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CME

Impaired Resting Myocardial Annular Velocities Are Independently Associated With Mental Stress–Induced Ischemia in Coronary Heart Disease

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CME Objective for This Article: After reading this article the reader should understand: 1) the prevalence and clinical importance of mental stress induced ischemia as well as previously established demographic characteristics associated with its occurrence; 2) the generally accepted criteria for detection of mental stress induced ischemia; and 3) the relationship between annular myocardial velocities and the development of mental stress induced ischemia.

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Impaired Resting Myocardial Annular Velocities Are Independently Associated With Mental Stress–Induced Ischemia in Coronary Heart Disease

OBJECTIVES The aim of this study was to investigate the association between resting myocardial function as assessed by tissue Doppler myocardial velocities and the propensity to develop mental stress–induced ischemia (MSIMI).

BACKGROUND Tissue Doppler myocardial velocities detect preclinical cardiac dysfunction and clinical outcomes in a range of conditions. However, little is known about the interrelationship between myocardial velocities and the propensity to develop MSIMI compared with exercise stress–induced myocardial ischemia.

METHODS Resting annular myocardial tissue Doppler velocities were obtained in 225 patients with known coronary heart disease who were subjected to both conventional exercise stress testing as well as a battery of 3 mental stress tests. Diastolic early (e′) and late (a′) as well as systolic (s′) velocities were obtained, and the eas index, an integrated measure of myocardial velocities, was calculated as e′/(a′ × s′). MSIMI was defined as: 1) the development or worsening of regional wall motion abnormality; 2) a reduction in left ventricular ejection fraction ≥ 8%; and/or 3) ischemic ST-segment changes during 1 or more of the 3 mental stress tests.

RESULTS A total of 98 of 225 patients (43.7%) exhibited MSIMI. Patients developing MSIMI had significantly lower s′ (7.0 ± 1.7 vs. 7.5 ± 1.2, $p = 0.016$) and a′ (8.9 ± 1.8 vs. 10.0 ± 1.9, $p < 0.001$) at baseline, whereas e′ did not differ (6.5 ± 1.7 vs. 6.5 ± 1.8, $p = 0.85$). Furthermore, the eas index was significantly higher (0.11 ± 0.04 vs. 0.09 ± 0.03, $p < 0.0001$). The eas index remained significantly associated with the propensity to develop MSIMI (odds ratio per 0.05-U increase: 1.85; 95% confidence interval: 1.21 to 2.82; $p = 0.004$) after adjustment for resting left ventricular ejection fraction, resting wall motion index score, sex, and social circumstances of living. There was no association between resting eas index and exercise stress–induced myocardial ischemia.

CONCLUSIONS MSIMI but not exercise stress–induced myocardial ischemia is independently associated with resting abnormalities in myocardial systolic and late diastolic velocities as well as the integrated measure of the eas index in patients with known coronary artery disease. (Responses of Myocardial Ischemia to Escitalopram Treatment [REMIT]; NCT00574847) (J Am Coll Cardiol Img 2014;7:351–61) © 2014 by the American College of Cardiology Foundation

Mental stress–induced myocardial ischemia (MSIMI) is prevalent in patients with coronary artery disease (CAD) (1,2) and portends adverse outcome independently of traditional risk factors in this population (3). Several studies have demonstrated distinct physiological alterations coupling mental stress to cardiovascular changes, such as dynamic reductions in coronary blood flow demonstrated during mental stress in patients with CAD (4,5) and exaggerated catecholaminergic response during mental stress with increased systemic vascular resistance, opposite of the pattern seen during exercise (6). Recently, treatment with escitalopram has been demonstrated to reduce the rate of MSIMI in patients with CAD in the REMIT (Responses of Myocardial Ischemia to Escitalopram Treatment) trial (7).

World Expanded Multicenter Study of the MitraClip System, funded by Abbott Vascular. Dr. O'Connor is a co-owner of Biscardia; is a stockholder in Neurotronik/Interventional Autonomics Corporation; and has received financial support from Actelion Pharmaceuticals, Amgen, Astellas Pharma, BG Medicine, Critical Diagnostics, GE Healthcare, Gilead Sciences, HeartWare, Ikaria, Johnson & Johnson, Novartis, Otsuka Pharmaceutical Company, Pfizer Inc., Pozen, ResMed, and Roche Diagnostics. Dr. Velazquez is a consultant for Novartis; and has received research grants from Abbott Vascular and Ikaria Pharmaceuticals. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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The available data suggest that MSIMI may be present in 45% to 60% of patients with CAD, usually coexisting with exercise stress–induced myocardial ischemia (ESIMI); a smaller subset also exhibits isolated MSIMI (6,8). The propensity to develop MSIMI correlates with female sex, marital status, and social living arrangements (8). Tissue Doppler imaging (TDI) enables the assessment of myocardial annular velocities during systole (s′) and early as well as late diastole (e′ and a′, respectively), which confer important prognostic information in patients with CAD (9). A combination of these indexes has been proposed as the eas index (e′/[a′ × s′]), which combines the individual velocities while accounting for their significant interrelationship (10). Both annular left ventricular (LV) TDI velocities and the eas index have been associated with adverse outcomes in the general population (10) but have never been studied in relation to MSIMI. Abnormal myocardial velocities have been associated with hypertensive heart disease (11) and abnormal ventricular-vascular coupling (12), suggesting that the eas index as an integrated measure of myocardial function and the development of MSIMI could be related.

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In this study, we sought to assess the association between resting myocardial annular velocities and the propensity to develop MSIMI in a subgroup of patients screened for inclusion in the REMIT study (13).

METHODS

Patients with documented CAD ages 21 years and older were recruited for screening in the REMIT study. Patients were eligible for the randomized REMIT study if they demonstrated MSIMI during the screening procedure. The study protocol was approved by the Duke University Health System Institutional Review Board. All participants provided written informed consent before screening. Detailed inclusion and exclusion criteria have previously been published (13).

Study procedures. A detailed description of the study procedure has previously been published (13). Briefly, participants were interviewed with the purpose of obtaining clinical characteristics, a structured psychiatric assessment, and psychometric tests and afterward were followed by measurements of resting vital parameters.

The details of the mental stress testing procedure have previously been published (8,13). Briefly, participants underwent 3 mental stress tasks in the following sequence, with 6 min of rest in between: 1) mental arithmetic; 2) mirror tracing; and 3) anger-recall public speech. Finally, after a resting period, patients underwent an exercise treadmill test using the Bruce protocol.

Assessment of myocardial ischemia. Echocardiography and electrocardiography were used to assess myocardial ischemia. Blood pressure, heart rate, and a standard 12-lead electrocardiogram were recorded simultaneously with the echocardiographic examination. Echocardiography was performed using the Philips iE33 platform (Philips Ultrasound, Bothell, Washington). LV wall motion was graded qualitatively according to the American Society of Echocardiography's recommended 16-segment model (14). Each segment was graded as normal (1), hypokinetic (2), akinetic (3), dyskinetic (4), or aneurysmal (5). The sum of all segment scores divided by the number of scored segments constituted the wall motion score index (WMSI). LV ejection fraction (LVEF) was calculated according to the biplane Simpson method (14). All analyses of LV wall motion were performed by 2 experienced cardiologists (E.J.V., Z.S.), with kappa values for intraobserver and interobserver variability ranging from 0.80 to 0.87. Biplane LVEF was calculated by 1 experienced reader (B.S.) and repeated in 15 random subjects by an experienced cardiologist (F.A.E.), with no significant systematic difference (bias = −1.7, p = 0.6646) and an intraclass coefficient of correlation of 0.90 (95% confidence interval [CI]: 0.74 to 0.97).

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CI = confidence interval
ESIMI = exercise stress–induced myocardial ischemia
LA = left atrial
LV = left ventricular
LVEF = left ventricular ejection fraction
MSIMI = mental stress–induced myocardial ischemia
MV = mitral valve
OR = odds ratio
TDI = tissue Doppler imaging
WMSI = wall motion score index

Stress induced myocardial ischemia was defined by 1 or more of the following: 1) development of a new or worse wall motion abnormality; 2) reduction in LVEF ≥ 8%; and 3) horizontal or downsloping ST-segment depression ≥1 mm in at least 2 leads lasting ≥3 consecutive beats. MSIMI was defined by the aforementioned ischemic changes during 1 or more of the 3 mental stress tasks (13).

Doppler echocardiography. Doppler recordings were performed at baseline and during each mental stress task. Doppler recording of mitral inflow was performed by placing a 2.5-mm sample volume at the tip of the mitral valve (MV) leaflets during diastole. Peak velocities of early (E) and late (A) MV inflow were recorded as well as MV deceleration time. Pulsed-wave TDI traces were obtained from

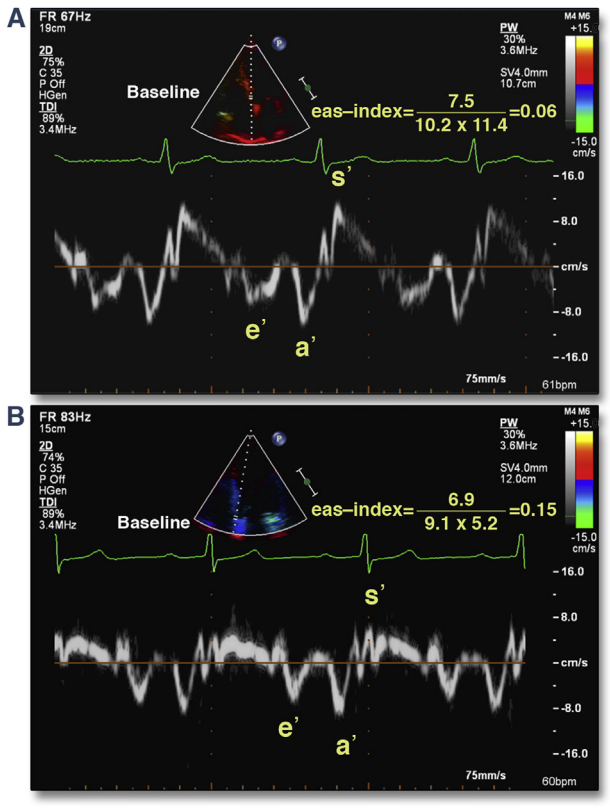

Figure 1. Examples of Different Annular Myocardial Velocity Patterns in Patients With and Without MSIMI

Example of 2 patients exhibiting differential patterns of response to mental stress and exercise stress tests. Patient A **(A)** had preserved myocardial velocities at baseline, with an eas index (e′/[a′ × s′]) of 0.06, and had positive exercise stress test results but negative mental stress test results (isolated exercise stress–induced myocardial ischemia). Patient B **(B)** had impaired baseline myocardial velocities, with markedly reduced s′ and an eas index of 0.15, and experienced isolated mental stress–induced myocardial ischemia (MSIMI). Both patient A and patient B had preserved left ventricular ejection fractions (61% and 57%, respectively).

the lateral mitral annulus in the 4-chamber view using a 2.5-mm sample volume. From the average of 3 cardiac cycles, we calculated peak systolic velocity (s′), early diastolic velocity (e′), and late diastolic velocity (a′). From the myocardial velocities, an integrated index (e′/[a′ × s′]), termed the eas index (10), was calculated (Fig. 1). All TDI measurements were performed by an experienced cardiologist (F.A.E.) and repeated in 15 random subjects by another experienced reader (M.E.), with excellent reproducibility for the eas index (bias = −0.005; 95% limits of agreement: −0.024 to 0.015; p = 0.7240).

Statistical analysis. All data are reported as mean ± SD or as median (interquartile range). Baseline clinical, and echocardiographic characteristics are given according to tertiles of the eas index and whether patients developed MSIMI. Student *t* tests and chi-square tests were used for continuous and categorical variables, respectively, and all tests were 2 sided, with the significance level set at $p < 0.05$. Correlation analyses between continuous variables were performed using Spearman correlation coefficients. The associations between resting echocardiographic parameters, clinical information, and MSIMI were analyzed using multiple logistic regression analysis with the binary outcome MSIMI as previously defined. The association between resting eas index and MSIMI was adjusted for resting LVEF, resting WMSI, and variables combining information on sex, marital status, and living arrangements, which have previously been associated with MSIMI (8). Finally, we compared the resting eas index between patients with isolated MSIMI and those with isolated ESIMI. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) and R version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics. Of 335 patients who presented for baseline mental stress testing, a total of 225 had complete data on all stress tests and TDI measurements at baseline. Reasons for not fulfilling requirements for the present study were as follows: 1) poor acoustic window (n = 19); 2) cancellation because of safety concerns (n = 6); 3) uninterpretable mental stress test images or uninterpretable exercise stress test images (n = 20); and 4) missing TDI recordings (n = 65).

The baseline characteristics according to eas index tertiles and MSIMI status are given in Tables 1 and 2, respectively. Patients with higher eas indexes were more likely to be younger (p = 0.0297), female (p = 0.0267), and unmarried (p = 0.0060). However, there was no difference in resting LVEF (p = 0.5819), WMSI (p = 0.1279), or E/e′ ratio (p = 0.0793). Overall, results of the exercise and mental stress tests were as follows: 105 patients (46.7%) developed neither MSIMI nor ESIMI, 22 (9.8%) developed isolated ESIMI, 53 (23.6%) developed both MSIMI and ESIMI, and 45 (20.0%) developed isolated MSIMI. Thus, a total of 98 (43.5%) developed MSIMI either isolated or in combination with ESIMI. Among the 98 patients who developed MSIMI, 60 (61.2%) developed only new or worsening wall motion abnormalities, 19 (19.4%) developed only decreases in LVEF ≥ 8%, and 19 (19.4%) had a combination of wall motion

Table 1. Baseline and Echocardiographic Characteristics According to Tertiles of eas Index

	eas Index < 0.08 (n = 75)	0.08 < eas Index < 0.11 (n = 75)	eas Index > 0.11 (n = 75)	p Value
Age, yrs	65.6 ± 8.2	62.7 ± 10.2	61.4 ± 11.1	0.0297
Race, white	66 (88.0)	61 (81.3)	62 (82.7)	0.4994
Women	7 (9.3)	11 (14.7)	19 (25.3)	0.0267
BMI, kg/m^2	28.68 ± 4.35	29.27 ± 4.47	28.19 ± 4.60	0.3534
Living arrangements, alone	8 (10.7)	12 (16.0)	14 (18.7)	0.3790
Marital status, not married	11 (14.7)	13 (17.3)	26 (34.7)	0.0060
Current smoker	3 (4.0)	11 (14.7)	14 (18.7)	0.0642
Current medical therapy				
ASA	73 (97.3)	70 (94.6)	72 (97.3)	0.5891
Other antiplatelet agent	34 (45.3)	36 (48.0)	26 (35.1)	0.2466
ACEi	48 (64.0)	46 (61.3)	47 (63.5)	0.9373
ARB	11 (14.9)	16 (21.3)	5 (6.8)	0.0395
Beta-blocker	62 (82.7)	58 (77.3)	65 (87.8)	0.2394
Calcium-channel blocker	19 (25.3)	18 (24.3)	12 (16.2)	0.3391
Statin	69 (93.2)	66 (89.2)	70 (94.6)	0.4369
History of MI	39 (52.0)	31 (41.3)	28 (37.3)	0.3740
History of CABG	29 (38.7)	29 (38.7)	36 (48.0)	0.4085
History of PCI	47 (62.7)	49 (65.3)	47 (62.7)	0.9261
History of DM	22 (29.3)	23 (30.7)	18 (24.0)	0.6294
History of HTN	60 (80.0)	58 (77.3)	58 (77.3)	0.9009
History of hyperlipidemia	70 (93.3)	71 (94.7)	69 (92.0)	0.8071
NYHA functional class				
I	68 (90.7)	70 (93.3)	67 (89.3)	
II	6 (8.0)	4 (5.3)	5 (6.7)	0.4268
III	1 (1.3)	1 (1.3)	3 (4.0)	
History of depression	8 (10.7)	9 (12.0)	11 (14.7)	0.7516
Resting LVEF, %	58.5 ± 9.3	59.0± 8.4	57.4 ± 9.8	0.5819
Resting WMSI	1.16 ± 0.32	1.09 ± 0.20	1.19 ± 0.37	0.1279
Resting MV deceleration time, ms	245.3 ± 63.2	225.2 ± 50.7	220.0 ± 59.9	0.0219
Resting E/A ratio	0.85 ± 0.24	1.02 ± 0.28	1.07 ± 0.38	<0.0001
Resting E/e′	12.8 ± 4.2	11.8 ± 4.3	11.2 ± 4.6	0.0793
Resting eas index	0.07 ± 0.01	0.09 ± 0.01	0.14 ± 0.03	<0.0001
MSIMI	23 (30.7%)	30 (40.0)	45 (60.0)	0.0011

Values are mean ± SD or n (%).
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = aspirin; BMI = body mass index; CABG = coronary artery bypass grafting; DM = diabetes mellitus; eas index = (e′/[a′ × s′]); HTN = hypertension; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MSIMI = mental stress–induced myocardial ischemia; MV = mitral valve; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; WMSI = wall motion score index.

abnormalities and a decrease in LVEF ≥ 8% during 1 or more mental stress tasks. No patients had ST-segment changes during the mental stress tasks. Among the 98 patients with MSIMI, ischemia was detected in 51 (52.0%) during mental arithmetic, in 66 (67.3%) during mirror tracing, and in 73 (74.5%) during anger-recall speech.

Baseline s′ correlated significantly with both e′ (rho = 0.42, p < 0.0001) and a′ (rho = 0.49, p < 0.0001), whereas the correlation between e′ and a′ was less strong (rho = 0.24, p < 0.0001).

Myocardial velocities in relation to MSIMI. Patients developing MSIMI were more likely to be living alone (19.4% vs. 11.8%), to be unmarried (27.6% vs. 18.1%), and to be female (20.4% vs. 13.4%), but none of these differences were statistically different in the present subset of the REMIT screening patients (p > 0.05 for all). Development of

Table 2. Baseline and Echocardiographic Characteristics According to Presence of MSIMI

	No MSIMI (n = 127)	MSIMI (n = 98)	p Value
Age, yrs	63.5 ± 10.0	62.8 ± 10.0	0.5861
Race, white	109 (85.8)	80 (81.6)	0.5045
Women	17 (13.4)	20 (20.4)	0.2196
BMI, kg/m^2	29.0 ±4.5	28.4 ±4.5	0.3256
Living arrangements, alone	15 (11.8)	19 (19.4)	0.1658
Marital status, not married	23 (18.1)	27 (27.6)	0.1267
Current smoker	12 (9.4)	16 (16.3)	0.2302
Current medical therapy			
ASA	121 (96.0)	94 (96.9)	1.0000
Other antiplatelet agents	50 (39.4)	46 (47.4)	0.2844
ACE inhibitors	79 (62.2)	62 (63.9)	0.9018
ARBs	15 (11.9)	17 (17.5)	0.3201
Beta-blockers	103 (81.1)	82 (84.5)	0.6215
Calcium-channel blockers	29 (23.0)	20 (20.6)	0.7906
Statins	113 (89.7)	92 (95.8)	0.1463
History of MI	51 (40.2)	47 (48.0)	0.4844
History of CABG	51 (40.2)	43 (43.9)	0.6711
History of PCI	79 (62.2)	64 (65.3)	0.7342
History of DM	38 (29.9)	25 (25.5)	0.7342
History of HTN	102 (80.3)	74 (75.5)	0.4821
History of hyperlipidemia	119 (93.7)	91 (92.9)	1.0000
NYHA functional class			
I	115 (90.6)	90 (91.8)	
II	8 (6.3)	7 (7.1)	0.7053
III	4 (4.1)	1 (1.0)	
History of depression	15 (11.8)	13 (13.3)	0.9013
Resting LVEF, %	58.7 ± 8.2	57.8 ± 10.3	0.4817
Resting WMSI	1.11 ± 0.28	1.19 ± 0.34	0.0725
Resting MV deceleration time, ms	228.1 ± 58.2	232.6 ± 60.0	0.5726
Resting E/A ratio	0.97 ± 0.34	1.00 ± 0.30	0.4976
Resting E/e′	11.7 ± 4.2	12.2 ± 4.7	0.4785
Resting eas index	0.09 ± 0.03	0.11 ± 0.04	<0.0001

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

MSIMI was associated with higher resting WMSI (1.19 ± 0.34 vs. 1.11 ± 0.28, p = 0.0725) whereas resting LVEF did not differ significantly (57.8 ± 10.3% vs. 58.7 ± 8.2%, p = 0.4817). The eas index was significantly higher in patients developing MSIMI compared with those without MSIMI (0.11 ± 0.04 vs. 0.09 ± 0.03, p < 0.0001). The cumulative number of positive mental stress tasks was significantly higher among patients in the highest tertile of the eas index (p = 0.005) (Fig. 2). The number of patients having MSIMI by each mental stress task was proportionally higher with increasing tertile of the eas index (Fig. 3), but only mirror tracing (p = 0.0137) and anger-recall speech (p = 0.0039) were statistically significant, whereas mental arithmetic was not significant (p = 0.1543).

Among the individual components of the eas index, only resting s′ (7.0 ± 1.7 vs. 7.5 ± 1.2, p = 0.0205) and a′ (8.9 ± 1.8 vs. 10.0 ± 1.9, p < 0.0001) differed

between patients exhibiting MSIMI, whereas e′ (6.5 ± 1.7 vs. 6.5 ± 1.8, p = 0.8475) did not.

There were significant correlations between mean change in LVEF from baseline to all 3 mental stress tests and resting LVEF (rho = −0.30, p < 0.0001), resting s′ (rho = 0.20, p = 0.0034), resting a′ (rho = 0.17, p = 0.0132), MV deceleration time (rho = −0.15, p = 0.0311) and eas index (rho = −0.17, p = 0.0106). There was no correlation between resting e′ (rho = 0.06, p = 0.4195) and resting WMSI (rho = −0.01, p = 0.8341). Female patients (−1.18 ± 4.61 vs. −0.31 ± 4.75, p = 0.3234), those not married (−1.40 ± 6.20 vs. −0.18 ± 4.17, p = 0.2024), and those living alone (−2.11 ± 6.72 vs. −0.17 ± 4.24, p = 0.1275) had more pronounced changes in LVEF during mental stress testing, but none of these differences were statistically significant.

Multivariate logistic regression analysis revealed that eas index was independently related to MSIMI after adjustment for age, resting LVEF, resting WMSI, female sex, single living, and unmarried status (odds ratio [OR] per 0.05-U increase: 1.85; 95% CI: 1.21 to 2.82; p = 0.0043). In the adjusted model, resting LVEF (OR: 1.01; 95% CI: 0.97 to 1.05; p = 0.7376), resting WMSI (OR per 0.1-U increase: 1.09; 95% CI: 0.96 to 1.22; p = 0.1780), age (OR: 1.01; 95% CI: 0.98 to 1.04; p = 0.5232), female sex (OR: 1.01; 95% CI: 0.43 to 2.39; p = 0.9769), single living (OR: 1.38; 95% CI: 0.42 to 4.55; p = 0.5931), and unmarried status (OR: 1.10; 95% CI: 0.37 to 3.27; p = 0.8661) did not maintain significant associations with the development of MSIMI. When adjusting for a combination of sex and single living, higher eas index was borderline significantly associated with MSIMI (OR per 0.05-U increase: 1.34; 95% CI: 0.92 to 1.94; p = 0.1235), whereas nonsignificant associations were found for single women compared with nonsingle men (OR: 1.83: 95% CI: 0.62 to 5.39; p = 0.5492) and for single men compared with nonsingle men (OR: 1.97; 95% CI: 0.75 to 5.16; p = 0.4055).

Patients with isolated MSIMI had higher eas indexes compared with patients with isolated ESIMI (0.11 ± 0.04 vs. 0.09 ± 0.03, p = 0.0224). After adjusting for the combination of sex and single living as described previously, eas index remained independently associated with isolated MSIMI (OR per 0.05-U increase: 2.50; 95% CI: 1.02 to 6.17; p = 0.0462).

Changes in myocardial velocities during mental stress. Between-group (MSIMI vs. no MSIMI) differences in the eas index remained significant during the mental arithmetic (p = 0.0198) and mirror drawing (p = 0.0133) tasks, whereas no significant difference was found during the anger-recall speech task (p = 0.2154). Decreasing eas index was seen for patients with and without MSIMI across the 3 mental stress tasks (Fig. 4). The decrease in the eas index was driven by increases in a′, whereas e′ and s′ remained constant, although the patients developing MSIMI continued to exhibit relatively lower a′ and s′ velocities (Fig. 5).

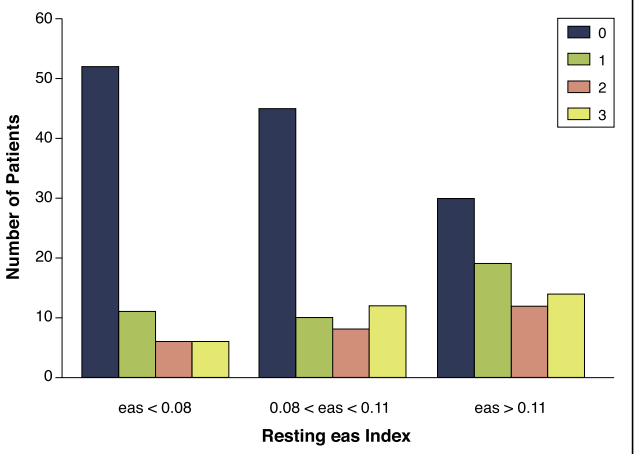

Figure 2. Positive Mental Stress Tasks According to Resting eas Index

Cumulative number of positive mental stress tasks according to tertiles of resting eas index (e′/[a′ × s′]).

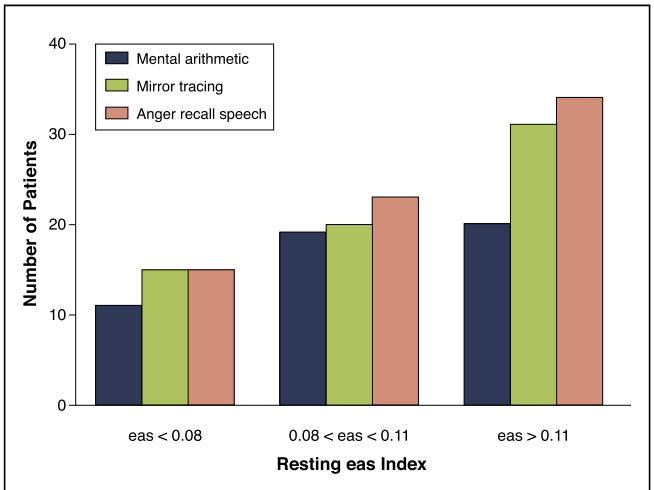

Figure 3. Positive Response to Mental Stress Tasks According to Resting eas Index

Distribution of mental stress–induced ischemia by mental stress task according to tertiles of resting eas index (e′/[a′ × s′]).

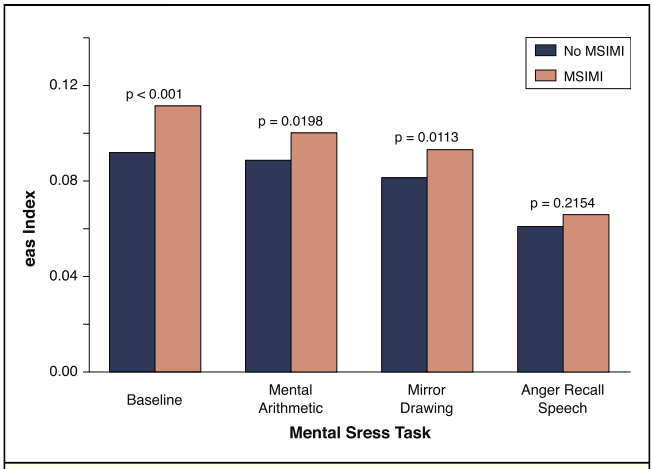

Figure 4. eas Index During Mental Stress Tests

Relationship between the eas index (e′/[a′ × s′]) obtained at each mental stress task according to whether patients developed mental stress–induced myocardial ischemia (MSIMI).

DISCUSSION

The main findings of the present study can be summarized as follows: 1) in a population with stable CAD, we demonstrate that an integrated measure of annular myocardial velocities is associated with the propensity for developing MSIMI; and 2) an integrated measure of myocardial velocities correlates with demographic characteristics that have been linked to MSIMI in previous studies (8).

Mechanisms underlying MSIMI. The underlying mechanisms of MSIMI are not fully understood, but several distinctive features have been identified that set MSIMI apart from ESIMI. The myocardial ischemic response to mental stress occurs at a lower rate-pressure product compared with ESIMI, implying that MSIMI is present at lower levels of oxygen demand (6). Although the blood pressure increase accompanying MSIMI is relatively smaller in magnitude compared with that seen with ESIMI, a distinctive feature of MSIMI seems to be the increase in systemic vascular resistance, which is opposite to ESIMI (6). The mechanism for this response is not elucidated, but it has been suggested that central neurogenic peripheral vasoconstriction may be involved (1). Studies using functional magnetic resonance imaging have demonstrated distinct areas in the medial prefrontal cortex that together modulate cardiovascular response to mental stress with significant individual differences (15). Abnormal myocardial systolic velocities have also been demonstrated to be independently associated with increased vascular stiffness and abnormal ventricular-vascular coupling (11,12). However, we cannot draw from the present data any definite

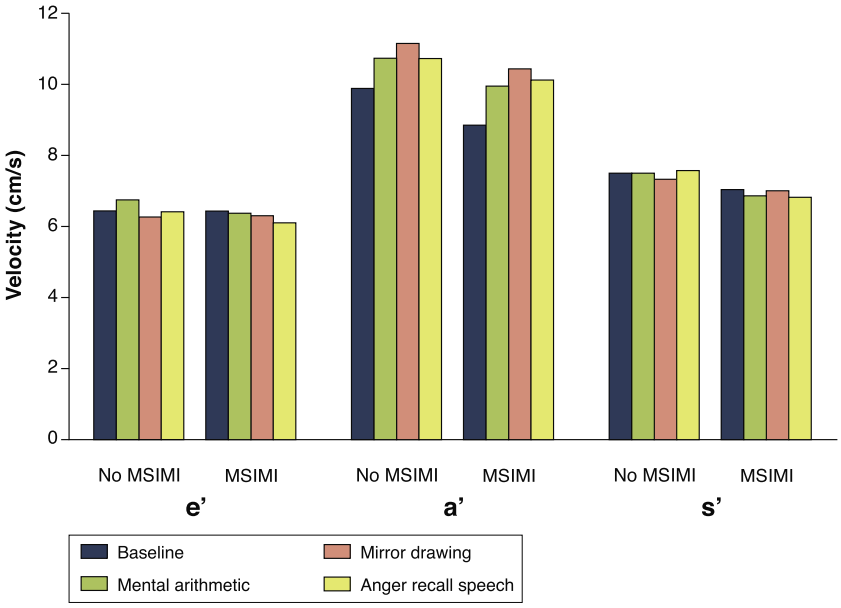

Figure 5. Pattern of Annular Myocardial Velocities During Mental Stress

Relationship between myocardial annular velocities (e′, a′, and s′) obtained at each mental stress task according to whether the patient developed mental stress–induced myocardial ischemia (MSIMI).

conclusions on the association between myocardial tissue velocities and peripheral vasoconstriction at baseline or during mental stress in patients exhibiting MSIMI.

Abnormal coronary vasomotor response has been implicated in the pathogenesis of MSIMI. Compared with healthy control subjects, patients with CAD did not demonstrate increased coronary blood flow during mental stress, and local inability of endothelium-mediated vasodilation in diseased coronary vessels has been implicated in the occurrence of MSIMI (5). Other studies have demonstrated blunted myocardial blood flow in normal epicardial arteries in response to mental stress suggestive of microvascular dysfunction (16). Subclinical myocardial dysfunction assessed by TDI has been associated with abnormal coronary flow reserve in patients with hypertension, diabetes, and recent acute myocardial infarctions (17–19). This could suggest that lower resting myocardial velocities in patients with a propensity to develop MSIMI may reflect pre-existing microvascular dysfunction.

MSIMI in relation to annular myocardial velocities. The observed independent association between resting eas index and MSIMI could reflect a shared etiology, with both of these being affected by a complex interplay of neurogenic vasoactive response, inhomogenous coronary vasoreactivity, and myocardial microvascular dysfunction. The present study cannot give any indication of causality between impaired resting myocardial velocities and MSIMI. However, to the best of our knowledge, this is the first study to demonstrate resting myocardial abnormalities in patients exhibiting MSIMI. Interestingly, factors previously associated with increased propensity for MSIMI, namely female sex and marital status (8), were also associated with increased eas index in this study.

The rationale for integrating myocardial annular velocities has previously been proposed (10). The significant internal dependency of annular myocardial velocities was confirmed in our study, in which s′ correlated significantly with both a′ and e′, whereas the correlation between e′ and a′ was less pronounced. Decreases in e′ are associated with normal aging due to the progressive age-related impairment of myocardial active relaxation (20), whereas a′ increases. However, progressive myocardial passive stiffness due to a loss of viscoelastic properties will lead to additional reductions in a′, which herald adverse outcomes, especially when accompanied by low s′ (21). Low s′ is seen with deteriorating LV long-axis systolic function and has been demonstrated to improve the diagnostic accuracy of suspected CAD independently of exercise electrocardiographic and conventional echocardiographic parameters (22). Furthermore, impaired long-axis LV systolic function leads to less potential energy being stored during systole, which directly interacts with subsequent early diastole through diminished elastic recoil (23). The integrated approach to the myocardial annular velocities was favored by Mogelvang et al. (10) because of the observed close relationship between aging and e′ in the normal population. The REMIT study included a higher risk population of patients with known CAD, which is different from the population described by Mogelvang et al. (10) However, the association between the eas index and MSMI reported in our study does not affect the documented relationship between e′ and long-term clinical outcomes in patients with CAD (9). Taken together, these considerations suggest that an integrated approach to quantifying myocardial velocities should be more appropriate than assessing each parameter in isolation (10,21).

During the mental stress tasks, the eas index decreased in a similar fashion whether or not patients developed MSIMI, and this change was driven by relatively unchanged s′ and e′ velocities, whereas a′ increased. Higher a′ values are seen in patients with impaired relaxation compared with the more advanced pseudonormal pattern, and key determinants of a′ have previously been identified as left atrial (LA) dP/dt, LA relaxation, and LV end-diastolic pressure (24–26). Whether mental stress tasks induce changes in LA function cannot be conclusively answered from the present study because of the lack of invasive measurements and high-resolution LA planimetry. These findings deserve further exploration in future studies of MSIMI.

Study limitations. Several limitations must be noted. First and foremost, TDI assessment was not available in all patients completing the REMIT screening program, which diminishes our sample size compared with prior results (8). Recordings of TDI were available only for the lateral annulus of the 4-chamber view, which limits our ability to more accurately assess the global myocardial velocities. More accurate measures of global LV function such as strain (27) could potentially have added further information with regard to the development of MSIMI, but these novel parameters were not assessed in the REMIT screening program (13).

CONCLUSIONS

An integrated measure of resting myocardial velocities is independently associated with the propensity to develop MSIMI in patients with CAD. These novel results imply that subclinical myocardial dysfunction may coexist with previously described pathophysiological alterations in peripheral vasculature and coronary vasoreactivity in patients with MSIMI.

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Key Words: echocardiography ■ mental stress–induced ischemia ■ tissue Doppler.

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