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ORIGINAL RESEARCH

Cardiovascular Reactivity to Mental Stress and Adverse Cardiovascular Outcomes in Patients With Coronary Artery Disease

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BACKGROUND: Acute psychological stress may induce physiological changes predisposing individuals to adverse health outcomes through hemodynamic and vascular effects. We studied the association between the aggregated stress-induced changes in hemodynamic and vascular function tests with adverse cardiovascular outcomes in patients with coronary artery disease, after adjusting for sociodemographic and clinical factors.

METHODS AND RESULTS: Individuals with stable coronary artery disease from 2 prospective cohort studies were studied. Hemodynamic reactivity, changes in endothelial function, and vasoconstriction during mental stress were evaluated using changes in rate-pressure product, brachial artery flow-mediated vasodilation, and peripheral arterial tonometry, respectively. A cardiovascular reactivity risk score was calculated by allotting 0 to 3 points for each quartile of increasing abnormality for each of the 3 reactivity responses and summing the quartile points from the MIPS (Mental Stress Ischemia Prognosis Study) to yield a cardiovascular reactivity risk score ranging from 0 to 9. The outcome was a composite of cardiovascular death, nonfatal myocardial infarction, and heart failure hospitalizations during follow-up. A total of 629 participants were included. After adjustment for demographic and traditional risk factors, a blunted hemodynamic response, a greater decrease in flow-mediated vasodilation, and a greater degree of peripheral vasoconstriction to mental stress were all independently associated with a higher risk of adverse outcomes in both cohorts. By adding the cardiovascular reactivity risk score, the C-statistic increased significantly by 10% (P<0.001).

CONCLUSIONS: Among individuals with stable coronary artery disease, a risk score derived from cardiovascular reactivity to mental stress was predictive of adverse cardiovascular outcomes beyond traditional cardiovascular risk factors.

Key Words: adverse outcomes ■ coronary artery disease ■ endothelial function ■ hemodynamic reactivity ■ mental stress ■ vasoconstriction

Individuals with established coronary artery disease (CAD) have an increased risk of morbidity and mortality.[1] The identification of factors that might contribute to this increased risk may lead to improved outcomes in this population. One such factor is psychological stress, which has been linked to both the development and progression of CAD.[2] The laboratory-based assessment of cardiovascular reactivity to a mental stress challenge has been adopted as a valuable strategy to help gain insight into stress response physiology that may be detrimental for cardiovascular health. We and others have shown that a low or blunted hemodynamic

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CLINICAL PERSPECTIVE

What Is New?

- A higher cardiovascular reactivity risk score, which is based on blunted hemodynamic reactivity, endothelial dysfunction, and greater degree of peripheral vasoconstriction during mental stress, is associated with worse outcomes in patients with coronary artery disease.

What Are the Clinical Implications?

- Development of the cardiovascular reactivity risk score improves our ability to identify high-risk groups with coronary artery disease based on their psychological stress response physiology.

Nonstandard Abbreviations and Acronyms

CRR	cardiovascular reactivity risk
FMD	flow-mediated vasodilation
MIPS	Mental Stress Ischemia Prognosis Study
MIMS2	Myocardial Infarction and Mental Stress Study 2
PAT	peripheral arterial tonometry
RPP	rate-pressure product

response to acute mental stress, as measured by changes in rate-pressure product (RPP) with stress, is linked to a higher risk for adverse outcomes in the CAD population.[3–5] Additionally, our group and others have demonstrated that an acute mental stress challenge can induce transient endothelial dysfunction, evident as a decrease in brachial artery flow-mediated vasodilation (FMD), and that this reduction in FMD with stress is associated with worse outcomes as compared with those without endothelial dysfunction with stress.[6–8] Finally, we have previously investigated peripheral microvascular constriction, measured using peripheral arterial tonometry (PAT)-derived changes in the digital pulse amplitude during mental stress, and have found that greater peripheral vasoconstriction, calculated as a ratio of digital pulse amplitude with stress compared with rest (PAT ratio <1), was associated with worse cardiovascular outcomes.[9] However, it is unclear whether these responses are interconnected or if they independently contribute to worse cardiovascular outcomes.

Herein, we examine the combined prognostic value of hemodynamic and vascular (endothelial and vasoconstrictive) responses to stress in 2 parallel cohorts of patients with stable CAD. We hypothesized that each of these 3 cardiovascular reactivity indices are independently associated with incident adverse cardiovascular outcomes and that a cardiovascular reactivity risk (CRR) score derived combining all 3 indices would provide additional prognostic information compared with traditional risk models.

METHODS

Study Participants and Protocol Overview

The data that support the findings of this study are available from the corresponding author upon reasonable request. Between 2011 and 2016, we recruited individuals with stable CAD in 2 parallel studies that followed similar protocols: the MIPS (Mental Stress Ischemia Prognosis Study)[10] and the MIMS2 (Myocardial Infarction and Mental Stress Study 2).[11] In both cohorts, patients with stable CAD were enrolled from hospitals and clinics affiliated with Emory University and shared protocols, staff, facilities, and equipment. For the MIPS cohort, participants were included if they were 30 to 79 years of age and had a documented history of CAD. For the MIMS2 cohort, inclusion criteria included a verified myocardial infarction within the past 8 months and age between 18 and 60 years at the time of the myocardial infarction. MIMS2 also included 50% women by design. Patients were excluded from either study if they were pregnant or had medical comorbidities that would shorten life expectancy. The research protocol for both study cohorts was approved by the Institutional Review Board of Emory University and all participants provided written informed consent.

Mental Stress Procedure

After a 12-hour fast, all patients underwent mental stress testing in the morning. Following a 30-minute rest in a quiet room, we conducted the mental stress test, which was induced by a standardized public speaking task as previously described.[10] Each patient was given 2 minutes to prepare a speech and 3 minutes to deliver it in front of an evaluative audience of at least 4 people wearing laboratory coats.

Hemodynamic and Vascular Function Measurements

We monitored blood pressure and heart rate during the resting stage (every 5 minutes) and during the entire mental stress testing including both preparation and speaking and stress test (every 1 minute). We calculated the RPP as the mean systolic blood pressure × the mean heart rate. RPP reactivity was calculated as the maximum RPP during stress minus the minimum RPP at rest.

We measured endothelium-dependent brachial artery FMD to evaluate conductance artery endothelial function using ultrasonography (Acuson 10-mHz linear-array transducer [Acuson]), before and 30 minutes after the mental stress test, as described previously.[12–14]

The PAT (Itamar-Medical, Israel) device was used to measure digital arterial pulse wave amplitude continuously during rest and mental stress testing, as previously described.[15,16] Briefly, the PAT device was positioned on the index finger of the contralateral side to blood pressure measurement and applies a constant subdiastolic pressure over the distal two thirds of the finger to prevent distal venous blood stasis, unload arterial wall tension, and stabilize the probe to reduce noise. As a result, the changes in pulsatile volume reflect only changes in digital arterial blood perfusion. The baseline pulse wave amplitude during rest was determined by averaging the last 3 minutes of recording that preceded the mental stress test. The pulse wave amplitude during the mental stress test was determined visually as the area of maximum vasoconstriction during the speaking period with a duration 30 seconds to 2 minutes. sPAT ratio during mental stress was calculated as the ratio of pulse wave amplitudes during mental stress over the resting baseline, such that a ratio <1 signifies peripheral arterial vasoconstriction during mental stress.

Calculation of the Cardiovascular Reactivity Risk Score

The distribution of each cardiovascular reactivity indices is shown in Figure S1. For each individual in the MIPS cohort, a CRR score was calculated by allotting 0 to 3 points for each quartile of increasing abnormality for each of the 3 reactivity responses (changes in RPP, FMD, and sPAT ratio with mental stress). The quartile points were summed across measures to yield a CRR score ranging from 0 to 9. To replicate findings in the MIPS cohort, the cutoff values from the MIPS cohort were used to calculate the CRR score for the MIMS2 cohort (validation cohort).

Other Measures

Information on demographics (age, sex, and race), clinical factors (history of smoking, body mass index, history of hypertension, diabetes, heart failure, left ventricular ejection fraction, and previous myocardial infarction,) and medications (β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin) was obtained using standardized questionnaires and chart reviews. Depressive symptoms were assessed with the Beck Depression Inventory II,[17] general stress with the 10-item Cohen Perceived Stress Scale, and state anxiety with the Spielberger State–Trait Anxiety Inventory.[18]

Follow-Up and Study Outcomes

We collected follow-up data through patient contacts, review of medical records, and the Social Security Death Index. If any hospitalizations or procedures were reported, patients' physicians were contacted and hospital records were obtained.[10,19–22] Patients from the MIPS cohort were contacted at 6-month intervals for the first 3 years and then at 5 years.[10,20,21] Individuals from the MIMS2 cohort were contacted at their approximate 3- and 5-year anniversary from the initial visit.[19,22] Clinical events were adjudicated by study cardiologists blinded to other study data. The end point was a composite of cardiovascular death, nonfatal myocardial infarction, and hospitalizations for heart failure.

Statistical Analysis

Continuous variables are presented as mean±SD or median (interquartile range), and categorical variables are presented as proportions. Linear regression models were used to examine the association between the CRR score and sociodemographic factors, medical history factors, medication use, and psychological factors. We tested for multicollinearity using the Variance Inflation Factor and confirmed that none of the covariates entered in our model met criteria for collinearity. Fine and Gray's subdistribution hazard models were constructed to assess the association between each of the mental stress reactivity indices and the study end points while treating noncardiovascular death as a competing risk.[23] Cumulative event rate plots were calculated for tertiles of CRR score. Subgroup analyses were also performed to examine whether the association of CRR score with outcomes varied according to a priori selected strata, including age (≤60 versus >60 years), sex, race (Black versus non-Black), previous myocardial infarction, diabetes, and history of heart failure by adding the corresponding interactions in the models. We tested the incremental value of adding the CRR score to a model that included sociodemographic, traditional risk factors, current medications, and psychological factors. The Harrell C statistic (ie, area under the receiver operating characteristic curve), and category-free net reclassification improvement, were calculated as indices of risk discrimination.[24] Significance testing was 2 sided with a significance threshold of $P<0.05$, and all statistical analyses were performed using Stata software, version 14.0 (StataCorp).

RESULTS

Study Population

Demographic and clinical characteristics of the MIPS and MIMS2 cohorts are shown in Table 1. A total of

Table 1. Baseline Characteristics of the 2 Study Cohorts

	MIPS (N=411)	MIMS2 (N=218)
Demographic factors		
Age, y, mean±SD	63 (8.7)	51 (6.6)
Male sex, n (%)	327 (79.6)	108 (49.5)
Black, n (%)	105 (25.8)	142 (65.1)
College education, n (%)	300 (73.0)	129 (59.2)
Cardiovascular risk factors		
Body mass index, mean±SD, kg/m^2	29.5 (5.0)	31.6 (7.2)
Diabetes, n (%)	132 (32.1)	67 (30.7)
Dyslipidemia, n (%)	342 (83.2)	181 (83.0)
Hypertension, n (%)	310 (75.4)	173 (79.4)
Smoking status, n (%)		
Ever smoker	257 (62.5)	117 (53.7)
Current smoker	200 (48.7)	52 (23.9)
Clinical characteristics		
Coronary artery revascularization, n (%)	220 (53.5)	180 (82.6)
Left ventricular ejection fraction, mean±SD	66.3 (13.6)	50.0 (12.1)
History of myocardial infarction, n (%)	132 (32.1)	281 (100)
History of heart failure, n (%)	52 (12.7)	20 (9.2)
Medications		
Aspirin, n (%)	359 (87.3)	176 (80.7)
Statin, n (%)	351 (85.4)	186 (85.3)
Angiotensin-converting enzyme inhibitor, n (%)	181 (44.0)	102 (46.8)
Beta blocker, n (%)	294 (71.5)	186 (85.3)
Clopidogrel, n (%)	125 (30.4)	155 (71.1)
Antidepressants, n (%)	91 (22.1)	34 (15.6)
Psychological factors, mean±SD		
Beck Depression Inventory II	8.1 (8.8)	11.8 (10.3)
Cohen Perceived Stress Scale	11.9 (7.7)	16.5 (8.3)
State anxiety	30.9 (11.5)	36.3 (12.8)
Events		
Cardiovascular death, n (%)	42 (10.2)	16 (7.3)
Myocardial infarction, n (%)	32 (7.8)	24 (11.0)
Heart failure hospitalization, n (%)	12 (2.9)	13 (6.0)

MIMS2 indicates Myocardial Infarction and Mental Stress Study 2; and MIPS, Mental Stress Ischemia Prognosis Study.

629 (411 in MIPS and 218 in MIMS2) individuals had information on all 3 cardiovascular reactivity indices and were included in the final analyses. By design, participants in MIMS2 were younger and had higher proportions of women and Black subjects than those in MIPS. Resting systolic blood pressure and heart rate were similar in both groups, whereas the MIMS2 patients had a higher baseline diastolic blood pressure (Table 2). Following mental stress challenges, the systolic blood pressure increased similarly in both cohorts, but individuals in the MIMS2 cohort showed higher increases in diastolic blood pressure and heart rate with mental stress. Participants in the MIMS2 cohort had a lower FMD at baseline and also showed larger decreases in FMD with mental stress compared with MIPS patients (Table 2). Additionally, MIMS2 patients had a lower resting pulse wave amplitude compared with the MIPS cohort, but both groups showed similar degrees of vasoconstriction in response to mental stress (sPAT ratio) (Table 2).

Association Between Cardiovascular Reactivity Indices and Adverse Cardiovascular Outcomes

Participants were followed for a median of 6.0 years (interquartile range, 5.5–6.0 years) in MIPS and 4.5 years (interquartile range, 3.7–5.2 years) in MIMS2. The composite end point of incident cardiovascular death, nonfatal myocardial infarction, or heart failure hospitalizations occurred in 86 (20.9%) and 53 (24.3%) individuals in MIPS and MIMS2, respectively. As shown in Table 3, the unadjusted hazard ratio (HR) for cardiovascular death, myocardial infarction or heart failure hospitalizations for every SD lower RPP reactivity with mental stress was 1.61 (95% CI, 1.23–2.08), and 1.31 (95% CI, 1.14–1.53) for MIPS and MIMS2, respectively. Similarly, for every SD worsening of endothelial function (lower FMD) and greater degree of peripheral vasoconstriction (lower sPAT ratio), the unadjusted HR

Table 2. Mental Stress Testing Characteristics of the 2 Study Cohorts

	MIPS (N=411)	MIMS2 (N=218)
Hemodynamic characteristics, mean±SD		
Blood pressure, baseline, mm Hg		
Systolic	134.6 (17.6)	133.9 (22.1)
Diastolic	77.9 (9.6)	83.1 (12.6)
Heart rate, baseline, beats/min	63.3 (10.1)	63.7 (10.3)
RPP, baseline, per 1000	7.7 (1.7)	7.3 (1.9)
Blood pressure, change, mm Hg		
Systolic	40.3 (17.1)	40.1 (16.6)
Diastolic	23.7 (10.9)	28.6 (11.3)
Heart rate, change, beats/min	16.3 (9.4)	22.4 (13.2)
RPP, change, per 1000	5.2 (2.4)	6.0 (2.8)
Endothelial function, mean±SD		
Flow-mediated vasodilation, baseline, %	4.8 (3.7)	3.8 (2.8)
Flow-mediated vasodilation, change, %	−0.98 (2.9)	−1.6 (2.1)
Peripheral vasoconstriction, mean±SD		
Rest pulse amplitude	2.1 (0.6)	1.7 (0.5)
Peripheral arterial tonometry ratio (stress/rest pulse amplitude)	0.72 (0.33)	0.78 (0.46)

MIMS2 indicates Myocardial Infarction and Mental Stress Study 2; MIPS, Mental Stress Ischemia Prognosis Study; and RPP, rate-pressure product.

Table 3. Association Between Maladaptive Stress Responses to Mental Stress and Composite End Point of Cardiovascular Death, Nonfatal Myocardial Infarction, and Hospitalizations for Heart Failure in Patients With Coronary Artery Disease

	RPP	FMD	sPAT ratio
	HR (95% CI)		
MIPS			
Model 1	1.61 (1.23–2.08)	1.49 (1.25–1.78)	1.28 (1.06–1.64)
Model 2	1.60 (1.21–2.05)	1.33 (1.12–1.58)	1.21 (1.05–1.59)
Model 3	1.58 (1.20–2.03)	1.18 (1.09–1.33)	1.09 (1.02–1.35)
MIMS2			
Model 1	1.31 (1.14–1.53)	1.35 (1.14–1.59)	1.12 (1.06–1.32)
Model 2	1.28 (1.10–1.48)	1.29 (1.10–1.48)	1.07 (1.03–1.26)
Model 3	1.24 (1.08–1.42)	1.21 (1.08–1.42)	1.05 (1.02–1.25)

Data shown for every SD decrease in RPP, FMD, and sPAT ratio. Model 1: unadjusted. Model 2: adjusted for sociodemographics (age, sex, race, and college education), cardiovascular risk factors and other relevant medical factors (smoking, body mass index, history of hypertension, diabetes, heart failure, and previous myocardial infarction). Model 3: adjusted for Model 2+peripheral vasoconstriction, endothelial dysfunction and blunted hemodynamic response. FMD indicates flow-mediated vasodilation; MIMS2, myocardial infarction and mental stress study 2; MIPS, mental stress ischemia prognosis study; RPP, rate-pressure product; and sPAT ratio, Stress induced peripheral arterial tonometry.

for the composite adverse events were 1.49 (95% CI, 1.25–1.78) and 1.28 (95% CI, 1.06–1.64) for MIPS and 1.35 (95% CI, 1.14–1.59) and 1.12 (95% 1.06v1.32) for MIMS2, respectively. Further adjustment for demographic, clinical, and psychological factors and medications did not affect the association substantially (Table 3, Model 2). When all 3 cardiovascular reactivity indices were included in the fully adjusted model (Model 3), all 3 indices were independently associated with outcomes in both the MIPS and MIMS2 cohorts. The magnitude of this association was greatest for a low hemodynamic response to mental stress, followed by worsening endothelial function and greater vasoconstriction in both cohorts (Table 3, Model 3).

Association Between the Cardiovascular Reactivity Risk Score and Baseline Characteristics and Future Outcomes

The mean±SD CRR score was 4.5 (1.8) and 4.4 (1.7) for the MIPS and MIMS2 cohort, respectively (Figure S2). In unadjusted analyses from the MIPS cohort, a higher CRR score was associated with a higher body mass index, history of heart failure, use of antidepressants, and higher score for depressive symptoms (Beck Depression Inventory score) (Table S1). On multivariable linear regression analyses, a higher CRR score remained significantly associated with a higher body mass index and history of heart failure (Table S1).

In a Cox proportional hazards regression analysis adjusted for demographic, clinical, and psychological factors and medications, every unit increase in the CRR score was associated with an 18% increase in the hazard of future events (HR, 1.18 [95% CI 1.06–1.33]) in the MIPS cohort. Similar results were obtained when applying the CRR risk score to the MIMS2 cohort (HR, 1.15 [95% CI 1.03–1.31]). Cumulative incidence curves for both cohorts demonstrated a dose–response relationship, with higher CRR scores corresponding with higher risk of future cardiovascular events (Figure). Sensitivity analysis showed that the association between RPP reactivity with mental stress and the risk of future events was similar across subgroups stratified by baseline demographics including age (≤60 versus >60 years), sex, race (Black versus non-Black), and clinical characteristics such as previous myocardial infarction, diabetes, and history of heart failure (Figure S3).

Risk Discrimination

Using the pooled sample, we tested the incremental value of adding the CRR score to a statistical model with baseline demographics and traditional and psychosocial risk factors in predicting future outcomes. The C-statistic increased significantly with the addition of the risk score by 10% (P<0.001) (Table 4). The continuous net-reclassification-improvement metric also showed significant reclassification of participant risk after adding the CRR score by 44% (P<0.001) (Table 4).

DISCUSSION

In a retrospective analysis of 2 separate cohorts of patients with CAD, we showed that blunted hemodynamic response, greater reduction in endothelial function, and greater degree of peripheral vasoconstriction in response to acute mental stress were all independently associated with a higher risk of incident adverse cardiovascular events. By combining all 3 indices of cardiovascular reactivity in response to mental stress into a CRR score, a measure of maladaptive cardiovascular reactivity to stress, we demonstrated a progressive increase in the risk of future cardiovascular events with increasing level of the risk score. Finally, addition of the CRR score was associated with significant improvements in the discrimination of future risk of adverse outcomes compared with a standard clinical model. These findings demonstrate that these maladaptive responses to mental stress increase the risk of cardiovascular events in patients with CAD through distinct hemodynamic and vascular mechanisms. Second, such an evaluation identifies individuals with stable CAD who have higher residual risk and opens the door to investigating interventions designed to normalize these responses and thus reduce risk.

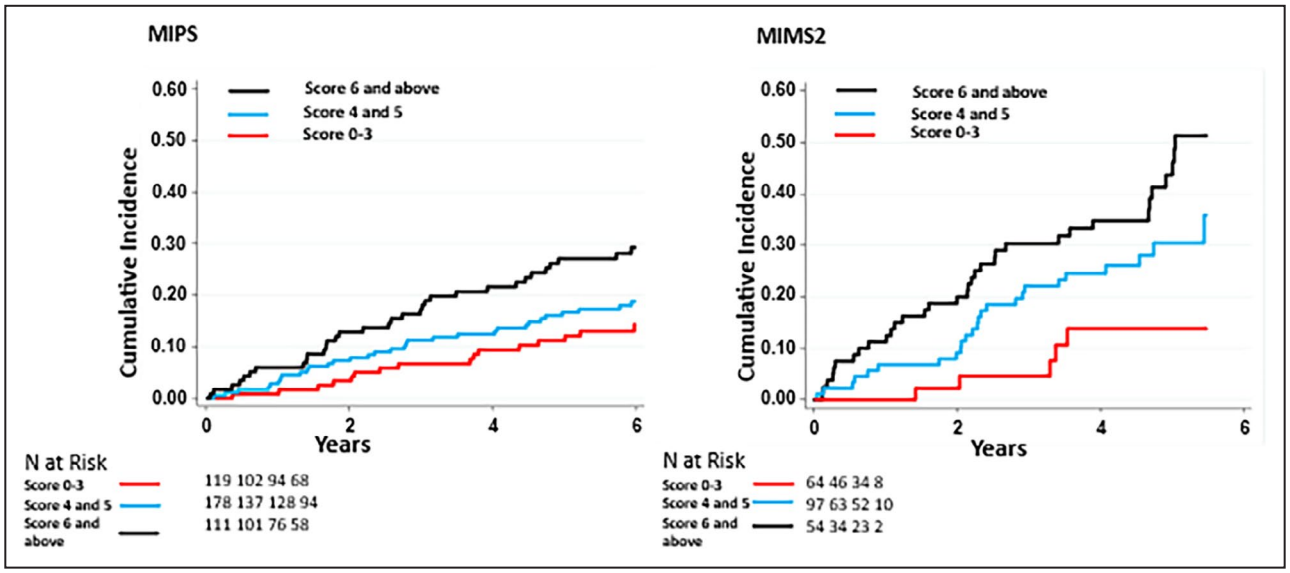

Figure. Cumulative incidence of cardiovascular death, nonfatal myocardial infarction, and heart failure hospitalization in each of the 2 study populations with respect to tertiles of cardiovascular reactivity risk score.
Compared with the reference group (score 0–3), patients in the highest tertile of cardiovascular reactivity risk score had the highest risk of adverse events (HR, 1.96 [95% CI, 1.05–3.55]) for MIPS, and HR, 2.03 [95% CI, 1.07–4.01]) for MIMS2), followed by the middle tertile (HR, 1.54 [95% CI, 1.02–2.73]) for MIPS, and HR, 1.63 [95% CI, 1.03–3.13]) for MIMS2). HR indicates hazard ratio; MIMS2. Myocardial Infarction and Mental Stress Study 2; and MIPS, Mental Stress Ischemia Prognosis Study.

We and others have previously shown that in patients with established CAD, a low hemodynamic reactivity to mental stress was associated with a greater risk of clinical cardiovascular events.[3–5,25] This association has been found to be independent of clinical characteristics, stress perception, or the magnitude of physiological responses to stress measured by changes in plasma epinephrine levels with mental stress.[25]

Our results showed that a decrease in FMD with mental stress was independently associated with worse outcomes in both cohorts of CAD. Assessing endothelial function through FMD testing has emerged as a valuable biomarker of cardiovascular risk both in populations with and without known CAD.[26,27] We have also previously shown that the FMD response to mental stress is a powerful prognostic indicator for adverse events in patients with CAD and potentially even more informative than resting FMD alone.[8] Prior observations have also documented that brachial artery FMD levels reflect coronary vascular endothelial function, and that mental stress promotes endothelium-dependent coronary vasoconstriction.[28,29] These findings suggest that the noninvasive method of measuring changes in FMD with mental stress could reflect the changes in coronary endothelial function with stress and be used clinically in identifying patients with CAD who are at high risk of developing major adverse outcomes.

We demonstrated that a greater degree of peripheral vasoconstriction during mental stress was associated with worse cardiovascular outcomes. These findings were in line with our previous study indicating the prognostic importance of peripheral vasoconstriction in response to mental stress in patients with CAD.[9] Our group has previously demonstrated by simultaneous measurements in the coronary and digital circulations that the peripheral vasoconstrictive response during mental stress closely correlates with coronary vasomotion.[28] Previous studies have also shown that greater coronary vasoconstriction with mental stress may trigger atherosclerotic plaque disruption and

Table 4. Risk Prediction Metrics for the Cardiovascular Reactivity Risk Score for the Composite End Point of Cardiovascular Death, Nonfatal Myocardial Infarction, and Hospitalizations for Heart Failure in the Pooled Sample (N=629)

	C-Statistics (95% CI)	ΔC-statistic (95% CI)	Continuous NRI (95% CI)
Cardiovascular death, nonfatal myocardial infarction, or congestive heart failure hospitalizations			
Full model without CRR score	0.71 (0.61–0.80)	…	
Full model + CRR score	0.81 (0.69–0.91)	0.10 (0.05–0.21)	0.44 (0.25–0.76)

Model included demographic factors (age, sex, and race), cardiovascular risk factors and other relevant medical factors (smoking, body mass index, history of hypertension, diabetes, heart failure, and previous myocardial infarction), current medications (β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin), and psychological factors (depressive symptoms, general stress, and state anxiety). CRR indicates cardiovascular reactivity risk; and NRI, net reclassification index.

rupture due to changes in wall shear stress, ultimately leading to acute coronary events.[30,31] These observations suggest that peripheral arterial tonometry-derived changes in the digital pulse amplitude during mental stress could act as a noninvasive surrogate for coronary vasomotion and be applied as a predictor for cardiovascular events.

Our findings demonstrated a dose–response relationship between a higher CRR score, representing a greater maladaptive response, and future outcomes. The survival curves revealed that the risk tied to a higher CRR score manifests early in the clinical follow-up and remain consistent over time. This observation, along with the fact that the CRR reactivity score improved the C-statistic by 10% and reclassified risk in 44% of participants, imply that hemodynamic and vascular responses to mental stress are key in delineating residual risk among individuals with stable CAD, beyond established risk factors.

This study is strengthened by investigating 2 independent populations with CAD validating the results. We also used a standardized mental stress protocol which allowed a controlled assessment of the stress exposure on hemodynamic and vascular changes. Other strengths of the study include the prospective study design with adjudicated cardiovascular outcomes. The study also has limitations. The observational nature of the study could not preclude the possibility of residual and unmeasured confounding. Our study was also conducted at a single institution in a population with CAD. The lack of external validation and generalizability to broader populations underscores the need for additional research in diverse clinical settings to understand the broader implications of cardiovascular reactivity to stress.

Our results highlight the potential for incorporating psychological factors and stress response profiles to risk stratify patients with CAD. The CRR score could enhance prevention and clinical care for the population with CAD by improving our ability to identify high-risk groups based on their psychological stress response physiology. Although more data are needed from implementation studies, a formal mental stress protocol could complement exercise stress testing in identifying individuals at risk of future cardiovascular events. Furthermore, the ability to identify patients with CAD exhibiting maladaptive cardiovascular responses to stress allows for more personalized management strategies. High-risk patients identified through the CRR score may benefit from intensified preventive measures or closer monitoring to mitigate their risk of future cardiovascular events. Additionally, interventions aimed at improving the CRR score could be explored as adjunctive strategies to standard medical therapy in patients with CAD.

Conclusions

In conclusion, among individuals with stable CAD, a maladaptive cardiovascular reactivity to mental stress consisting of a blunted hemodynamic response, a decrease in endothelial function, and greater degree of peripheral vasoconstriction is associated with adverse outcomes and improves the discrimination of future risk of cardiovascular events beyond traditional risk indicators. Future studies are needed to assess the molecular mechanisms underlying this association and evaluate the clinical significance and cost-effectiveness of testing cardiovascular reactivity to stress in the clinical setting. It is also crucial to explore how changes in these cardiovascular reactivity measures may influence the long-term outcomes for patients with CAD. Future studies could explore the dynamic nature of these responses over time and their predictive value in guiding personalized treatment strategies for individuals with stable CAD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1
Figures S1–S3

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