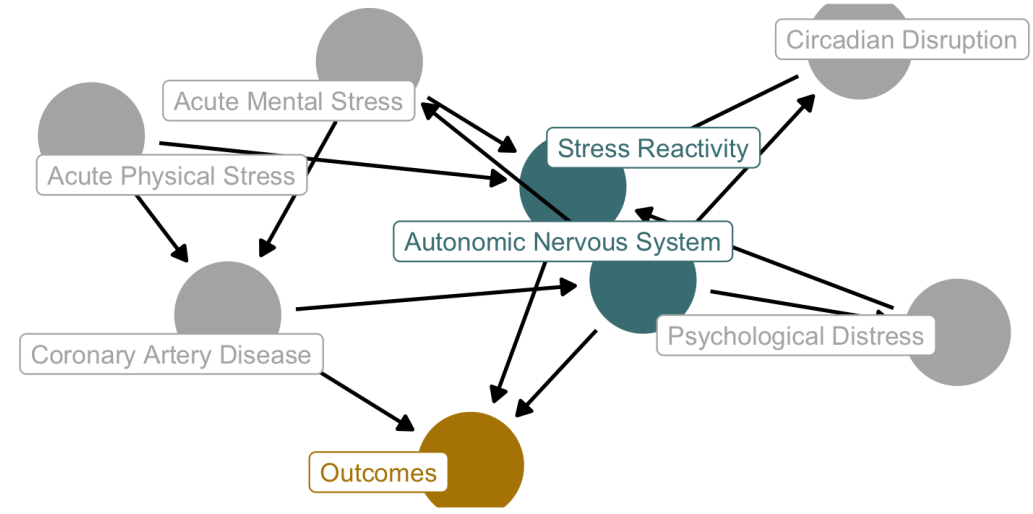
15.1.1 Overview of Stress Reactivity



Directed acyclic graph of the relationship between neurocardiac stressors and pote

15.1.2 Biobank Cohort Description

Emory Cardiovascular Biobank
Cohort Description

Characteristic	**N = 56**[1]
Age (years)	62 (52, 70)
Race	
African American Black	14 (26%)
Asian	2 (3.8%)
Caucasian White	37 (70%)
BMI (kg/m^2)	29.3 (26.2, 34.0)
Sex	
Female	9 (17%)
Male	44 (83%)
PHQ-9 Score	4.5 (1.0, 9.0)
Depression	10 (21%)
Gensini Score	26 (20, 51)
Stenosis	34 (71%)
CASS-70 Score	
0	21 (44%)
1	13 (27%)
2	9 (19%)
3	5 (10%)

[1]Median (IQR); n (%)

A description of subjects undergoing left heart catheterization with coronary angiography, including burden of coronary artery disease. CASS = Coronary Artery Surgery Score, PHQ = Patient Health Questionnaire, BMI = Body Mass Index.

15.1.3 Twin Cohorts Description

Emory Twins Study
Cohort Discription

Characteristic	**ETSF** N = 279[1]	**SAVEIT** N = 206[1]	**THS1** N = 360[1]	**THS2** N = 164[1]
Age (years)	55.0 (52.0, 57.0)	57.0 (56.0, 59.0)	61.0 (59.0, 62.0)	68.4 (66.8, 69.5)
BMI (kg/m^2)	28.0 (26.0, 32.0)	30.0 (27.0, 33.0)	30.0 (27.0, 33.0)	29.0 (27.0, 32.0)
Race				
White	345 (96%)	198 (96%)	157 (95%)	269 (96%)
African American	12 (3.3%)	8 (3.9%)	6 (3.6%)	7 (2.5%)
Asian	4 (1.1%)	0 (0%)	2 (1.2%)	4 (1.4%)
Current Smoker	131 (36%)	50 (24%)	43 (26%)	102 (36%)
Known IHD	327 (91%)	176 (85%)	136 (82%)	268 (96%)
Congestive Heart Failure	359 (99%)	206 (100%)	161 (98%)	276 (99%)
Hypertension	255 (71%)	137 (67%)	73 (45%)	115 (41%)
Diabetes Mellitus	328 (91%)	172 (83%)	137 (84%)	216 (77%)
Post-Traumatic Stress Disorder	339 (94%)	147 (71%)	120 (73%)	238 (85%)
Depression	321 (89%)	163 (80%)	138 (84%)	252 (90%)
Abnormal Myocardial Perfusion	274 (87%)	160 (94%)	130 (82%)	240 (88%)

[1]Median (IQR); n (%)

Description of the veteran twin subjects within each follow-up period. They were evaluated for clinical characteristics, including quantitative myocardial perfusion imaging. THS = Twins Heart Study, SAVEIT = Stress and Vascular Evaluation in Twins, ETSF = Emory Twins Study Follow-Up.

15.1.4 Mental Stress Cohorts Description

MIMS and MIPS
Cohort Discription

Characteristic	MIMS		MIPS	
	MSIMI = 0, N = 256[1]	**MSIMI = 1**, N = 50[1]	**MSIMI = 0**, N = 440[1]	**MSIMI = 1**, N = 188[1]
Age (years)	52.0 (47.0, 56.2)	51.5 (46.6, 54.7)	66 (58, 71)	64 (57, 71)
Sex (Female)	117 (46%)	33 (66%)	92 (21%)	76 (40%)
Race				
White	79 (31%)	9 (18%)	308 (70%)	115 (61%)
Black	165 (64%)	36 (72%)	110 (25%)	67 (36%)
Other	12 (4.7%)	5 (10%)	22 (5.0%)	6 (3.2%)
BMI (kg/m^2)	30 (26, 35)	30 (26, 38)	29.1 (25.6, 32.1)	29.5 (26.2, 32.8)
Current Smoker	62 (25%)	11 (22%)	215 (49%)	84 (45%)
Obstructive Coronary Artery Disease	201 (84%)	41 (89%)	316 (83%)	132 (85%)
Diabetes Mellitus	79 (31%)	18 (36%)	137 (31%)	69 (37%)
Coronary Artery Bypass Graft	51 (20%)	12 (24%)	139 (32%)	75 (40%)
Percutaneous Coronary Intervention	177 (69%)	35 (70%)	226 (51%)	100 (53%)
Hyperlipidemia	206 (80%)	40 (80%)	369 (84%)	151 (80%)
Hypertension	205 (80%)	42 (84%)	325 (74%)	147 (78%)
PSIMI	49 (20%)	20 (40%)	121 (28%)	96 (53%)
Depression	92 (37%)	16 (32%)	111 (26%)	51 (28%)
Post-Traumatic Stress Disorder	32 (13%)	12 (24%)	35 (8.2%)	8 (4.4%)

[1]Median (IQR); n (%)

MSIMI = Mental Stress Induced Myocardial Ischemia; PSIMI = Physical Stress Induced Myocardial Ischemia, MIMS = Myocardial Infarction and Mental Stress, MIPS = Mental Stress Ischemia Mechanisms and Prognosis Study

15.1.5 HRV in Twins Cohorts

Description of HRV
Emory Twins Study

ECG Metric	**ETSF** N = 279[1]	**SAVEIT** N = 206[1]	**THS1** N = 360[1]	**THS2** N = 164[1]
RR Interval	915 (806, 1,020)	870 (774, 973)	918 (816, 1,018)	923 (828, 1,025)
SDNN	48 (36, 62)	52 (40, 68)	60 (46, 74)	53 (40, 68)
RMSSD	25 (18, 37)	24 (17, 33)	27 (20, 35)	25 (18, 35)
PNN50	0.03 (0.01, 0.09)	0.03 (0.01, 0.09)	0.05 (0.02, 0.11)	0.04 (0.01, 0.10)
Ultra Low Frequency	6.00 (5.30, 6.67)	6.39 (5.68, 7.08)	6.60 (5.87, 7.21)	6.42 (5.73, 7.11)
Very Low Frequency	7.29 (6.76, 7.79)	7.55 (7.03, 8.08)	7.81 (7.27, 8.25)	7.54 (7.02, 8.05)
Low Frequency	6.28 (5.70, 6.86)	6.57 (6.00, 7.08)	6.79 (6.28, 7.23)	6.45 (5.85, 6.95)
High Frequency	5.32 (4.64, 6.11)	5.30 (4.64, 5.92)	5.48 (4.94, 6.00)	5.31 (4.66, 6.03)
Low/High Frequency Ratio	3.01 (1.71, 4.83)	4.02 (2.50, 5.92)	4.13 (2.63, 6.05)	3.24 (2.02, 5.16)
Total Power	7.97 (7.47, 8.46)	8.20 (7.70, 8.70)	8.45 (7.94, 8.86)	8.18 (7.69, 8.67)
Acceleration Capacity	-8.1 (-11.6, -6.1)	-9.5 (-12.5, -6.9)	-11.0 (-14.1, -7.9)	-9.4 (-12.2, -6.7)
Deceleration Capacity	7.3 (5.2, 10.8)	8.8 (6.1, 11.8)	10.3 (7.0, 13.5)	8.5 (5.9, 11.4)
Sample Entropy	1.55 (1.35, 1.77)	1.50 (1.32, 1.70)	1.52 (1.33, 1.69)	1.53 (1.32, 1.72)
Approximate Entropy	0.96 (0.89, 1.04)	0.95 (0.89, 1.03)	0.93 (0.87, 1.00)	0.94 (0.87, 1.01)
DYX	2.58 (2.03, 3.13)	2.80 (2.31, 3.33)	2.91 (2.37, 3.47)	2.81 (2.30, 3.34)

[1]Median (IQR)

Heart rate variability is described in each of the follow-up periods. HRV = heart rate variability, Dyx = kurtosis of Poincare plot, SDNN = the standard deviation of normally conducted RR intervals, RMSSD = the root mean square of successive differences in normally conducted RR intervals, PNN50 = proportion of normally conducted RR intervals that differ by more than 50 ms divided by the total number of normally conducted RR intervals

15.2 Myocardial Ischemia

15.2.1 Relationship Between Obstructive and Non-Obstructive Coronary Artery Disease

HRV and Obstructive CAD
Emory Cardiovascular Biobank

HRV Metric	**No Revascularization** N = 14[1]	**Revascularization** N = 34[1]	**p-value**[2]
n_nmean	648 (608, 872)	868 (775, 932)	0.019
sdnn	18 (15, 49)	37 (26, 51)	0.11
rmssd	16 (13, 32)	28 (20, 40)	0.11
pnn50	0.01 (0.01, 0.02)	0.05 (0.01, 0.10)	0.086
ulf	99 (56, 269)	200 (130, 477)	0.11
vlf	205 (94, 1,465)	826 (414, 1,336)	0.2
lf	70 (42, 833)	383 (145, 689)	0.2
hf	96 (89, 480)	306 (140, 620)	0.2
lfhf	0.99 (0.41, 1.28)	1.45 (0.65, 2.00)	0.2
ttlpwr	431 (216, 3,156)	1,865 (881, 3,562)	0.2
ac	-4.12 (-7.06, -2.08)	-6.52 (-9.39, -4.06)	0.3
dc	4.83 (2.05, 6.49)	5.07 (4.00, 8.58)	0.4
samp_en	1.14 (1.06, 1.39)	1.37 (1.16, 1.56)	0.15
ap_en	0.95 (0.91, 1.11)	0.92 (0.85, 1.00)	0.2
dyx	1.36 (1.17, 1.78)	2.03 (1.52, 2.71)	0.063

[1]Median (IQR)
[2]Wilcoxon rank sum exact test

In patients undergoing angiography, HRV metrics were described in those with both obstructive (>70%) and nonobstructive CAD, and evaluated for differences in distribution. HRV = Heart Rate Variability, CAD = Coronary Artery Disease.

15.2.2 HRV by Timing of Revascularization

HRV and Timing of Myocardial Reperfusion
Emory Cardiovascular Biobank

	No Revascularization			Revascularization		
ECG Metrics	**Balloon** N = 6[1]	**Start** N = 5[1]	**p-value**[2]	**Balloon** N = 15[1]	**Start** N = 20[1]	**p-value**[2]
RR Interval	711.7 (688.2, 855.9)	749.3 (723.6, 869.5)	0.8	849.5 (746.4, 949.6)	865.8 (801.1, 925.2)	0.6
SDNN	38.2 (16.8, 60.9)	47.4 (19.0, 49.0)	>0.9	30.7 (22.4, 62.4)	32.9 (25.5, 51.3)	0.8
RMSSD	28.8 (14.4, 48.6)	30.2 (20.6, 38.7)	>0.9	21.1 (16.3, 35.2)	20.7 (15.7, 27.8)	0.9
PNN50	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	>0.9	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.6
Ultra Low Frequency	110.3 (36.3, 177.9)	96.2 (92.7, 185.2)	0.8	151.6 (78.6, 623.7)	99.3 (52.1, 368.8)	0.5
Very Low Frequency	684.7 (115.1, 2,018.6)	1,000.1 (118.5, 1,340.7)	>0.9	507.3 (313.6, 1,643.5)	490.8 (230.2, 1,425.3)	0.7
Low Frequency	608.7 (74.9, 1,139.7)	867.6 (48.6, 875.5)	0.8	241.8 (83.9, 530.6)	276.2 (77.5, 551.9)	>0.9
High Frequency	539.6 (132.5, 967.8)	387.0 (127.5, 591.6)	0.8	107.7 (68.8, 579.8)	150.6 (92.7, 322.5)	>0.9
Low/High Frequency Ratio	0.6 (0.4, 1.1)	1.8 (0.4, 2.2)	0.4	1.2 (0.4, 1.8)	1.1 (0.5, 2.9)	0.6
Total Power	1,941.4 (360.8, 4,653.2)	2,559.9 (363.5, 3,097.1)	>0.9	1,208.3 (600.6, 4,185.2)	1,109.0 (672.4, 2,980.9)	0.7
Acceleration Capacity	-7.3 (-9.5, -4.6)	-4.8 (-11.5, -4.3)	>0.9	-5.0 (-7.1, -3.8)	-6.4 (-8.8, -3.7)	0.6
Deceleration Capacity	7.1 (4.7, 9.5)	6.4 (4.4, 12.1)	>0.9	4.4 (3.6, 6.8)	5.9 (3.8, 7.5)	0.7
Sample Entropy	1.0 (0.7, 1.4)	1.4 (0.8, 1.5)	0.7	1.2 (1.0, 1.4)	1.3 (1.2, 1.5)	0.2
Approximate Entropy	0.8 (0.7, 1.1)	0.8 (0.8, 0.9)	>0.9	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	0.9

[1]Median (IQR)
[2]Wilcoxon rank sum exact test

HRV was measured at the start of coronary angiography, as well as intervention. Coronary arteries with obstructive disease are reperfused using balloon angioplasty and potential stenting. HRV = Heart Rate Variability, CAD = Coronary Artery Disease.

15.2.3 Relationship of HRV with both Mental and Physical Stress

Myocardial Perfusion Imaging with Physical and Mental Stress
MIMS/MIPS Cohorts

ECG/HRV Metric	Combined MSIMI/PSIMI[1]	MSIMI[1]	
Heart Rate			
Rest	1 (0.99, 1.02) AUC 0.51	1.01 (1, 1.03) AUC 0.54	1 (0.98
Stress	1 (0.99, 1.01) AUC 0.49	1.01 (1, 1.02) AUC 0.54	1 (0.9
Recovery	1 (0.99, 1.01) AUC 0.52	1.01 (1, 1.02) AUC 0.52	0.99 (0.98
T Wave Area			
Rest	1 (0.99, 1) AUC 0.49	1 (0.98, 1) AUC 0.51	1
Stress	1 (0.99, 1.01) AUC 0.51	1 (0.98, 1.01) AUC 0.5	1.01 (0.99
Recovery	1 (0.99, 1.01) AUC 0.51	0.98 (0.97, 1) AUC 0.56	1 (0.9
High Frequency HRV			
Rest	0.71 (0.45, 1.13) AUC 0.55	0.57 (0.34, 0.95) AUC 0.56	0.71 (0.43
Stress	0.7 (0.47, 1.05) AUC 0.54	0.48 (0.31, 0.76) AUC 0.58	0.85 (0.55
Recovery	0.82 (0.52, 1.27) AUC 0.53	0.62 (0.38, 1.02) AUC 0.55	0.85 (0.53
Low Frequency HRV			
Rest	0.67 (0.41, 1.1) AUC 0.55	0.53 (0.31, 0.92) AUC 0.56	0.64 (0.37
Stress	0.64 (0.4, 1.01) AUC 0.56	0.45 (0.27, 0.74) AUC 0.59	0.63 (0.38
Recovery	0.64 (0.39, 1.04) AUC 0.56	0.43 (0.25, 0.74) AUC 0.59	0.64 (0.38

[1]Logistic regression model, OR with 95% CI and concordance statistic.

15.2.4 Quantitative Myocardial Perfusion and HRV

Myocardial Perfusion Imaging and Morning HRV
Emory Twins Study

	AC	*Dyx*	HF	LF	
Coronary Flow Reserve					
Model 1	0.96 (0.95, 0.98)	1.13 (1.05, 1.22)	1.10 (1.02, 1.20)	1.23 (1.11, 1.35)	1.
Model 2	0.97 (0.95, 0.99)	1.09 (1.01, 1.17)	1.10 (1.02, 1.20)	1.21 (1.10, 1.34)	1.
Model 3	0.97 (0.95, 0.99)	1.04 (0.97, 1.12)	1.09 (1.00, 1.18)	1.16 (1.04, 1.28)	1.
Abnormal MPI					
Model 1	0.96 (0.89, 1.03)	0.72 (0.53, 0.99)	1.20 (0.87, 1.64)	0.93 (0.63, 1.37)	0.
Model 2	0.96 (0.89, 1.04)	0.71 (0.52, 0.98)	9.07 (0.34, 241.85)	0.90 (0.60, 1.33)	0.
Model 3	0.95 (0.87, 1.03)	0.71 (0.51, 0.98)	1.20 (0.87, 1.65)	0.92 (0.61, 1.39)	0.

[1]Model 1 = HRV
[2]Model 2 = Model 1 + Age + BMI
[3]Model 3 = Model 2 + Smoking + HTN + Cardiovascular Disease

Relationship between abnormal MPI and CFR with HRV. HRV = heart rate variability, MPI = myocardial perfusion imaging, CFR = coronary flow reserve, LF = low frequency HRV, HF = high frequency HRV, VLF = very low frequency HRV, AC = acceleration capacity

15.2.5 Circadian HRV and Myocardial Perfusion

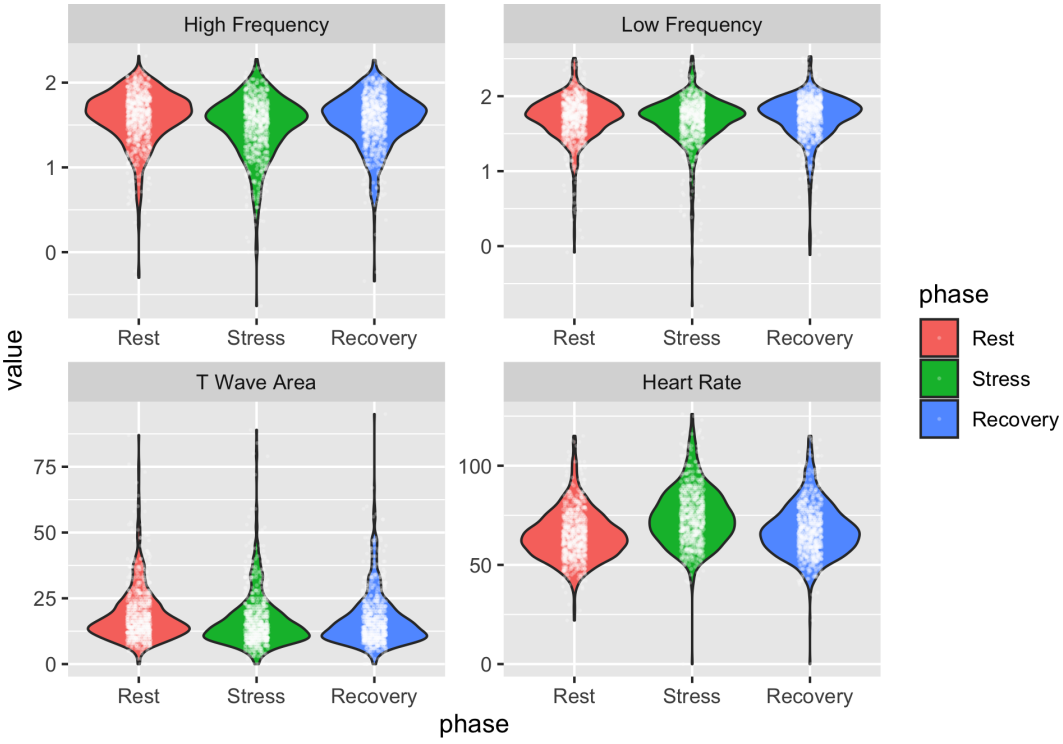
Circadian HRV and Myocardial Perfusion Abnormalities
Emory Twins Study

	MESOR	Amplitude	Phi
Coronary Flow Reserve			
High Frequency HRV	1.09 (1, 1.19)	1.08 (0.96, 1.21)	0.98 (0.94, 1.03)
Low Frequency HRV	1.16 (1.04, 1.29)	1.1 (0.93, 1.31)	1.01 (0.97, 1.06)
Very Low Frequency HRV	1.1 (1, 1.22)	1.11 (0.99, 1.24)	1.02 (0.96, 1.09)
Acceleration Capacity	0.97 (0.96, 0.99)	1 (0.97, 1.04)	1.03 (0.98, 1.09)
RR Intervals	1 (1, 1)	1 (1, 1)	1 (0.96, 1.03)
Dyx	1.09 (0.99, 1.19)	1.08 (0.94, 1.22)	0.99 (0.94, 1.05)
Abnormal MPI			
High Frequency HRV	1.33 (0.91, 1.96)	1.9 (0.94, 3.88)	0.99 (0.81, 1.2)
Low Frequency HRV	0.85 (0.55, 1.31)	1.09 (0.57, 2.07)	0.9 (0.74, 1.1)
Very Low Frequency HRV	0.86 (0.55, 1.36)	0.98 (0.61, 1.58)	0.95 (0.74, 1.23)
Acceleration Capacity	0.97 (0.9, 1.05)	1.14 (1.01, 1.29)	0.91 (0.71, 1.16)
RR Intervals	1 (1, 1)	1 (1, 1.01)	0.91 (0.8, 1.04)
Dyx	0.89 (0.6, 1.33)	0.75 (0.38, 1.49)	0.87 (0.69, 1.08)

Myocardial perfusion was quantified as a ccontinuous variable and as a binary of abnormal or normal. The HRV metrics are measured over 24 hours using cosinor statistics. MPI = myocardial perfusion imaging, CFR = coronary flow reserve, HRV = heart rate variability, LF = low frequency HRV, HF = high frequency HRV, VLF = very low frequency HRV, AC = acceleration capacity, MESOR = midline estimating statistic of rhythm, Amplitude = maximum distance from MESOR, Phi = shift of acrophase

15.3 Mental Stress and Myocardial Perfusion

15.3.1 HRV and Mental Stress Challenge



15.3.2 Distribution of HRV and Mental Stress Challenge

	Mean (95% CI)	T-statistic
Heart Rate		
Stress	9.6 (8.7, 10.4)	22.1
Recovery	2.7 (2.0, 3.3)	8.2
High Frequency HRV		
Stress	−0.1 (−0.1, −0.1)	−11.5
Recovery	−0.0 (−0.1, −0.0)	−5.7
Low Frequency HRV		
Stress	−0.0 (−0.0, −0.0)	−3.0
Recovery	0.0 (−0.0, 0.0)	1.9
T Wave Area		
Stress	−3.7 (−5.9, −1.5)	−3.4
Recovery	−3.2 (−5.2, −1.3)	−3.3

15.3.3 Distribution of HRV and MSIMI

HRV distribution by MSIMI
MIMS/MIPS cohorts

Characteristic	**MSIMI = 0**, N = 710[1]	**MSIMI = 1**, N = 243[1]
Heart Rate		
Rest	64 (56, 72)	64 (59, 75)
Stress	73 (64, 83)	75 (66, 85)
Recovery	66 (59, 74)	66 (59, 78)
T Wave Area		
Rest	16 (12, 23)	16 (12, 23)
Stress	14 (10, 19)	14 (10, 20)
Recovery	15 (10, 20)	13 (9, 19)
High Frequency HRV		
Rest	1.65 (1.48, 1.81)	1.61 (1.39, 1.76)
Stress	1.57 (1.34, 1.74)	1.48 (1.22, 1.65)
Recovery	1.62 (1.43, 1.78)	1.55 (1.35, 1.74)
Low Frequency HRV		
Rest	1.76 (1.60, 1.89)	1.70 (1.49, 1.86)
Stress	1.74 (1.59, 1.87)	1.66 (1.48, 1.81)
Recovery	1.79 (1.61, 1.91)	1.71 (1.52, 1.85)

[1]Median (IQR)

The distribution of HRV between those with MSIMI and those without. The HRV metric are stratified by phase of mental stress challenge. MSIMI = mental stress-induced myocardial ischemia, HRV = heart rate variability.

15.3.4 Depression and PTSD with Mental Stress Challenge

Mental Stress Challenge HRV and Chronic Psychological Stress
MIMS/MIPS Cohorts

ECG/HRV Metric	SCID Depression[1]	SCID PTSD[1]
Heart Rate		
Rest	1.01 (1, 1.03) AUC 0.55	1.03 (1.01, 1.05) AUC 0.6
Stress	1 (0.99, 1.01) AUC 0.51	1 (0.99, 1.02) AUC 0.53
Recovery	1.01 (1, 1.02) AUC 0.54	1.01 (1, 1.03) AUC 0.56
T Wave Area		
Rest	1 (0.99, 1.01) AUC 0.54	1 (0.99, 1.01) AUC 0.56
Stress	1.01 (1, 1.02) AUC 0.5	1.01 (1, 1.03) AUC 0.5
Recovery	1.01 (1, 1.02) AUC 0.54	1.02 (1, 1.03) AUC 0.58
High Frequency HRV		
Rest	0.98 (0.6, 1.64) AUC 0.48	0.6 (0.31, 1.23) AUC 0.54
Stress	0.79 (0.51, 1.21) AUC 0.51	0.63 (0.35, 1.17) AUC 0.54
Recovery	0.71 (0.44, 1.15) AUC 0.52	0.53 (0.28, 1.04) AUC 0.55
Low Frequency HRV		
Rest	0.71 (0.42, 1.19) AUC 0.52	0.58 (0.29, 1.21) AUC 0.57
Stress	0.74 (0.46, 1.21) AUC 0.53	0.63 (0.34, 1.26) AUC 0.55
Recovery	0.5 (0.29, 0.83) AUC 0.54	0.51 (0.26, 1.07) AUC 0.56

[1]Logistic regression model, OR with 95% CI and concordance statistic.

The association between HRV during mental stress challenge and the chronic psychological stressors of depression and PTSD are described. HRV = heart rate variability.

15.3.5 HRV and Chronic Mental Stress in Twins

Morning HRV and Chronic Psychological Stress
Emory Twins Study

	AC	*Dyx*	HF	LF	VLF
PTSD					
Model 1	1.11 (1.03, 1.21)	0.90 (0.67, 1.20)	0.69 (0.50, 0.94)	0.60 (0.42, 0.86)	0.70 (0.48, 1.03)
Model 2	1.11 (1.02, 1.20)	1.53 (0.58, 4.04)	0.70 (0.51, 0.96)	0.63 (0.43, 0.92)	0.73 (0.48, 1.09)
Model 3	1.14 (1.05, 1.24)	1.08 (0.77, 1.51)	0.69 (0.50, 0.94)	0.65 (0.45, 0.94)	0.79 (0.53, 1.18)
Depression					
Model 1	1.25 (1.12, 1.39)	0.60 (0.25, 1.47)	0.53 (0.16, 1.78)	0.46 (0.46, 0.46)	0.22 (0.12, 0.42)
Model 2	1.28 (1.13, 1.44)	0.59 (0.59, 0.60)	0.50 (0.32, 0.78)	0.24 (0.13, 0.45)	0.19 (0.09, 0.43)
Model 3	2.32 (1.22, 4.41)	0.54 (0.54, 0.54)	0.25 (0.02, 2.98)	0.02 (0.00, 1.60)	0.30 (0.16, 0.54)

[1]Model 1 = HRV
[2]Model 2 = Model 1 + Age + BMI
[3]Model 3 = Model 2 + Smoking + HTN + Cardiovascular Disease

Depression is measured as a binary outcome with Beck Depression Inventory score > 14. PTSD = Post-Traumatic Stress Disorder, HRV = heart rate variability, LF = low frequency HRV, HF = high frequency HRV, VLF = very low frequency HRV, AC = acceleration capacity

15.3.6 Circadian HRV and Chronic Mental Stress

Circadian HRV and Chronic Psychological Stress
Emory Twins Study

	MESOR	Amplitude	Phi
PTSD			
High Frequency HRV	0.65 (0.45, 0.96)	0.3 (0.09, 0.99)	1.16 (0.95, 1.42)
Low Frequency HRV	0.53 (0.35, 0.82)	0.32 (0.12, 0.86)	1.02 (0.85, 1.22)
Very Low Frequency HRV	0.65 (0.41, 1.04)	0.55 (0.28, 1.09)	1.13 (0.88, 1.47)
Acceleration Capacity	1.09 (0.99, 1.2)	0.74 (0.58, 0.94)	0.86 (0.69, 1.06)
RR Intervals	1 (1, 1)	1 (1, 1.01)	1 (0.86, 1.16)
Dyx	0.74 (0.11, 4.75)	0.01 (0, 0.24)	1.38 (0.53, 3.56)
Depression			
High Frequency HRV	0.49 (0.31, 0.76)	0.5 (0.26, 0.97)	1.1 (0.87, 1.39)
Low Frequency HRV	0.19 (0.1, 0.34)	0.23 (0.1, 0.55)	1.09 (0.84, 1.42)
Very Low Frequency HRV	0.07 (0, 2.58)	0.08 (0, 4.13)	2.1 (0.47, 9.36)
Acceleration Capacity	2.36 (1.08, 5.14)	0.4 (0.08, 2.03)	2.39 (0.52, 10.93)
RR Intervals	1 (0.99, 1)	1 (0.99, 1.02)	0.95 (0.68, 1.33)
Dyx	0.3 (0.17, 0.52)	0.51 (0.24, 1.11)	0.76 (0.57, 1.02)

Depression is measured as a binary outcome with Beck Depression Inventory score > 14. The HRV metrics are measured over 24 hours using cosinor statistics. PTSD = Post-Traumatic Stress Disorder, HRV = heart rate variability, LF = low frequency HRV, HF = high frequency HRV, VLF = very low frequency HRV, AC = acceleration capacity, MESOR = midline estimating statistic of rhythm, Amplitude = maximum distance from MESOR, Phi = shift of acrophase

15.3.7 Modeling Mental Stress-Induced Myocardial Ischemia and HRV

Mental Stress-Induced Myocardial Ischemia and
MIMS/MIPS Cohorts

Sequential Models	Stress LF	Rest LF	
Model 1	0.45 (0.27, 0.74) AUC 0.59	0.53 (0.31, 0.92) AUC 0.56	0.48 (0.31, 0
Model 2	0.49 (0.29, 0.81) AUC 0.64	0.59 (0.34, 1.04) AUC 0.62	0.45 (0.28, 0
Model 3	0.51 (0.3, 0.87) AUC 0.63	0.64 (0.36, 1.13) AUC 0.62	0.48 (0.29, 0
Model 4	0.53 (0.31, 0.91) AUC 0.65	0.65 (0.36, 1.15) AUC 0.63	0.49 (0.3, 0
Model 5	0.52 (0.3, 0.91) AUC 0.65	0.66 (0.36, 1.18) AUC 0.63	0.47 (0.29, 0

[1]Model 1 = MSIMI ~ HRV
[2]Model 2 = Model 1 + Age + BMI + Sex + Race
[3]Model 3 = Model 2 + Smoking + Diabetes + Hypertension + Hyperlipidemia
[4]Model 4 = Model 3 + Known Coronary/Peripheral Artery Disease
[5]Model 5 = Model 4 + Depression + Post-Traumatic Stress Disorder

The association between the exposure of HRV with the finding of MSIMI is described. The HRV metric are stratified by phase of mental stress challenge. MSIMI = mental stress-induced myocardial ischemia, HRV = heart rate variability.

15.4 Clinical Outcomes

15.4.1 Recurrent Events in those Mental Stress

15.4.2 Outcomes in Twins

Clinical Outcomes by HRV
Emory Twins Study

	Acceleration Capacity	Dyx	High Frequency HRV	Low Frequency HRV	RR
Model 1	1.12 (1.01, 1.23)	0.49 (0.35, 0.68)	0.72 (0.48, 1.09)	0.52 (0.36, 0.75)	
Model 2	1.12 (1, 1.26)	0.44 (0.3, 0.65)	0.63 (0.4, 1)	0.48 (0.33, 0.71)	
Model 3	1.15 (1.01, 1.31)	0.4 (0.26, 0.62)	0.65 (0.42, 1.01)	0.49 (0.33, 0.75)	
Model 4	1.14 (1, 1.3)	0.41 (0.27, 0.64)	0.66 (0.43, 1.03)	0.49 (0.31, 0.77)	
Model 5	1.14 (1, 1.31)	0.41 (0.27, 0.64)	0.68 (0.43, 1.05)	0.48 (0.31, 0.76)	

Every unit increased in HRV had the associated hazard ratio (95% CI) for both overall and cardiovascular mortality. HRV = heart rate variability.