Stress Reactivity

Disturbances of the Neurocardiac Axis

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Contents

Preface

Acknowledgements

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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
CFR	Coronary Flow Reserve
HRV	Heart Rate Variability
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MIMS	Myocardial Infarction and Mental Stress
MIPS	Mental Stress Ischemia Prognosis Study
MPI	Myocardial Perfusion Imaging
PTSD	Post-Traumatic Stress Disorder
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

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

Burden of Depression in Coronary Artery Disease: An Untreated Epidemic

Depression is the leading cause of disability in the world,2 and CAD is the leading cause of death.3 Depression is estimated to occur in over 300 million people, which accounts for roughly 4% of the global population.2 The estimated yearly economic burden of depression in US is $210 billion dollars and the estimated direct and indirect costs of CAD is $204 billion, with the cost of both continuing to climb.34,35 In individuals with CAD, the prevalence of depression is up to 20%.4 In comorbid depression and CAD, there is a 3-fold increase in the incidence of secondary cardiovascular disease (CVD) outcomes;6 however only in the last several years has depression been recognized as an additional prognostic marker of mortality.5 The rate of increased mortality in CAD with depression has remained unchanged over the past 35 years.6

Critical Gap in the Evidence Linking Depression Treatment with CVD Risk Reduction

Although interventions such as cognitive behavioral therapy and antidepressants are well-proven in reducing depressive symptoms, their impacts are only modest in CAD patients, and they do not impact event-free survival.7 Although the American College of Cardiology recommends depression should be routinely screened for in patients with cardiovascular disease,4 there is limited evidence that this leads to an improvement in overall mortality.8 More research is needed to understand the potential therapeutic mechanisms underlying depression and CAD1 in order to develop more effective therapies for the high-risk individuals in which both occur together. Our key premise for this investigation is that autonomic mechanisms can help fill this critical gap and provide insight into future novel, more effective therapies for both depression and CAD.

Autonomic Nervous System Plays an Important Mechanistic Role in both Depression and CAD

Dysfunction of the autonomic nervous system (ANS) has been found to occur in diseases of both the brain and heart, and may also underly somatic symptoms and vasomotor abnormalities observed in depression.36 Autonomic dysfunction occurs at multiple levels, from central neurological processes to peripheral cardiovascular reflexes.37 This includes vagal withdrawal in depression and heightened sympathetic tone in cardiovascular disease, for example. Depression has been linked to dysregulation of the ANS though increased levels of catecholamines,38 increased cardiovascular reactivity to stress,39 and decreased baroreflex sensitivity.40 The heart itself harbors an intrinsic cardiac nervous system that responds to changes in autonomic tone, such as in myocardial ischemia and infarction (MI), by changing heart rate, strength contraction, or the speed of nerve conduction.32,41

Study of ANS-related mechanisms may inform future therapies. Interventions targeting ANS dysfunction show improved symptom burden in both depression and CAD and warrant additional research.10 For example, the vagal nerve activity may protect against ventricular fibrillation,42 and vagal nerve stimulation has been shown to relieve angina pectoris and cardiac arrhythmias.12,13 Vagal nerve stimulation (VNS) is also effective in treatment-resistant depression.11 Dr. Shah has studied non-invasive VNS in PTSD and found that it blunts the sympathetic response to stress.43 In summary, ANS dysfunction occurs in both depression and CAD, and research in this area is important as neuromodulation therapies such as non-invasive VNS are studied and become increasingly available.

Advances in Electrocardiography can Assess Autonomic Dysfunction

A novel ECG-based biomarker for ANS dysfunction, Dyx, has surfaced in the last several years, and is actively being investigated by the company HeartTrends, LLC for its clinical application in CAD risk stratification. Dyx is an advanced heart rate variability (HRV) metric that strongly associates with myocardial ischemia and future adverse outcomes.19,20 HRV is an accepted measure of cardiac autonomic activity, which is the integration of the multiple levels of sympathetic and parasympathetic efferent input at the level of the sinoatrial node. 15,16 Dyx is derived from heart rate time series analysis and measures the variability and randomness of the heart rhythm. Dyx is generated through the multipole method analysis of Poincaré plot, in which beat-to-beat (RR) interval lengths are plotted as a function of prior RR intervals to form an ellipse, as seen in our prior work (Figure D1).44 Dyx is calculated as the ratio of the kurtosis along the y-axis and the x-axis of the ellipse, better capturing the density of heart beats and thus including non-linear features of heart rate dynamics.17,18 Low Dyx predicts ventricular dysrhythmia and cardiovascular mortality after myocardial infarction, with a hazard ratio of 2.4 (95% CI 1.5 – 3.8).18,19 In addition, individuals with chest pain and low Dyx had an odds ratio of 8 (95% CI 3.1 – 23.9) for having abnormal exercise stress test results.20,21 This makes Dyx a strong candidate for assessing ANS dysfunction in our proposal.

METHODS

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.

To achieve these aims, we will leverage the several data sets, including the Emory Cardiovascular Biobank (*Biobank*), the Myocardial Infarction and Mental Stress (*MIMS*) and Mental Stress Ischemia Prognosis Study (*MIPS*), and the Emory Twins Study (*Twins*). Each of these data sets contribute variations of coronary artery physiology, acute and chronic mental stressors, and electrocardiographic data of varying recording lengths.

6 Study Design

6.1 Population Characteristics and Study Overview

6.1.1 Emory Cardiovascular Biobank

The *Biobank* studies major cardiovascular events, and also evaluates additional biomarkers for inflammation, cardiac injury, and genetics, with the goal of predicting CVD outcomes.(1) All patients aged 18 years and older undergoing cardiac catherization were included. During the index cardiac catheterization, additional measures including lifestyle factors, psychological status, medical comorbidities, revascularization and previous procedures were ascertained via patient interview and chart review. Additionally, ambulatory ECG was collected with the VivaLNK patch, which was placed on the morning of cardiac catheterization and removed after catheterization for up to 24 h of data recording. Patients were excluded if they have congenital heart disease, severe valvular heart disease, severe anemia, a recent blood transfusion, myocarditis, history of active inflammatory disease, cancer or are unable or not willing to provide consent (approximately 5%). Those that are found to have atrial fibrillation or have >20% ectopic beat burden or noise, as well as those that are pacer dependent were excluded. Those with known CAD were also excluded.

6.1.2 Emory Twins Study

The *Twins* is a cross-sectional study was designed to evaluate the relationship of abnormal stress myocardial perfusion with autonomic function, measured hourly over the course of 24 h, in individuals without known ischemic heart disease. Subjects were drawn from the Emory Twin Study, which recruited middle-aged male twin pairs from the Vietnam Era Twin Registry.(2–4) Pairs of twins were examined at the Emory University General Clinical Research Center, and all data collection occurred during a 24-hour admission under controlled conditions. The twins in each pair maintained a nearly identical schedule, with all data collection beginning and ending at the same time. The twins arrived at 11 AM, with ECG recording started at approximately 1 PM, questionnaires and exam performed between 2 and 4 PM, dinner at 5 PM, bedtime at 10 PM, wake-up time at 6:30 AM, and PET scans performed between 8 and 10 AM the following morning. The twins were followed longitudinally for follow-up events, including review of national registries, which were adjudicated. Subjects were excluded from analysis if they were unable to complete pharmacological stress testing.

6.1.3 Mental Stress Ischemia Mechanisms and Prognosis, Myocardial Infarction and Mental Stress

The study design has been described prior, and is the same between the two cohorts.(5) The *MIMS* cohorts had recent myocardial ischemia within the 8 months prior to enrollment and were younger than 61 years of age at time of screening. The *MIPS* cohort included patients with stable CAD diagnosed via coronary angiogram, documented MI, or positive nuclear stress test. All patients underwent mental stress test and physical stress test using either treadmill or regadenosine, and were randomly assigned to complete one and then the other in two separate visits within a week. During the initial visit, medical history and psychological assessments were performed as well. During the mental stress testing, all patients had ECG recordings made of variable duration. Patients were followed longitudinally for 3-5 years for follow-up events, which were adjudicated. Patients were excluded for having acute coronary syndrome or decompensated heart failure, severe psychiatric conditions other than depression, pregnancy, uncontrolled high blood pressure, or contraindications to pharmacological stress testing.

6.2 Measurements

6.2.1 Electrocardiography Measures

In all three cohorts, ECG data was collected and analyzed using similar techniques. As described, in the *Biobank*, ECG was collected through a single, bipolar lead using the VivaLNK patch, with data being recorded for up to 24 h. In the *Twins*, ambulatory ECG was collected through Holter monitor (GE Marquette SEER digital system; GE Medical Systems, Waukesha, Wisconsin) for 24 h. Holter monitor was also used in the *MIMS/MIPS*, however the recording time was only for several hours.

Variations in heart rate can be assessed by a number of mathematical measures, usually divided into the time and frequency domains.(6) Time domain measures we used include the RR interval duration (converted to heart rate in beats-per-minute), the standard deviation of normally conducted RR intervals (SDNN), the root mean square of successive differences in normally conducted RR intervals (RMSSD), and the proportion of normally conducted RR intervals that differ by more than 50 ms divided by the total number of normally conducted RR intervals (PNN50). Frequency-domain measures computed through power spectral analysis categorize variability as very low frequency (VLF, 0.0033 to <0.04 Hz), low frequency (LF, 0.04 to <0.15 Hz) or high frequency (HF, 0.15 to 0.40 Hz).(7) These frequency categories reflect autonomically mediated heart rate responses to physiologic stimuli, including influences of the renin-angiotensin-aldosterone system, baroreceptor activity, and respiration.(7) The sympathetic and parasympathetic nervous systems influence them to different degrees. HF reflects primarily parasympathetic nervous system activity, while LF reflects both sympathetic and parasympathetic activity.(8) Total power HRV is a nonspecific global measure. RMSSD is an approximate correlate of HF, and SDNN is an approximate correlate of TP, supporting the physiological basis of these markers.[Electrophysiology1996b] Acceleration capacity and deceleration capacity were also included where available, based on signal quality and recording length, as they also reflect clinically relevant sympathetic and vagal activity.(9) These metrics are well-known as physiologic markers of acute and chronic stress, and measure slightly different aspects of autonomic nervous system function. HRV was also analyzed hourly through the commercial HeartTrends algorithm (Lev-El Diagnostics Ltd, Israel), which generated the *Dyx* measure. *Dyx* is derived from heart rate time series analysis and measures the variability and randomness of the heart rhythm. *Dyx* is generated through the multipole method analysis of Poincaré plot, in which beat-to-beat (RR) interval lengths are plotted as a function of prior RR intervals to form an ellipse, as seen in Figure 15.1.2. *Dyx* is calculated as the ratio of the kurtosis along the y-axis (long-term variability) and the x-axis (beat-to-beat random variation) of the ellipse, and higher values indicate more beat-to-beat randomness and/or decreased variability.(10,11)

In addition to summary and hourly assessments of HRV, diurnal rhythms were examined using cosinor metrics.

6.2.2 Psychological Measures

In all cohorts, chronic psychological variables were measured through patient interviews. In the *Biobank*, depressive symptoms were assessed via the 9-question Primary Care Evaluation of Mental Disorders Brief Patient Health Questionnaire (PHQ-9).(12) Moderate-severe depression is considered when the PHQ-9 score is 10 points or higher (out of 27), with this cutpoint having a sensitivity and specificity of 88% for major depression. Within the *Twins* and *MIMS/MIPS* cohorts, depressive symptomers were assessed with Beck's Depression Inventory, which includes 21 items with 4 statements scored 0-3, with higher scores indicating higher severity of depression.(13) A cut-off of $\geq$ 14 points was used to identify patients with moderate-to-severe depressive symptom burden. The diagnosis of post-traumatic stress disorder (PTSD) was defined using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).(14)

In the *MIMS/MIPS* cohort, there was a separate protocol for acute mental stress challenge. Patients were initially allowed to rest for 30 minutes in a calm, quiet, dimly lit, and temperature-regulated room. After the resting period, mental stress was induced by a standardized public speaking task, as previously described.(15)

The patients were asked to imagine a real-life stressful situation, such as a close relative having been mistreated in a nursing home, and then asked to make up a realistic story around this scenario. They were given two minutes to prepare the statement, and three minutes to present it in front of a video camera and an audience. The patients were told that the speech would be evaluated for content, quality, and duration.

6.2.3 Cardiac Measures

All cohorts underwent imaging of the heart through different modalities, which all assess complementary aspects of myocardial blood flow.

The *Biobank* used direct coronary angiography through cardiac catheterization. Obstructive CAD was defined as $\geq 70\%$ stenosis or hemodynamic significance by fractional flow reserve. Coronary angiography was used to determine the Gensini score, which is a visual estimation of luminal narrowing in multiple segments based on a modified form of the American Heart Association classification of the coronary tree by trained cardiologists.(16) Coronary angiography was also evaluated using the Coronary Artery Surgery Study (CASS), which evaluates the number of major epicardial vessels that have a certain percent stenosis, e.g. the CASS-50 score determines the number of vessels with $\geq 50\%$ stenosis.(17) Importantly, direct coronary angiography is limited to visualization of the large, epicardial conduit vessels.

TWINS All subjects, for research purposes, underwent MPI using nitrogen-13-ammonia positron emission tomography with adenosine as the pharmacologic stressor. Adenosine doses were calculated to induce maximal coronary vasodilation [32]. Areas of diminished uptake indi- cate reduced capacity to maximally vasodilate, thereby causing relative coronary hypoperfusion. Images were visually interpreted by experi- enced cardiologists and radiologists with training in nuclear cardiology. Quantitative analysis was performedwith the Emory Cardiac Toolbox to generate: a) coronary flow reserve (CFR) for absolute myocardial blood flow during stress and rest, and b) the stress total severity score (STSS), which measures the sum of the number of standard deviations below the expected value for eachpixel compared to a database ofnormal con- trols [33]. CFRwas defined as the ratio ofmean stress to rest myocardial blood flow (mL/min/g), and low CFR was defined as a ratio b1.5 [34]. Abnormal MPI findings were defined as N5% MPI deficit. For generaliz- ability, semi-quantitative assessments were used as the primary out- come. Gallium (Ge-68) was used for attenuation correction, and thus coronary

MIMS/MIPS Subjects underwent three SPECT myocardial perfusion imag- ing scans following injection of sestamibi radiolabelled with Technetium-99m (99mTc sestamibi), at rest, after mental stress, and after physical (exercise or pharmacological) stress. Testing was done on a dedicated ultra-fast solid-state camera (Discovery NM 530c, General Electric, Milwaukee, WI) without attenuation correction [17]. Only one resting scan was performed, with myocardial perfusion images acquired after the injection of 10–15 mCi of [99mTc] sestamibi according to body weight. The stress scan (either mental or physical) followed at least 2 hours later and 30–45 mCi of [99mTc] sestamibi were administered, with a 3:1 ratio of stress to rest radiotracer dose. On the mental stress day, [99mTc]sestamibi was injected one minute after the onset of the public speech. On the exercise stress day, subjects were submitted to a standard Bruce protocol with exercise target set at 85% of maximum predicted heart rate and the radiotracer was injected at peak exertion. For both stress conditions, stress images were acquired 45–60 minutes after radiotracer injection using previously described methodology [18]. The ECG, blood pressure and heart rate were continuously monitored during the test. For patients undergoing a pharmaco- logical stress test, 0.4 mg of regadenoson (Astellas, Northbrook, Illinois), an adenosine receptor agonist, were administered intravenously in approximately 10 seconds, and [99mTc] sestamibi was injected right after regadenoson. SPECT images were then obtained as described above. Myocardial perfusion abnormalities were quantified by means of the Emory Cardiac Toolbox software, which provides objective quantitative assessment of perfusion with established validity and reproducibility [19,20]. Automated analysis for SPECT myocar- dial perfusion imaging is equivalent to visual analysis by expert readers [21,22], but is more reproducible, since interpreter variability is an important source of heterogeneity in imaging results [23,24]. With automated analysis, such variability is removed, making this technique more reproducible and thus better suited for studies with serial SPECT scans such as ours. Briefly, the three-dimensional tracer uptake distribution in the left ventricle was oriented along the short axis and sampled onto a two-dimensional polar map. An operator-independ

6.3 Sample size and power considerations

7 Analysis

7.1 Descriptive analysis

7.2 Statistical inference

RESULTS

8 Clinical Characteristics

The study populations in the three cohorts are uniquely suited for these analyses. They are complementary in their description of cardiovascular disease, autonomic function, and psychological factors, and are described here.

The *Biobank* cohort, as described in Table 15.1.3, had 56 participants, with a mean (95% CI) age in years of 62 (52, 70). 9 (17%) were female, and 14 (26%) were Black. There were 34 (71%) that had obstructive CAD on coronary angiography, and 10 (21%) had depression.

The *MIMS/MIPS* cohort had 958 participants. The mean age was 59 (52, 68), 323 (34%) were female, and 385 (41%) were Black. 700 (84%) had obstructive CAD. 273 (30%) had a diagnosis of depression, and 87 (9.5%) had a diagnosis of PTSD. In this population, 238 (25%) had MSIMI. Additional breakdown by study group is described in **??**.

The *Twins* cohort, as described in both Table 15.1.4 and 15.1.6, had 1012 participants over 4 follow-up visits, with 610 unique participants. The mean age was 55.0 (52.0, 57.0) during the initial enrollment period, and was 68.4 (66.8, 69.5) during the final enrollment period. All participants were male, and 95.75% were White. The average rate over the enrollment periods of abnormal MPI was 12.13%. The average rate of PTSD was 16.52% and the average rate of depression was 13.38%.

9 Myocardial Ischemia

The relationship of autonomic dysfunction to CAD as measured by coronary angiography was assessed in the *Biobank* cohort. When comparing summary HRV metrics between those with obstructive CAD versus nonobstructive CAD, there were no significant differences between HRV distributions (15.2.1). When comparing those that had revascularization of the CAD and those that did not (15.2.2), there was a difference seen in RR interval. Those that underwent revascularization had a mean (95% CI) RR interval of 868 (775, 932), while those that did not had a mean RR interval of 648 (608, 872). There was a trend towards an increased *Dyx* in those that underwent revascularization (2.03 (1.52, 2.71)) than those that did not (1.36 (1.17, 1.78)). No other HRV metrics were associated with revascularization. To effect of the timing of revascularization on the subsequent changes in HRV acutely were assessed, as described in Table 15.2.3. No differences were seen between HRV before or after cardiac catheterization.

The relationship of autonomic dysfunction to qualitative MPI was assessed using both mental stress and physical stress in the *MIMS/MIPS* cohorts. ECG and HRV metrics did not have an association with abnormal MPI with combined mental and physical stress nor with physical stress. Both lf HRV and LF HRV most prominently had an association with MSIMI, with stress HRV HRV having an odds ratio (OR) = 0.48 (95% CI 0.31, 0.76) and LF HRV having an OR = 0.45 (95% CI 0.27, 0.74). The other associations are described in Table 15.2.4.

This relationship between myocardial perfusion and autonomic dysfunction was further explored using quantitative MPI in the *Twins* cohort. Morning HRV at approximately 7 AM was predominately associated with coronary flow reserve, as described in Table 15.2.5. A change in 1 unit of LF HRV was associated with an 1.16 (95% CI 1.04, 1.28) in adjusted models. *Dyx* had an OR = 0.71 (95% CI 0.51, 0.98) for abnormal MPI.

Within the *Twins*, diurnal HRV metrics were measured using cosinor analysis. The relationship of the MESOR, amplitude, and acrophase with abnormal MPI and coronary flow reserve were evaluated (Table 15.2.6). The MESOR in particular showed a consistent relationship with coronary flow reserve, with a 0.88 (0.58, 1.32) increase in every 1 unit increase in LF HRV, and a 0.89 (0.61, 1.31) increase for every 1 unit increase in *Dyx*.

10 Psychological Stress and Myocardial Ischemia

Chronic psychological stressors were analyzed using all three cohorts. In the *Biobank* cohort, there were no significant differences seen in HRV by depressive symptoms as measured on the PHQ-9.

In the *Twins*, early morning HRV was measured against both PTSD and depression. There was a significant relationship between HRV and both depression and PTSD as seen in Table 15.3.2. In adjusted logistic models for PTSD, every 1 unit increase in HF HRV had an OR = 0.69 (95% CI 0.5, 0.94), and LF HRV had an OR = 0.65 (95% CI 0.45, 0.94). In adjusted models logistic models for depression, every 1 unit of increase in VLF HRV had an OR = 0.3 (95% CI 0.16, 0.54). *Dyx* and VLF HRV were not strongly associated with PTSD.

WHen using the diurnal HRV metrics, measured by cosinor analysis, significant relationships were seen with both depression and PTSD in the MESOR and amplitude (Table 15.3.3). For example, every 1 unit increase in the MESOR of LF HRV had an OR = 0.46 (95% 0.31, 0.69) and every 1 unit increase in the amplitude had an OR = 0.31 (95% 0.13, 0.72) for PTSD. Every 1 unit increase in the MESOR of LF HRV had an OR = 0.26 (95% 0.15, 0.45) and every 1 unit increase in the amplitude had an OR = 0.31 (95% 0.14, 0.68) for depression.

Acute mental stress was also assessed primarily using the *MIMS/MIPS* cohorts. The distribution of HRV metrics based on the phase of acute mental stress challenge was evaluated, as seen in Figure 15.3.4. There were small differences between stress and rest HRV, as seen in Table 15.3.5. The difference in distribution of HRV was compared between those that had MSIMI and those that did not, as described in 15.3.6. There was a decrease in HRV in those with MSIMI compared to those without, except with heart rate.

The association between HRV during acute mental stress and chronic mental stress was also assessed (Table 15.3.7). Every 10 beat/minute increase in resting heart rate had an OR = 1.33 (95% CI 1.11, 1.58) for PTSD and an OR = 1.15 (95% CI 1.01, 1.3) for depression. Every 1 unit increase in LF HRV during recovery had an OR = 0.51 (95% CI 0.26, 1.07) for depression. No other HRV metrics were strongly associated.

To assess the relationship of acute mental stress with myocardial perfusion abnormalities, the relationship between HRV and MSIMI was assessed. As seen in Table 15.3.8, there was a robust association between LF and HF HRV during rest and stress with MSIMI. In fully adjusted models, including adjustment for both cardiovascular and psychological risk factors, every 1 unit increase in stress HF HRV had an OR = 0.47 (95% CI 0.29, 0.77) and stress LF HRV had an OR = 0.47 (95% CI 0.3, 0.91) for MSIMI.

11 Clinical Outcomes

Clinical outcome data was available in both the *Twins* and the *MIMS/MIPS* cohorts. With the *Twins*, early morning HRV showed a robust association with overall mortality and with cardiovascular disease, as seen in Table 15.4.1. In fully adjusted models for overall mortality, *Dyx* and VLF HRV had the strongest association. With every 1 unit of increase in *Dyx*, there was a hazard ratio (HR) = 0.41 (95% CI 0.27, 0.64), and with every 1 unit increase in VLF HRV, there was a HR = 0.49 (95% CI 0.27, 0.88). When evaluating the relationship of circadian changes in HRV and clinical outcomes, *Dyx* was a significant predictor of both overall and cardiovascular mortality. The MESOR of *Dyx* had a HR = 0.34 (95% CI 0.21, 0.56) and the amplitude of *Dyx* had a HR = 0.42 (95% CI 0.22, 0.79). Further relationships are outlined in 15.4.2.

Using the *MIMS/MIPS* cohorts, stress HRV was compared with clinical outcomes. There was a robust relationship between stress HRV and overall mortality, cardiovascular mortality, and recurrent cardiovascular events as described in Table 15.4.3. In fully adjusted models for cardiovascular mortality, including adjustment for MSIMI, 1 unit increase in stress LF HRV had a HR = 0.25 (95% CI 0.11, 0.56) and HF HRV had a HR = 0.25 (95% CI 0.11, 0.56).

DISCUSSION

12 Major Findings

12.1 Myocardial Ischemia

- DYX but not HRV associated with abnormal MPI
- HRV associated with CFR more than MPI

13 Strengths and Limitations

14 Next Steps

CONCLUSIONS

Here are my thoughts.

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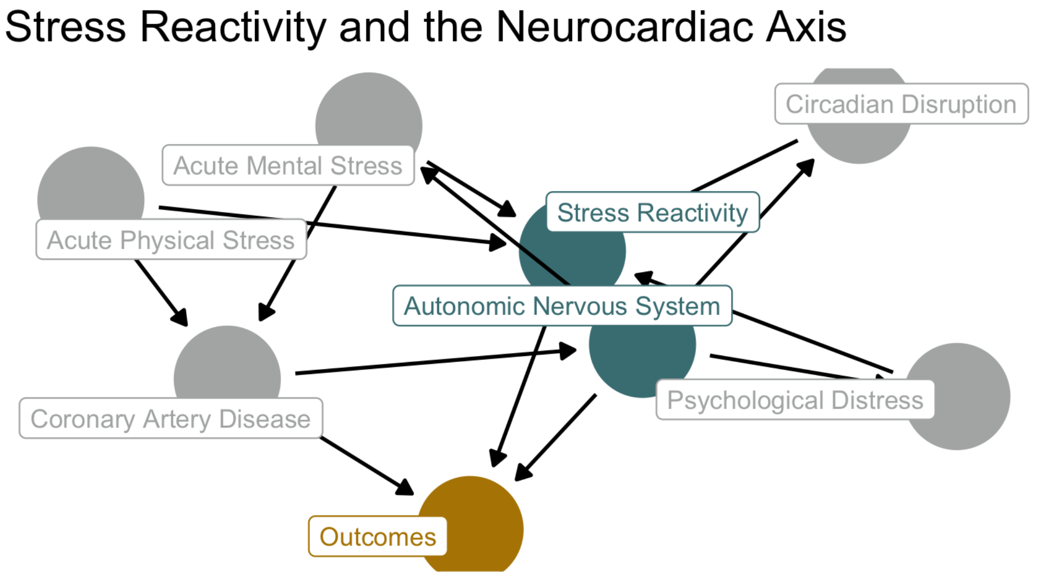
APPENDIX

15 TABLES AND FIGURES

15.1 Clinical Overview

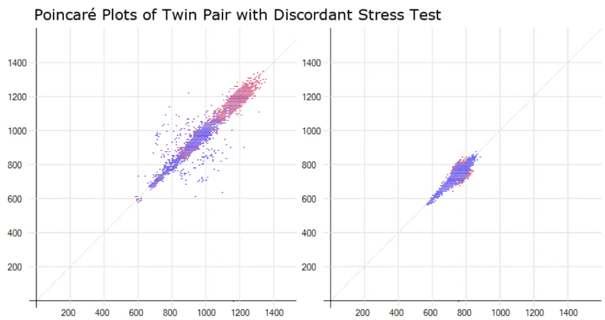
The follow section divides the relevant figures and tables into those describing the study, aims, and clinical cohorts.

15.1.1 Overview of Stress Reactivity



Directed acyclic graph of the relationship between neurocardiac stressors and pote

15.1.2 Poincaré Plot of HRV



15.1.3 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.

15.1.4 Twin Cohorts Description

Emory Twins Study
Cohort Discription

Characteristic	**THS1**, N = 361[1]	**SAVEIT**, N = 206[1]	**THS2**, N = 165[1]	**ETSF**, N = 280[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	230 (64%)	155 (76%)	120 (74%)	178 (64%)
Known IHD	34 (9.4%)	30 (15%)	29 (18%)	11 (3.9%)
Congestive Heart Failure	2 (0.6%)	0 (0%)	3 (1.8%)	4 (1.4%)
Hypertension	106 (29%)	69 (33%)	91 (55%)	165 (59%)
Diabetes Mellitus	33 (9.1%)	34 (17%)	27 (16%)	64 (23%)
Post-Traumatic Stress Disorder	22 (6.1%)	59 (29%)	45 (27%)	41 (15%)
Depression	40 (11%)	42 (20%)	26 (16%)	27 (9.7%)
Abnormal Myocardial Perfusion	40 (13%)	10 (5.9%)	29 (18%)	32 (12%)

[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.

15.1.5 Mental Stress Cohorts Description

MIMS and MIPS
Cohort Discription

	MIMS		MIPS	
Characteristic	**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

15.1.6 HRV in Twins Cohorts

Description of HRV

Emory Twins Study

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

[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

The follow section divides the relevant figures and tables into those that pertain to the relationship of autonomic function and myocardial ischemia, including both obstructive coronary artery disease and myocardial perfusion.

15.2.1 Relationship Between Obstructive and Non-Obstructive Coronary Artery Disease

HRV and Obstructive CAD

Emory Cardiovascular Biobank

Characteristic	**Nonobstructive CAD**, N = 29[1]	**Obstructive CAD**, N = 27[1]	**p-value**[2]
RR Interval	733 (655, 932)	868 (786, 922)	0.12
SDNN	27 (17, 54)	43 (26, 52)	0.3
RMSSD	21 (15, 33)	29 (19, 43)	0.3
PNN50	0.02 (0.01, 0.07)	0.06 (0.02, 0.10)	0.2
Ultra Low Frequency	141 (86, 294)	202 (133, 497)	0.2
Very Low Frequency	474 (158, 1,687)	887 (444, 1,347)	0.3
Low Frequency	184 (56, 923)	486 (138, 704)	0.4
High Frequency	193 (94, 865)	327 (148, 687)	0.4
Low/High Frequency Ratio	1.08 (0.49, 1.76)	1.42 (0.73, 1.92)	0.3
Total Power	1,005 (378, 4,144)	1,915 (929, 3,914)	0.4
Acceleration Capacity	-4.71 (-9.54, -3.85)	-7.04 (-10.08, -4.25)	0.4
Deceleration Capacity	4.84 (3.85, 9.36)	6.20 (3.98, 8.96)	0.6
Sample Entropy	1.36 (1.07, 1.47)	1.37 (1.18, 1.61)	0.3
Approximate Entropy	0.94 (0.87, 1.04)	0.88 (0.85, 1.03)	0.3
Dyx	1.72 (1.19, 2.11)	2.07 (1.60, 2.66)	0.093

[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 Effective of Revascularization on Autonomic Function

HRV and Revascularization

Emory Cardiovascular Biobank

HRV Metric	**No Revascularization** N = 14[1]	**Revascularization** N = 34[1]	**p-value**[2]
RR Interval	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
Ultra Low Frequency	99 (56, 269)	200 (130, 477)	0.11
Very Low Frequency	205 (94, 1,465)	826 (414, 1,336)	0.2
Low Frequency	70 (42, 833)	383 (145, 689)	0.2
High Frequency	96 (89, 480)	306 (140, 620)	0.2
Low/High Frequency Ratio	0.99 (0.41, 1.28)	1.45 (0.65, 2.00)	0.2
Total Power	431 (216, 3,156)	1,865 (881, 3,562)	0.2
Acceleration Capacity	-4.12 (-7.06, -2.08)	-6.52 (-9.39, -4.06)	0.3
Deceleration Capacity	4.83 (2.05, 6.49)	5.07 (4.00, 8.58)	0.4
Sample Entropy	1.14 (1.06, 1.39)	1.37 (1.16, 1.56)	0.15
Approximate Entropy	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 that received revascularization, and evaluated for differences in distribution. HRV = Heart Rate Variability, CAD = Coronary Artery Disease.

15.2.3 HRV by Timing of Revascularization

HRV and Timing of Myocardial Reperfusion
Emory Cardiovascular Biobank

	No Revascularization			Revascularization		
ECG Metrics	**Angiography** N = 6[1]	**Before** N = 5[1]	**p-value**[2]	**Balloon** N = 15[1]	**Before** 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 before the procedure started and during the time of coronary angiography (versus intervention). Coronary arteries with obstructive disease are reperfused using balloon angioplasty and potential stenting. HRV = Heart Rate Variability, CAD = Coronary Artery Disease.

15.2.4 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]	PSIMI[1]
Heart Rate			
Rest	1.03 (0.92, 1.16), AUC 0.51	1.15 (1.01, 1.32), AUC 0.54	0.97 (0.85, 1.1), AUC 0.51
Stress	1 (0.9, 1.1), AUC 0.49	1.08 (0.96, 1.21), AUC 0.54	1.02 (0.91, 1.14), AUC 0.5
Recovery	0.98 (0.88, 1.1), AUC 0.52	1.08 (0.96, 1.23), AUC 0.52	0.95 (0.84, 1.06), AUC 0.53
T Wave Area			
Rest	1 (0.99, 1), AUC 0.49	1 (0.98, 1), AUC 0.51	1 (0.99, 1), AUC 0.5
Stress	1 (0.99, 1.01), AUC 0.51	1 (0.98, 1.01), AUC 0.5	1.01 (0.99, 1.02), AUC 0.52
Recovery	1 (0.99, 1.01), AUC 0.51	0.98 (0.97, 1), AUC 0.56	1 (0.99, 1.01), AUC 0.5
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, 1.17), AUC 0.54
Stress	0.7 (0.47, 1.05), AUC 0.54	0.48 (0.31, 0.76), AUC 0.58	0.85 (0.55, 1.31), AUC 0.52
Recovery	0.82 (0.52, 1.27), AUC 0.53	0.62 (0.38, 1.02), AUC 0.55	0.85 (0.53, 1.39), AUC 0.52
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, 1.08), AUC 0.54
Stress	0.64 (0.4, 1.01), AUC 0.56	0.45 (0.27, 0.74), AUC 0.59	0.63 (0.38, 1.03), AUC 0.54
Recovery	0.64 (0.39, 1.04), AUC 0.56	0.43 (0.25, 0.74), AUC 0.59	0.64 (0.38, 1.08), AUC 0.55

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

HRV was measured during the three stages of mental stress challenge and compared in logistic regression models with the results of myocardial perfusion imaging. HRV = heart rate variability, MSIMI = mental stress-induced myocardial ischemia, PSIMI = physical stress-induced myocardial ischemia, AUC = area under receiver-operator curve. Bolded text signifies a p-value < 0.05.

15.2.5 Quantitative Myocardial Perfusion and HRV

Myocardial Perfusion Imaging and Morning HRV
Emory Twins Study

	AC	*Dyx*	HF	LF	VLF
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)	1.18 (1.06, 1.31)
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)	1.17 (1.05, 1.30)
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)	1.11 (1.00, 1.24)
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)	0.78 (0.51, 1.20)
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)	0.75 (0.48, 1.17)
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)	0.77 (0.49, 1.21)

[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

15.2.6 Circadian HRV and Myocardial Perfusion

Circadian HRV and Myocardial Perfusion Abnormalities
Emory Twins Study

	MESOR	Amplitude	Phi
Coronary Flow Reserve			
High Frequency HRV	1.1 (1.01, 1.2)	1.1 (0.98, 1.23)	0.98 (0.94, 1.03)
Low Frequency HRV	1.21 (1.09, 1.34)	1.13 (0.96, 1.34)	1.02 (0.97, 1.06)
Very Low Frequency HRV	1.12 (1.02, 1.24)	1.13 (1.01, 1.26)	1.02 (0.96, 1.09)
Acceleration Capacity	0.97 (0.95, 0.99)	1.01 (0.98, 1.04)	1.03 (0.97, 1.08)
RR Intervals	1 (1, 1)	1 (1, 1)	1 (0.97, 1.04)
Dyx	1.19 (1.08, 1.31)	1.14 (0.99, 1.3)	0.98 (0.92, 1.04)
Abnormal MPI			
High Frequency HRV	1.32 (0.9, 1.92)	1.88 (0.93, 3.8)	0.99 (0.81, 1.2)
Low Frequency HRV	0.88 (0.58, 1.32)	1.14 (0.61, 2.15)	0.92 (0.76, 1.1)
Very Low Frequency HRV	0.88 (0.57, 1.36)	1 (0.63, 1.6)	0.96 (0.75, 1.24)
Acceleration Capacity	0.98 (0.91, 1.05)	1.14 (1.01, 1.28)	0.89 (0.7, 1.15)
RR Intervals	1 (1, 1)	1 (1, 1.01)	0.92 (0.81, 1.05)
Dyx	0.89 (0.61, 1.31)	0.78 (0.4, 1.5)	0.88 (0.7, 1.09)

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 Psychological Stress

The follow section divides the relevant figures and tables into those that pertain to the relationship of autonomic function and psychological stress, including both acute mental stress and chronic psychological stress.

15.3.1 Depression by PHQ-9 and HRV

HRV and Depression by PHQ-9

Emory Cardiovascular Biobank

HRV Metric	**No Depression**, N = 38[1]	**Depression**, N = 10[1]	**p-value**[2]
RR Interval	872 (738, 929)	727 (689, 920)	0.6
SDNN	37 (21, 54)	26 (16, 44)	0.6
RMSSD	25 (19, 36)	16 (13, 26)	0.13
PNN50	0.03 (0.01, 0.09)	0.01 (0.01, 0.04)	0.089
Ultra Low Frequency	233 (108, 405)	173 (81, 358)	>0.9
Very Low Frequency	887 (310, 1,613)	444 (227, 1,561)	0.7
Low Frequency	486 (109, 725)	138 (67, 617)	0.6
High Frequency	306 (117, 824)	99 (51, 316)	0.14
Low/High Frequency Ratio	1.35 (0.64, 1.90)	1.28 (1.01, 1.98)	0.9
Total Power	1,865 (660, 3,914)	929 (438, 2,786)	0.5
Acceleration Capacity	-6.52 (-10.22, -4.21)	-3.88 (-7.42, -2.64)	0.3
Deceleration Capacity	5.2 (4.0, 9.0)	4.0 (3.1, 7.5)	0.4
Sample Entropy	1.41 (1.14, 1.62)	1.34 (1.07, 1.50)	0.4
Approximate Entropy	0.92 (0.85, 1.04)	0.99 (0.93, 1.04)	0.4
Dyx	1.75 (1.29, 2.57)	2.07 (1.76, 2.69)	0.4

[1]Median (IQR)

[2]Wilcoxon rank sum exact test

In patients undergoing angiography, HRV metrics were described in those with moderate to severe depressive symptoms to those with mild to minimal symptoms by PHQ-9. HRV = Heart Rate Variability, PHQ-9 = Patient Health Questionnaire.

15.3.2 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

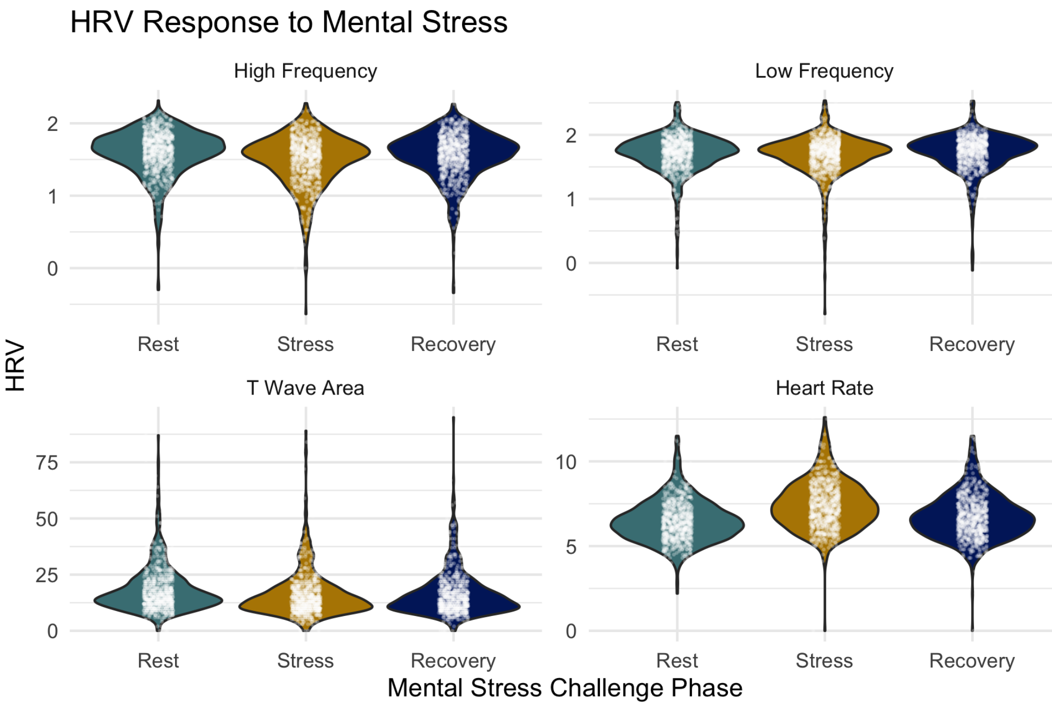
15.3.3 Circadian HRV and Chronic Mental Stress

Circadian HRV and Chronic Psychological Stress
Emory Twins Study

	MESOR	Amplitude	Phi
PTSD			
High Frequency HRV	0.61 (0.42, 0.88)	0.28 (0.09, 0.84)	1.16 (0.96, 1.4)
Low Frequency HRV	0.46 (0.31, 0.69)	0.31 (0.13, 0.72)	1.02 (0.86, 1.21)
Very Low Frequency HRV	0.56 (0.36, 0.87)	0.49 (0.28, 0.86)	1.1 (0.87, 1.39)
Acceleration Capacity	1.13 (1.03, 1.25)	0.75 (0.6, 0.94)	0.87 (0.71, 1.08)
RR Intervals	1 (1, 1)	1 (1, 1.01)	0.99 (0.86, 1.13)
Dyx	0.67 (0.47, 0.95)	0.93 (0.57, 1.51)	1.16 (0.94, 1.44)
Depression			
High Frequency HRV	0.43 (0.27, 0.69)	0.42 (0.22, 0.82)	1.09 (0.89, 1.35)
Low Frequency HRV	0.26 (0.15, 0.45)	0.31 (0.14, 0.68)	1.06 (0.86, 1.31)
Very Low Frequency HRV	0.24 (0.13, 0.45)	0.26 (0.13, 0.5)	1.12 (0.83, 1.53)
Acceleration Capacity	1.25 (1.11, 1.41)	0.79 (0.67, 0.94)	0.94 (0.73, 1.21)
RR Intervals	1 (1, 1)	1 (1, 1.01)	0.9 (0.78, 1.04)
Dyx	0.35 (0.23, 0.55)	0.61 (0.33, 1.12)	0.95 (0.75, 1.21)

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

15.3.4 HRV and Mental Stress Challenge



The distribution of HRV and ECG findings in different phases of mental stress challenges.

15.3.5 Distribution of HRV and Mental Stress Challenge

Difference between Mental Stress Challenge Phases and ECG Metrics
MIMS/MIPS Cohorts

	Mean (95% CI)	T-statistic
Heart Rate		
Stress	1.0 (0.9, 1.0)	22.1
Recovery	0.3 (0.2, 0.3)	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

HRV summarised during stress and recovery phase of the mental stress challenge were compared to rest HRV. HRV = heart rate variability.

15.3.6 Distribution of HRV and MSIMI

HRV distribution by MSIMI

MIMS/MIPS cohorts

Characteristic	**MSIMI = 0**, N = 710[1]	**MSIMI = 1**, N = 243[1]	**p-value**[2]
Heart Rate			
Rest	6.40 (5.60, 7.20)	6.40 (5.88, 7.50)	0.090
Stress	7.30 (6.40, 8.30)	7.50 (6.60, 8.50)	0.092
Recovery	6.65 (5.90, 7.40)	6.60 (5.90, 7.80)	0.5
T Wave Area			
Rest	16 (12, 23)	16 (12, 23)	0.8
Stress	14 (10, 19)	14 (10, 20)	0.9
Recovery	15 (10, 20)	13 (9, 19)	0.024
High Frequency HRV			
Rest	1.65 (1.48, 1.81)	1.61 (1.39, 1.76)	0.017
Stress	1.57 (1.34, 1.74)	1.48 (1.22, 1.65)	<0.001
Recovery	1.62 (1.43, 1.78)	1.55 (1.35, 1.74)	0.034
Low Frequency HRV			
Rest	1.76 (1.60, 1.89)	1.70 (1.49, 1.86)	0.010
Stress	1.74 (1.59, 1.87)	1.66 (1.48, 1.81)	<0.001
Recovery	1.79 (1.61, 1.91)	1.71 (1.52, 1.85)	<0.001

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

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.

15.3.7 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	1.15 (1.01, 1.3), AUC 0.55	1.33 (1.11, 1.58), AUC 0.6
Stress	1.01 (0.9, 1.13), AUC 0.51	1.04 (0.88, 1.22), AUC 0.53
Recovery	1.09 (0.97, 1.22), AUC 0.54	1.14 (0.96, 1.35), 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.

15.3.8 Modeling Mental Stress-Induced Myocardial Ischemia and HRV

Mental Stress-Induced Myocardial Ischemia and HRV
MIMS/MIPS Cohorts

Sequential Models	Stress LF	Rest LF	Stress HF	Rest HF
Model 1	0.45 (0.27, 0.74), AUC 0.59	0.53 (0.31, 0.92), AUC 0.56	0.48 (0.31, 0.76), AUC 0.58	0.57 (0.34, 0.95), AUC 0.56
Model 2	0.49 (0.29, 0.81), AUC 0.64	0.59 (0.34, 1.04), AUC 0.62	0.45 (0.28, 0.72), AUC 0.64	0.49 (0.29, 0.85), AUC 0.62
Model 3	0.51 (0.3, 0.87), AUC 0.63	0.64 (0.36, 1.13), AUC 0.62	0.48 (0.29, 0.77), AUC 0.64	0.53 (0.3, 0.93), AUC 0.62
Model 4	0.53 (0.31, 0.91), AUC 0.65	0.65 (0.36, 1.15), AUC 0.63	0.49 (0.3, 0.79), AUC 0.65	0.54 (0.31, 0.96), AUC 0.64
Model 5	0.52 (0.3, 0.91), AUC 0.65	0.66 (0.36, 1.18), AUC 0.63	0.47 (0.29, 0.77), AUC 0.66	0.54 (0.3, 0.95), AUC 0.63

[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

The follow section divides the relevant figures and tables into those describing the relationship between autonomic dysfunction and clinical outcomes.

15.4.1 Outcomes in Twins

Clinical Outcomes by HRV

Emory Twins Study

	Acceleration Capacity	Dyx	High Frequency HRV	Low Frequency HRV	Very Low Frequency HRV
Cardiovascular Death					
Model 1	1.04 (0.97, 1.11)	0.64 (0.51, 0.81)	0.84 (0.62, 1.13)	0.75 (0.54, 1.03)	0.64 (0.44, 0.92)
Model 2	1.03 (0.96, 1.1)	0.65 (0.5, 0.84)	0.81 (0.59, 1.12)	0.83 (0.58, 1.18)	0.67 (0.45, 1.01)
Model 3	1.03 (0.96, 1.1)	0.66 (0.51, 0.85)	0.82 (0.6, 1.13)	0.86 (0.59, 1.25)	0.68 (0.45, 1.04)
Model 4	1.03 (0.96, 1.12)	0.69 (0.53, 0.9)	0.79 (0.58, 1.09)	0.86 (0.57, 1.29)	0.76 (0.5, 1.18)
Model 5	1.03 (0.95, 1.12)	0.68 (0.52, 0.89)	0.8 (0.58, 1.11)	0.86 (0.57, 1.29)	0.77 (0.49, 1.21)
All Cause Mortality					
Model 1	1.12 (1.01, 1.23)	0.49 (0.35, 0.68)	0.72 (0.48, 1.09)	0.5 (0.33, 0.75)	0.43 (0.27, 0.68)
Model 2	1.12 (1, 1.26)	0.44 (0.3, 0.65)	0.64 (0.4, 1.01)	0.49 (0.31, 0.79)	0.4 (0.23, 0.69)
Model 3	1.13 (1.01, 1.27)	0.39 (0.26, 0.6)	0.64 (0.41, 1)	0.51 (0.32, 0.83)	0.41 (0.23, 0.73)
Model 4	1.12 (1, 1.26)	0.41 (0.27, 0.64)	0.66 (0.43, 1.03)	0.54 (0.32, 0.9)	0.44 (0.25, 0.8)
Model 5	1.11 (0.98, 1.24)	0.41 (0.27, 0.64)	0.71 (0.45, 1.12)	0.55 (0.32, 0.95)	0.49 (0.27, 0.88)

[1] Model 1 = HRV
[2] Model 2 = Model 1 + Myocardial Perfusion Imaging
[3] Model 3 = Model 2 + Age + BMI + Race
[4] Model 4 = Model 3 + Cardiovascular Disease + Hypertension + Diabetes + Smoking
[5] Model 5 = Model 4 + Depression + PTSD

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

15.4.2 Circadian Outcomes in Twins

Clinical Outcomes by Circadian HRV

Emory Twins Study

	MESOR	Amplitude	Phi
All Cause Mortality			
High Frequency HRV	0.64 (0.32, 1.26)	0.73 (0.29, 1.82)	1.38 (0.95, 1.99)
Low Frequency HRV	0.32 (0.16, 0.67)	0.37 (0.12, 1.15)	1.08 (0.79, 1.47)
Very Low Frequency HRV	0.36 (0.15, 0.89)	0.31 (0.05, 1.91)	1.32 (0.81, 2.16)
Acceleration Capacity	1.15 (0.98, 1.36)	0.83 (0.61, 1.13)	1.05 (0.74, 1.5)
RR Intervals	1 (1, 1)	0.99 (0.98, 1)	1.04 (0.83, 1.3)
Dyx	0.34 (0.21, 0.56)	0.42 (0.22, 0.79)	0.93 (0.67, 1.28)
Cardiovascular Death			
High Frequency HRV	0.83 (0.53, 1.32)	0.7 (0.17, 2.85)	1.13 (0.91, 1.42)
Low Frequency HRV	0.6 (0.33, 1.07)	0.66 (0.26, 1.65)	0.96 (0.76, 1.21)
Very Low Frequency HRV	0.64 (0.32, 1.3)	0.31 (0.04, 2.27)	1.05 (0.77, 1.42)
Acceleration Capacity	1.1 (0.97, 1.25)	0.8 (0.59, 1.1)	1.11 (0.88, 1.39)
RR Intervals	1 (1, 1)	0.99 (0.98, 1)	0.97 (0.83, 1.14)
Dyx	0.42 (0.28, 0.62)	0.54 (0.34, 0.85)	0.88 (0.68, 1.13)

The HRV metrics are measured over 24 hours using cosinor statistics. Every unit increase in HRV had an associated hazard ratio (95% CI) for both overall and cardiovascular mortality. 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

15.4.3 Outcomes in MIMS/MIPS

Outcomes Analysis for Mental Stress and HRV

Traditional and Recurrent Event Models in MIMS/MIPS

	Death	Cardiovascular Death	Marginal	PWP Total Time	PWP Gap Time	Anderson Gill
Stress Low Frequency HRV						
Model 1	0.39 (0.24, 0.64)	0.32 (0.18, 0.57)	0.52 (0.34, 0.8)	0.49 (0.29, 0.8)	0.51 (0.31, 0.81)	0.52 (0.34, 0.8)
Model 2	0.42 (0.25, 0.68)	0.32 (0.18, 0.58)	0.54 (0.35, 0.84)	0.5 (0.3, 0.85)	0.53 (0.32, 0.85)	0.54 (0.35, 0.84)
Model 3	0.37 (0.22, 0.63)	0.24 (0.12, 0.46)	0.52 (0.33, 0.82)	0.47 (0.27, 0.84)	0.5 (0.3, 0.84)	0.52 (0.33, 0.82)
Model 4	0.38 (0.21, 0.7)	0.25 (0.12, 0.52)	0.58 (0.36, 0.95)	0.48 (0.27, 0.86)	0.51 (0.3, 0.85)	0.58 (0.36, 0.95)
Model 5	0.37 (0.2, 0.7)	0.24 (0.11, 0.51)	0.51 (0.31, 0.84)	0.52 (0.28, 0.94)	0.53 (0.31, 0.92)	0.51 (0.31, 0.84)
Model 6	0.4 (0.2, 0.77)	0.25 (0.11, 0.56)	0.5 (0.3, 0.85)	0.54 (0.29, 1)	0.55 (0.31, 0.97)	0.5 (0.3, 0.85)
Stress High Frequency HRV						
Model 1	0.45 (0.26, 0.77)	0.32 (0.17, 0.61)	0.65 (0.43, 0.98)	0.51 (0.32, 0.8)	0.57 (0.38, 0.85)	0.65 (0.43, 0.98)
Model 2	0.48 (0.27, 0.83)	0.32 (0.16, 0.62)	0.68 (0.44, 1.04)	0.53 (0.33, 0.85)	0.6 (0.4, 0.9)	0.68 (0.44, 1.04)
Model 3	0.44 (0.25, 0.78)	0.28 (0.14, 0.56)	0.64 (0.42, 0.99)	0.54 (0.33, 0.87)	0.59 (0.39, 0.91)	0.64 (0.42, 0.99)
Model 4	0.5 (0.27, 0.92)	0.3 (0.14, 0.65)	0.71 (0.45, 1.14)	0.55 (0.34, 0.89)	0.61 (0.4, 0.94)	0.71 (0.45, 1.14)
Model 5	0.5 (0.26, 0.93)	0.3 (0.13, 0.66)	0.65 (0.4, 1.07)	0.57 (0.35, 0.95)	0.63 (0.41, 0.98)	0.65 (0.4, 1.07)
Model 6	0.57 (0.3, 1.12)	0.31 (0.14, 0.72)	0.66 (0.39, 1.1)	0.61 (0.37, 1.03)	0.67 (0.43, 1.05)	0.66 (0.39, 1.1)

[1]Model 1 = MSIMI ~ HRV

[2]Model 2 = Model 1 + MSIMI

[3]Model 3 = Model 2 + Age + BMI + Sex + Race

[4]Model 4 = Model 3 + Smoking + Diabetes + Hypertension + Hyperlipidemia

[5]Model 5 = Model 4 + Known Coronary/Peripheral Artery Disease

[6]Model 6 = Model 5 + Depression + Post-Traumatic Stress Disorder

This summarises the Cox proportional hazard models for both censoring events and for recurrent event analyses. Estimates = HR (95% CI). Bolded terms signify p-value < 0.05. PWP = Prentice, Williams, and Peterson models, MSIMI = Mental Stress-Induced Myocardial Ischemia, LF = Low Frequency, HF = High Frequency, HRV = Heart Rate Variability