Potential predictors for mental stress-induced myocardial ischemia in patients with coronary artery disease

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Abstract

Background: Mental stress-induced myocardial ischemia (MSIMI) is closely associated with adverse cardiac events in patients with coronary artery disease (CAD) and we aimed to determine whether biomarkers and blood pressure could be potential predictors of MSIMI.

Methods: This study enrolled 82 patients with documented CAD between June 1, 2017 and November 9, 2017. Patient blood samples were obtained at resting period and at the end of mental arithmetic. Then, patients were assigned to MSIMI positive group and MSIMI negative group. The main statistical methods included linear regression, receiver operating characteristic (ROC) curves, and logistic regression.

Results: Patients with CAD with MSIMI had significantly greater median resting N-terminal pro-brain natriuretic peptide (NT-proBNP, 141.02 [45.85–202.76] pg/mL *vs.* 57.95 [27.06–117.64] pg/mL; $Z = -2.23$, $P = 0.03$) and mean systolic blood pressure (SBP) (145.56 ± 16.87 mmHg *vs.* 134.92 ± 18.16 mmHg, $Z = -2.13$, $P = 0.04$) when compared with those without MSIMI. After 5-min mental stress task, those who developed MSIMI presented higher elevation of median post-stressor high sensitivity cardiac troponin I (hs-cTnI, 0.020 [0.009–0.100] ng/mL *vs.* 0.009 [0.009–0.010] ng/mL; $Z = -2.45$, $P = 0.01$), post-stressor NT-proBNP (138.96 [39.93–201.56] pg/mL *vs.* 61.55 [25.66–86.50] pg/mL; $Z = -2.15$, $P = 0.03$) compared with those without MSIMI. Using the ROC curves, and after the adjustment for basic characteristics, the multiple logistic regression analysis showed that patients presenting a post-stressor hs-cTnI ≥ 0.015 ng/mL had seven-fold increase in the risk of developing MSIMI (odds ratio [OR]: 7.09; 95% confidence interval [CI]: 1.65–30.48; $P = 0.009$), a rest NT-proBNP ≥ 80.51 pg/mL had nearly eight-fold increase (OR: 7.85; 95% CI: 1.51–40.82; $P = 0.014$), a post-stressor NT-proBNP ≥ 98.80 pg/mL had 35-fold increase (OR: 34.96; 95% CI: 3.72–328.50; $P = 0.002$), a rest SBP ≥ 129.50 mmHg had 11-fold increase (OR: 11.42; 95% CI: 1.21–108.17; $P = 0.034$).

Conclusions: The present study shows that CAD patients with higher hs-cTnI level, and/or greater NT-proBNP and/or SBP are at higher risk of suffering from MSIMI when compared with those without MSIMI, indicating that hs-cTnI, NT-proBNP, SBP might be potential predictors of MSIMI.

Keywords: Coronary artery disease; Depression; Anxiety; Blood pressure; Biomarkers

Introduction

Coronary artery disease (CAD) remains the leading cause of death around the world. About 30% to 60% of patients with CAD could present with myocardial ischemia induced by mental stress as mentioned by recent studies.[1,2] Mental stress-induced myocardial ischemia (MSIMI) is hypothesized to be associated with the following factors: inflammatory response,[3] hyperactivation of the sympathetic nervous system,[4] increased catecholamines,[5] anger,[6] and a diagnosis of depression[7] and anxiety.[8] Furthermore, some related studies have shown that MSIMI triggered in the laboratory is closely associated with adverse cardiac events in patients with CAD.[9-11] Wei *et al*[9] conducted a meta-analysis including five studies, with a total number of 555 patients with CAD and 117 subsequent cardiac events, demonstrating a two-fold increased risk of adverse outcomes in patients with MSIMI. In Sun *et al*'s[10] research on the relationship between mental stress-induced left ventricular dysfunction and adverse outcome in 310 patients with ischemia heart disease, after a median 4-year

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follow-up, they elucidated that the reduction of left ventricular ejection fraction induced by mental stress could predict the increased risk of adverse cardiac outcomes. In another study, myocardial annular velocity changes during mental stress were proved to be predictors of adverse cardiovascular outcomes; moreover, the greater decrease of diastolic early (e') and diastolic late (a') was associated with the higher possibility of major adverse cardiac events (MACE).[11] Therefore, it is of vital importance to identify patients with CAD susceptible to MSIMI. Until recently, MSIMI could be diagnosed via echocardiography or electrocardiography (ECG),[12] sestamibi single-photon emission computed tomography (SPECT) imaging,[13] or peripheral arterial tonometry technique.[14] In our recent study, we have not found any difference in vascular severity between the MSIMI negative group and the positive group in patients with CAD.[15] Regarding the convenience and important role of biomarkers (cardiac troponin I [cTnI],[16] C-reactive protein [CRP][17]) and blood pressure[18] in cardiovascular diseases and MSIMI, we aimed to determine whether biomarkers and blood pressure could be potential predictors of MSIMI in this study.

Materials and methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Beijing Anzhen Hospital (No: 2014015X). All patients provided written informed consent.

Sample size

According to the sample equation of receiver operating characteristic (ROC) curve,[19,20] we computed the sample size by the following equation and using Power Analysis and Sample Size (PASS) software 15.0 (NCSS, LLC; Kaysville, UT, USA).

$$N_A = \frac{[z_\alpha\sqrt{\{V_0(\widehat{\Delta})\}} + z_\beta\sqrt{\{V_{\mathrm{Alt}}(\widehat{\Delta})\}}]^2}{\Delta^2}$$

$V_0\,(\widehat{\Delta}) = N_{\mathrm{A}}\,\mathrm{var}_0\,(\widehat{\Delta})$, $V_{\mathrm{Alt}}\,(\widehat{\Delta}) = N_{\mathrm{A}}\,\mathrm{var}_{\mathrm{Alt}}\,(\widehat{\Delta})$, Δ was as the difference between the accuracies of two diagnostic tests, $\widehat{\Delta}$ was as maximum likelihood estimate of Δ, N_{A} was the number of MSIMI negative patients, $\mathrm{var}_{\mathrm{Alt}}\,(\widehat{\Delta})$ was the variance of $\widehat{\Delta}$ under the alternative hypothesis, Z_α and Z_β were the upper α and β percentiles of the standard normal distribution, $\alpha = 0.05$, Z_α=1.96 (two-sided test), Z_β=1.282.

The sample size computed by PASS 15.0 was 72, therefore the sample size in our study 82 was sufficient for this statistical analysis.

Patients enrollment

This was a prospective cohort study. This study enrolled 82 patients with documented CAD including 54 males and 28 females, at an average age of 60.1 ± 9.8 years. It was conducted between June 1, 2017 and November 9, 2017. Inclusion criteria were the following: (1) male or female; (2) >18 years of age; (3) documented CAD; and (4) signed informed consent. The exclusion criteria were the following: (1) severe major organ dysfunction; (2) severe psychiatric disorders; (3) acute coronary syndrome in recent 2 months; (4) pregnant; or (5) cognitive impairment [Figure 1].

Study design

All the patients received blood withdrawn and echocardiography before and after a 5-min mental stress task. MSIMI was diagnosed as follows. Then we analyzed the relationship between the biomarkers, blood pressure, heart rate, and MSIMI by statistical analysis.

Basic characteristics

After enrollment, patients were asked to complete a standardized questionnaire including sex, age, height, weight, history of hypertension, hyperlipidemia, diabetes, current or former smoking, and alcohol use. In addition, depression was assessed with the Patient Health Questionnaire 9-item (PHQ-9), and anxiety was assessed with Generalized Anxiety Disorder 7-item (GAD-7). Furthermore, we utilized the Gensini scoring system to value the

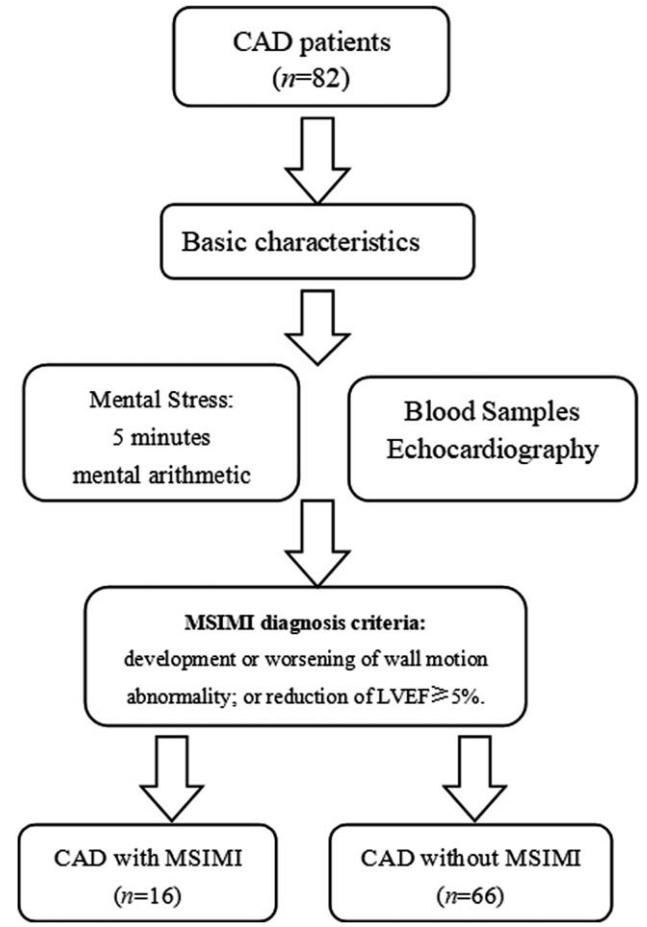

Figure 1: Flow chart of patient enrollment and diagnosis. CAD: Coronary artery disease; MSIMI: Mental stress-induced myocardial ischemia; LVEF: Left ventricular ejection fraction.

stenosis of each coronary artery, as it had been described previously.[21]

Blood collection

Beta-blockers and caffeine-containing products were withheld for 24 h prior to stress testing. Patient blood samples for biomarkers analysis were obtained at resting period in the morning after an 8-h fast and 5 min after mental arithmetic. The blood was collected into plastic tubes with ethylenediamine tetraacetic acid (final concentration of 0.5–1%). The tubes were then centrifuged and the supernatant collected and stored at −80°C until analysis. Biomarkers included high sensitivity cardiac troponin I (hs-cTnI), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), creatine kinase-muscle/brain (CK-MB), myoglobin, CRP, D-dimer. These biomarkers concentrations were measured by AFIAS-6 (AFIAS; automated fluorescent immunoassay system; Chimax Boditech Co. Ltd., Shanghai, China).

MSIMI diagnosis

Mental arithmetic was used as a mental stress task. Patients were asked to perform a series of subtraction with encouragement (subtracted 7 sequentially from a four-digit number) while being urged to calculate faster and more accurately in 5 min.

Left ventricular wall motion images were acquired before and during the stressor (mental arithmetic). Heart rate and blood pressure were recorded at rest, peri-stressor and post-stressor. Diagnostic criteria of MSIMI[22] included the following: compared to rest, any development or worsening of wall motion abnormality; or reduction of left ventricular ejection fraction (LVEF) ≥5%. The echocardiography was performed by a professional and experienced echocardiographic sonographer, calculating LVEF from 3 to 5 beats, and assessing wall motion from 30 to 40 frames of systole from one cardiac cycle according to the latest American Society of Echocardiography's 17-segment model.[10,23] Each segment was graded and scored as normal (1 = normal or hyperdynamic) or abnormal (2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, or 5 = aneurysmal) wall motion. A wall motion score index (WMSI) was calculated as the sum of the segmental wall motion scores divided by the total number of the scored segments. According to the echocardiography images, patients were assigned to MSIMI positive group and MSIMI negative group.

Statistical analysis

Statistical comparisons of the two groups were examined on baseline demographic and clinical characteristics, the value of biomarkers, blood pressure, heart rate, and LVEF. Continuous variables of normal distribution were displayed as mean ± standard deviation, and independent *t* test or paired *t* test was used for group comparison. Continuous variables of skewed distribution were displayed as median (P25- P75), and non-parametric test of two independent samples or two related samples was used for group comparison. Categorical variables were displayed as absolute values and percentage, and Chi-square was used for group comparison. Linear regression was used to assess the relationship between the value of biomarkers at rest and post-stressor.

To establish hs-cTnI and NT-proBNP cut-off values with appropriate sensitivity and specificity, ROC curves were plotted, and the area under the curve (AUC) was estimated. The optimal hs-cTnI and NT-proBNP cut-off value was determined as the value that maximized the Youden index, calculated as (sensitivity + specificity) − 1. Logistic regression was used to test the predictive value of the hs-cTnI and NT-proBNP cut-off and the other selected parameters. The *P* value <0.05 (two-tailed) was considered for statistical significance. IBM SPSS 24.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Study characteristics

We enrolled a total of 82 patients with stable CAD in this study. The mean age was 60.1 ± 9.8 years, 65.9% were males, 32.9% had diabetes mellitus, 68.3% had hypertension, 85.4% had hyperlipidemia, 34.1% had depression, and 35.4% had anxiety. The incidence of MSIMI was 19.5%. As many as 16 patients were assigned to MSIMI positive group and 66 patients were assigned to MSIMI negative group. No significant differences in demographic features were observed between the two groups. And there was no difference of coronary artery stenosis between MSIMI positive and negative groups (44.0 [21.0, 87.0] *vs.* 29.0 [15.0, 52.0], $Z = -1.19$, $P = 0.23$) [Table 1].

Biomarkers comparison in different groups

Comparisons between MSIMI positive group and MSIMI negative group

Compared with those without MSIMI, the median resting hs-cTnI level was slightly higher in patients with MSIMI (0.015 [0.009–0.040] ng/mL *vs.* 0.009 [0.009–0.010] ng/mL; $Z = -1.95$, $P = 0.05$), the median post-stressor hs-cTnI was significantly higher in patients with MSIMI (0.020 [0.009–0.100] ng/mL *vs.* 0.009 [0.009–0.010] ng/mL; $Z = -2.45$, $P = 0.01$) [Tables 2 and 3].

Compared with those without MSIMI, the median resting NT-proBNP level was significantly higher in patients with MSIMI (141.02 [45.85–202.76] pg/mL *vs.* 57.95 [27.06–117.64] pg/mL; $Z = -2.23$, $P = 0.03$), the median post-stressor NT-proBNP was significantly higher in patients with MSIMI (138.96 [39.93–201.56] pg/mL *vs.* 61.55 [25.66–86.50] pg/mL; $Z = -2.15$, $P = 0.03$) [Table 2].

There was no significance in the median resting CK-MB comparison between MSIMI positive and MSIMI negative groups (2.99 [2.99–2.99] ng/mL *vs.* 2.99 [2.99–2.99] ng/mL; $Z = -0.45$, $P = 0.66$). There was no significance in the median post-stressor CK-MB comparison between MSIMI positive and MSIMI negative groups (2.99 [2.99–2.99] ng/mL *vs.* 2.99 [2.99–2.99] ng/mL; $Z = -0.61$, $P = 0.54$) [Table 2].

Table 1: Study characteristics in patients with and without MSIMI.

Parameters	MSIMI positive ($n = 16$)	MSIMI negative ($n = 66$)	Total ($n = 82$)	Statistics	P
Age (years)	59.8 ± 10.2	60.2 ± 9.7	60.1 ± 9.8	0.12*	0.90
Male	10 (62.5)	44 (66.7)	54 (65.9)	0.1†	0.75
BMI (kg/m^2)	27.0 ± 3.7	26.7 ± 3.7	26.4 ± 3.7	–0.74*	0.46
Hypertension	14 (87.5)	42 (63.6)	56 (68.3)	3.39†	0.07
Hyperlipidemia	14 (87.5)	56 (84.8)	70 (85.4)	0.07†	0.79
Diabetes	4 (25)	23 (34.8)	27 (32.9)	0.57†	0.45
Current/former smoking	10 (62.5)	38 (57.6)	48 (58.5)	0.13†	0.72
Current/former drinking	7 (43.8)	32 (48.5)	39 (47.6)	0.12†	0.73
Depression	6 (37.5)	22 (33.3)	28 (34.1)	0.10†	0.75
PHQ-9	3.5 (2.0, 6.5)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	–0.78‡	0.44
Anxiety	9 (56.3)	20 (30.3)	29 (35.4)	3.79†	0.05
GAD-7	5.0 (1.3, 12.0)	2.0 (0.0, 5.0)	2.0 (0.8, 6.0)	–1.97‡	0.05
Gensini score	44.0 (21.0, 87.0)	29.0 (15.0, 52.0)	34.0 (16.0, 60.0)	–1.19‡	0.23

Data are presented as mean ± standard deviation, n (%), or median (P25, P75). * t values. † χ^2 values. ‡Z values. BMI: Body mass index; GAD-7: Generalized anxiety disorder 7-item; MSIMI: Mental stress induced myocardial ischemia; PHQ-9: Patient Health Questionnaire 9-item.

Table 2: Biomarkers comparisons between patients with and without MSIMI.

Parameters	MSIMI positive ($n = 16$)	MSIMI negative ($n = 66$)	Statistics	P^1
hs-cTnI (ng/mL)				
Rest	0.015 (0.009,0.040)	0.009 (0.009,0.010)	–1.95*	0.05
Post-stressor	0.020 (0.009,0.100)	0.009 (0.009,0.010)	–2.45*	0.01
Statistics	–1.68*	–0.76*		
P^2	0.09	0.45		
NT-proBNP (pg/mL)				
Rest	141.02 (45.85,202.76)	57.95 (27.06,117.64)	–2.23*	0.03
Post-stressor	138.96 (39.93,201.56)	61.55 (25.66,86.50)	–2.15*	0.03
Statistics	–0.05*	–0.76*		
P^2	0.96	0.45		
CK-MB (ng/mL)				
Rest	2.99 (2.99,2.99)	2.99 (2.99,2.99)	–0.45*	0.66
Post-stressor	2.99 (2.99,2.99)	2.99 (2.99,2.99)	–0.61*	0.54
Statistics	–1.34*	–0.30*		
P^2	0.18	0.77		
Myoglobin (ng/mL)				
Rest	44.00 (33.85,51.07)	41.88 (33.69,52.90)	–0.45*	0.66
Post-stressor	40.34 (28.57,53.91)	42.24 (34.68,56.73)	–0.53*	0.60
Statistics	–0.08*	–1.37*		
P^2	0.94	0.17		
CRP (mg/L)				
Rest	0.72 (0.50,2.10)	0.82 (0.49,1.69)	–0.30*	0.76
Post-stressor	0.74 (0.49,2.26)	0.85 (0.49,1.91)	–0.20*	0.85
Statistics	–1.30*	–1.21*		
P^2	0.20	0.23		
D-Dimer (ng/mL)				
Rest	203.87 ± 123.67	186.42 ± 94.31	1.02†	0.57
Post-stressor	201.88 ± 117.70	188.26 ± 94.19	1.03†	0.67
Statistics	–0.07†	0.89†		
P^2	0.95	0.39		

Data are presented as mean±standard deviation, or median (P25, P75). * Z values. † t values. CK-MB: Creatine kinase-muscle/brain; CRP: C-reactive protein; hs-cTnI: High-sensitivity cardiac troponin I; MSIMI: Mental stress-induced myocardial ischemia; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; P^1: Comparison between MSIMI positive group and MSIMI negative group; P^2: Comparison between rest and post-stressor value of six biomarkers.

There was no significance in the median resting myoglobin comparison between MSIMI positive and MSIMI negative groups (44.00 [33.85–51.07] ng/mL *vs.* 41.88 [33.69–52.90] ng/mL; $Z = -0.45$, $P = 0.66$). There was no significance in the median post-stressor myoglobin comparison between MSIMI positive and MSIMI negative groups (40.34 [28.57–53.91] ng/mL *vs.* 42.24 [34.68–56.73] ng/mL; $Z = -0.53$, $P = 0.60$) [Table 2].

There was no significance in the median resting CRP comparison between MSIMI positive and MSIMI negative groups (0.72 [0.50–2.10] mg/L *vs.* 0.82 [0.49–1.69] mg/L; $Z = -0.30$, $P = 0.76$). There was no significance in the median post-stressor CRP comparison between MSIMI positive and MSIMI negative groups (0.74 [0.49–2.26] mg/L *vs.* 0.85 [0.49–1.91] mg/L; $Z = -0.20$, $P = 0.85$) [Table 2].

There was no significance in the resting D-dimer comparison between MSIMI positive and MSIMI negative groups (203.87 ± 123.67 *vs.* 186.42 ± 94.31 ng/mL; $t = 1.02$, $P = 0.57$). There was no significance in the post-stressor D-dimer comparison between MSIMI positive and MSIMI negative groups (201.88 ± 117.70 *vs.* 188.26 ± 94.19 ng/mL; $t = 1.03$, $P = 0.67$) [Table 2].

Comparison between rest and post-stressor

In MSIMI positive and negative groups, there were no significance in the comparison between rest and post-stressor biomarkers [Table 2].

hs-cTnI

Regarding the unitary linear association between rest hs-cTnI and post-stressor hs-cTnI, we had built the linear equation as: $Y = 0.008 + 1.08X$ (Y: hs-cTnI post-stressor, X: rest hs-cTnI). The absolute value of standardized coefficients beta demonstrated the interaction of rest hs-cTnI and post-stressor hs-cTnI [Figure 2].

Post-stressor hs-cTnI

For asymptotic significance is 0.094, we could not describe ROC curve for rest hs-cTnI and MSIMI.

The ROC curve, in assessing the utility of post-stressor hs-cTnI as a predictor of MSIMI, yielded a cut-off value of 0.015 ng/mL, with a sensitivity of 56.3% and a specificity of 79.7% (AUC: 0.67, 95% confidence interval [CI]: 0.51–0.83; $P = 0.037$); a positive predictive value (PPV) of 40.9% and a negative predictive value (NPV) of 87.9%, a positive likelihood ratio of 2.77 and a negative likelihood ratio of 0.55. As a matter of fact, 56.3% of patients who developed MSIMI had post-stressor hs-cTnI ≥ 0.015 ng/mL [Figure 3].

Before adjustment, the logistic regression analysis showed that patients presenting a post-stressor hs-cTnI ≥ 0.015 ng/mL

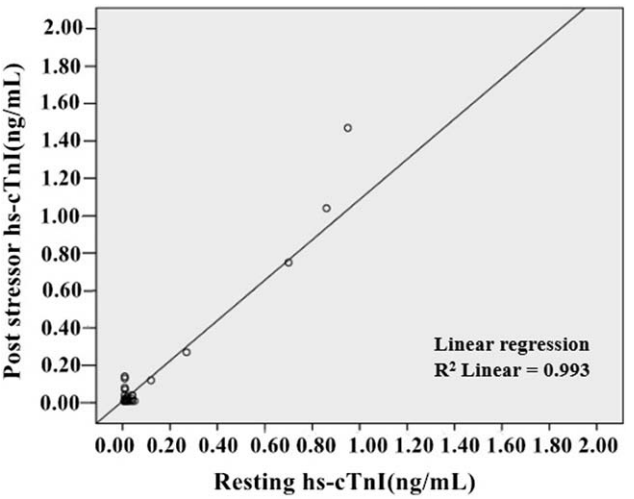

Figure 2: Unitary linear regression of resting and post-stressor hs-cTnI. hs-cTnI: High-sensitivity cardiac troponin I.

Table 3: BP, HR comparisons between patients with and without MSIMI.

Parameters	MSIMI positive ($n = 16$)	MSIMI negative ($n = 66$)	Statistics	*P*
SBP (mmHg)				
Rest	145.56 ± 16.87	134.92 ± 18.16	–2.13*	0.04
Peri-stressor	160.81 ± 17.35	148.56 ± 19.49	–2.30*	0.02
Post-stressor	142.63 ± 15.57	136.20 ± 18.16	–1.30*	0.20
DBP (mmHg)				
Rest	83.88 ± 12.93	79.14 ± 9.83	–1.62*	0.11
Peri-stressor	96.88 ± 18.78	88.15 ± 10.35	–1.79*	0.09
Post-stressor	85.75 ± 14.10	79.06 ± 9.35	–1.80*	0.09
HR (beats/min)				
Rest	64.88 ± 11.01	63.17 ± 9.30	–0.64*	0.53
Peri-stressor	74.00 ± 14.48	71.41 ± 11.55	–0.77*	0.45
Post-stressor	69.50 ± 12.51	65.55 ± 9.30	–1.42*	0.16

Data are presented as mean ± standard deviation. *t values. DBP: Diastolic blood pressure; HR: Heart rate; MSIMI: Mental stress-induced myocardial ischemia; SBP: Systolic blood pressure;1 mmHg = 0.133 kPa.

had a five-fold increase in the risk of developing MSIMI (odds ratio [OR]: 5.04; 95% CI: 1.58–16.10; $P = 0.006$). After adjustment for sex, age, body mass index (BMI), hypertension, diabetes, hyperlipidemia, smoking, drinking, depression, and anxiety, the multiple logistic regression analysis showed that patients presenting a post-stressor hs-cTnI ≥ 0.015 ng/mL had seven-fold increase in the risk of developing MSIMI (OR: 7.09; 95% CI: 1.65–30.48; $P = 0.009$) [Table 4].

NT-proBNP

Regarding the unitary linear association between rest NT-proBNP and post-stressor NT-proBNP, we had built the linear equation as: $Y = 23.20 + 0.7X$ (Y: NT-proBNP post-stressor; X: rest NT-proBNP). The absolute value of standardized coefficients beta demonstrated the interaction of rest NT-proBNP and post-stressor NT-proBNP [Figure 4].

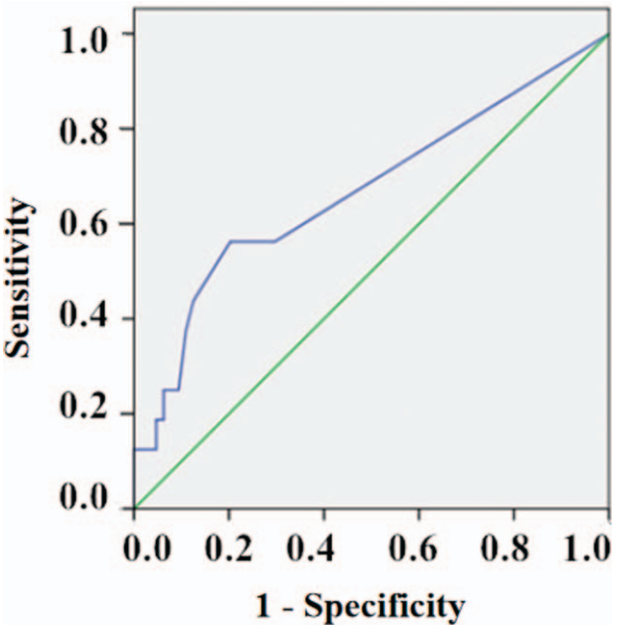

Figure 3: Receiver operating characteristic curve in assessing the utility of post-stressor hs-cTnI as a predictor of MSIMI, yielded a cut-off value of 0.015 ng/mL, with a sensitivity of 56.3% and a specificity of 79.7% (AUC: 0.67, 95% CI: 0.51–0.83; $P = 0.037$). AUC: Area under the curve; CI: Confidence interval; hs-cTnI: High-sensitivity cardiac troponin I; MSIMI: Mental stress-induced myocardial ischemia.

Resting NT-proBNP

The ROC curve, in assessing the utility of rest NT-proBNP as a predictor of MSIMI, yielded a cut-off value of 80.51 pg/mL, with a sensitivity of 68.8% and a specificity of 68.7% (AUC: 0.68, 95% CI: 0.54–0.83; $P = 0.026$); a PPV of 35.5% and an NPV of 89.8%, a positive likelihood ratio of 2.19 and a negative likelihood ratio of 0.45. As a matter of fact, 68.8% of patients who developed MSIMI had rest NT-proBNP ≥ 80.51 pg/mL [Figure 5].

Before adjustment, the logistic regression analysis showed patients presenting a rest NT-proBNP ≥ 80.51 pg/mL had a nearly five-fold increase

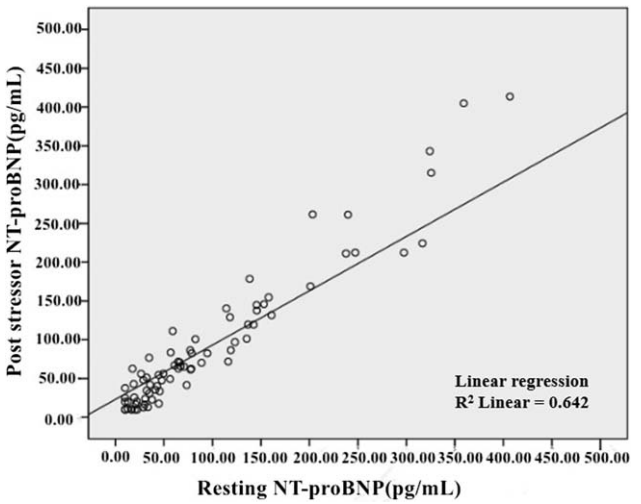

Figure 4: Unitary linear regression of resting and post-stressor NT-proBNP. NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

Table 4: Factors associated with MSIMI in patients with CAD.

Parameters	OR	95% CI	*P*
Unadjusted			
Post-stressor hs-cTnI	5.04	1.58–16.10	0.006
Resting NT-proBNP	4.84	1.48–15.78	0.009
Post-stressor NT-proBNP	7.70	2.29–25.89	0.001
Resting SBP	10.39	1.29–83.36	0.028
Adjusted			
Post-stressor hs-cTnI	7.09	1.65–30.48	0.009
Resting NT-proBNP	7.85	1.51–40.82	0.014
Post-stressor NT-proBNP	34.96	3.72–328.50	0.002
Resting SBP	11.42	1.21–108.17	0.034

Above *vs.* below cut-off value; post-stressor hs-cTnI cut-off value was 0.015 ng/mL; resting NT-proBNP cut-off value was 80.51 pg/mL; post-stressor NT-proBNP cut-off value was 98.80 pg/mL; resting SBP cut-off value was 129.50 mmHg. Adjusted for sex, age, BMI, hypertension, diabetes, hyperlipidemia, smoking, drinking, depression, and anxiety. CI: Confidence interval; CRP: C-reactive protein; hs-cTnI: High-sensitivity cardiac troponin I; MSIMI: Mental stress-induced myocardial ischemia; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; OR: Odds ratio; SBP: Systolic blood pressure.

in the risk of developing MSIMI (OR: 4.84; 95% CI: 1.48–15.78; $P = 0.009$). After adjustment for sex, age, BMI, hypertension, diabetes, hyperlipidemia, smoking, drinking, depression and anxiety, the multiple logistic regression analysis showed that patients presenting a rest NT-proBNP ≥ 80.51 pg/mL had nearly eight-fold increase in the risk of developing MSIMI (OR: 7.85; 95% CI: 1.51–40.82; $P = 0.014$) [Table 4].

Post-stressor NT-proBNP

In assessing the utility of post-stressor NT-proBNP as a predictor of MSIMI, the ROC curve yielded a cut-off value of 98.80 pg/mL, with a sensitivity of 68.8% and a specificity of 77.8% (AUC: 0.68, 95% CI: 0.51–0.84; $P = 0.032$); a PPV of 44% and an NPV of 90.7%, a positive likelihood ratio of 3.10 and a negative likelihood ratio of 0.40. As a matter of fact, 68.8% of patients who developed MSIMI had post-stressor NT-proBNP ≥ 98.80 pg/mL [Figure 6].

Before adjustment, the logistic regression analysis showed patients presenting a post-stressor NT-proBNP ≥ 98.80 pg/mL had a nearly eight-fold increase in the risk of developing MSIMI (OR: 7.70; 95% CI: 2.29–25.89; $P = 0.001$). After adjustment for sex, age, BMI, hypertension, diabetes, hyperlipidemia, smoking, drinking, depression, and anxiety, the multiple logistic regression analysis showed that patients presenting a post-stressor NT-proBNP ≥ 98.80 pg/mL had a 35-fold increase in the risk of developing MSIMI (OR: 34.96; 95% CI: 3.72–328.50; $P = 0.002$) [Table 4].

Blood pressure

comparisons between MSIMI positive group and MSIMI negative group

Compared to patients in MSIMI negative group, resting systolic blood pressure (SBP) value (145.56 ± 16.87 mmHg *vs.* 134.92 ± 18.16 mmHg, $Z = -2.13$, $P = 0.04$) and peri-stressor SBP value (160.81 ± 17.35 mmHg *vs.* 148.56 ± 19.49 mmHg, $Z = -2.30$, $P = 0.02$) were significantly higher in patients with MSIMI, but post-stressor SBP value was slightly higher without significance (142.63 ± 15.57 mmHg *vs.* 136.20 ± 18.16 mmHg, $Z = -1.30$, $P = 0.20$).

No significance was found in the comparison of resting DBP (83.88 ± 12.93 mmHg *vs.* 79.14 ± 9.83 mmHg, $Z = -1.62$, $P = 0.11$), peri-stressor DBP (96.88 ± 18.78 mmHg *vs.* 88.15 ± 10.35 mmHg, $Z = -1.79$, $P = 0.09$), post-stressor DBP (85.75 ± 14.10 mmHg *vs.* 79.06 ± 9.35 mmHg, $Z = -1.80$, $P = 0.09$), resting HR (64.88 ± 11.01 beats/min *vs.* 63.17 ± 9.30 beats/min, $Z = -0.64$, $P = 0.53$), peri-stressor HR (74.00 ± 14.48 *vs.* 71.41 ± 11.55 beats/min, $Z = -0.77$, $P = 0.45$), post-stressor HR (69.50 ± 12.51 beats/min *vs.* 65.55 ± 9.30 beats/min, $Z = -1.42$, $P = 0.16$) between MSIMI positive group and MSIMI negative group.

Rest SBP

The ROC curve, in assessing the utility of rest SBP as a predictor of MSIMI, yielded a cut-off value of

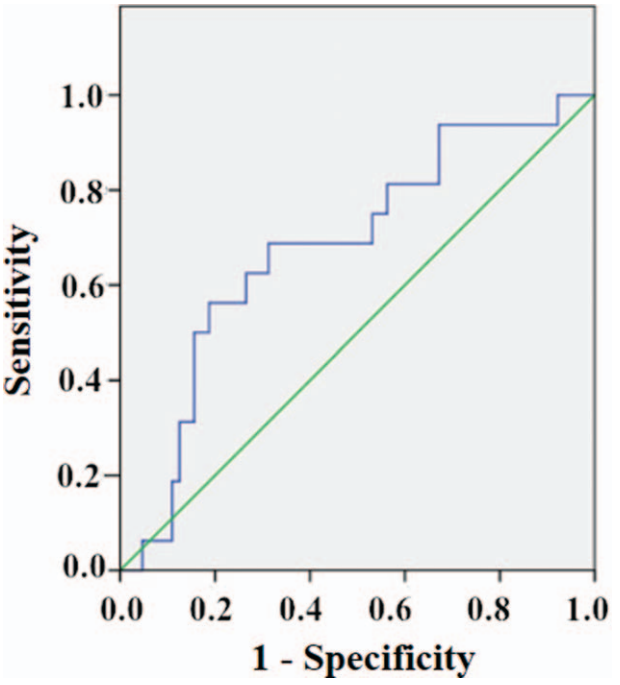

Figure 5: Receiver operating characteristic curve, in assessing the utility of rest NT-proBNP as a predictor of MSIMI, yielded a cut-off value of 80.51 pg/mL, with a sensitivity of 68.8% and a specificity of 68.7% (AUC: 0.68, 95% CI: 0.54–0.83; $P = 0.026$). AUC: Area under the curve; CI: Confidence interval; MSIMI: Mental stress-induced myocardial ischemia; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

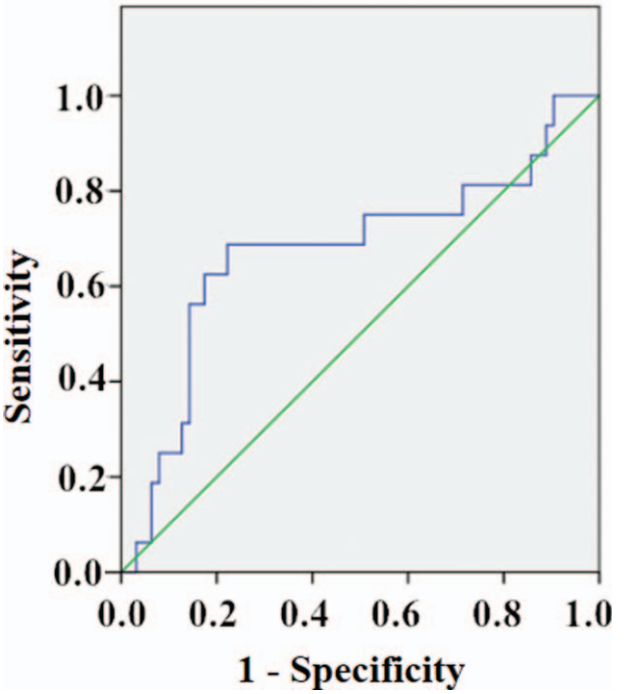

Figure 6: Receiver operating characteristic curve of post-stressor NT-proBNP and MSIMI. In assessing the utility of post-stressor NT-proBNP as a predictor of MSIMI, the ROC curve yielded a cut-off value of 98.80 pg/mL, with a sensitivity of 68.8% and a specificity of 77.8% (AUC: 0.68, 95% CI: 0.51–0.84; $P = 0.032$). AUC: Area under the curve; CI: Confidence interval; MSIMI: Mental stress-induced myocardial ischemia; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

129.50 mmHg, with a sensitivity of 93.8% and a specificity of 40.9% (AUC: 0.66, 95% CI: 0.54–0.79; $P = 0.045$); a PPV of 27.8% and an NPV of 96.4%, a positive likelihood ratio of 1.59 and a negative likelihood ratio of 0.15. Interestingly, 93.8% of patients who developed MSIMI had rest SBP ≥ 129.50 mmHg [Figure 7].

Before adjustment, the logistic regression analysis showed patients presenting a rest SBP ≥ 129.50 mmHg had a nearly ten-fold increase in the risk of developing MSIMI (OR: 10.39; 95% CI: 1.29–83.36; $P = 0.028$). After adjustment for sex, age, BMI, hypertension, diabetes, hyperlipidemia, smoking, drinking, depression, and anxiety, the multiple logistic regression analysis showed that patients presenting a rest SBP ≥ 129.50 mmHg had an 11-fold increase in the risk of developing MSIMI (OR: 11.42; 95% CI: 1.21–108.17; $P = 0.034$) [Table 4].

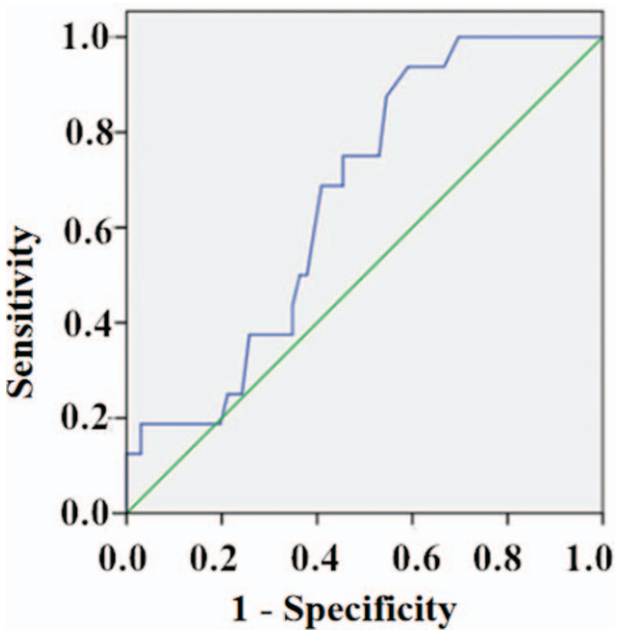

Figure 7: Receiver operating characteristic curve of rest SBP and MSIMI. In assessing the utility of rest SBP as a predictor of MSIMI, yielded a cut-off value of 129.50 mmHg, with a sensitivity of 93.8% and a specificity of 40.9% (AUC: 0.66, 95% CI: 0.54–0.79; $P = 0.045$). AUC: Area under the curve; CI: Confidence interval; MSIMI: Mental stress-induced myocardial ischemia; SBP: Systolic blood pressure.

Cardiographic indicators

No significance was found in the comparison of resting LVEF between MSIMI positive group and MSIMI negative group (66.06 ± 6.61% *vs.* 62.62 ± 8.04%, $Z = -1.80$, $P = 0.07$), while there was significance in the comparison of peri-stressor LVEF between the two groups (62.19 ± 5.98% *vs.* 64.26 ± 8.43%, $Z = -2.15$, $P = 0.03$).

No significance was found in the comparison of resting WMSI between MSIMI positive group and MSIMI negative group (1.00 [1.00, 1.00] *vs.* 1.00 [1.00, 1.00] score, $Z = -0.42$, $P = 0.67$); and there was no significance in the comparison of peri-stressor WMSI between the two groups (1.00 [1.00, 1.00] *vs.* 1.00 [1.00, 1.00] score, $Z = -0.36$, $P = 0.72$) [Table 5].

Discussions

The study results show that patients with CAD with MSIMI have slightly higher baseline resting hs-cTnI levels, significantly greater resting NT-proBNP levels, and significantly higher SBP when compared with those without MSIMI. After the 5-min mental stress task, those who develop MSIMI exhibit higher elevation of post-stressor hs-cTnI and NT-proBNP levels, and peri-stressor SBP compared with those without MSIMI. Using the ROC curves, the optimal cut-off points of post-stressor hs-cTnI, resting NT-proBNP, post-stressor NT-proBNP, and resting SBP were identified. After the adjustment for basic characteristics, the multiple logistic regression analysis showed that: (1) patients presenting a post-stressor hs-cTnI levels ≥0.015 ng/mL had a seven-fold increase in the risk of developing MSIMI; (2) a rest NT-proBNP ≥80.51 pg/mL had nearly eight-fold increase; (3) a post-stressor NT-proBNP ≥ 98.80 pg/mL had 35-fold increase; and (4) a rest SBP ≥129.50 mmHg had 11-fold increase.

According to previous literature, MSIMI is associated with a worse prognosis in subjects with stable CAD, as demonstrated in a two-fold increased risk of future cardiac events.[24] Nevertheless, a large body of research demonstrates that MSIMI is a silent phenomenon.[1] Therefore, it is difficult to screen patients susceptible to MSIMI. Williams[6] suggested that post-myocardial infarction patients with higher state and trait anger were

Table 5: LVEF, WMSI comparisons between patients with and without MSIMI.

Parameters	MSIMI positive ($n = 16$)	MSIMI negative ($n = 66$)	Statistics	P
LVEF				
Rest	66.06 ± 6.61	62.62 ± 8.04	–1.80*	0.07
Peri-stressor	62.19 ± 5.98	64.26 ± 8.43	–2.15*	0.03
WMSI				
Rest	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	–0.42†	0.67
Peri-stressor	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	–0.36†	0.72

Data are presented as mean ± standard deviation, or median (P25, P75). *t values. †Z values. LVEF: Left ventricular ejection fraction; MSIMI: Mental stress-induced myocardial ischemia; WMSI: Wall motion score index.

more likely to develop myocardial ischemia during a stress challenge. Pimple[25] reported that the higher frequency of angina during the day was associated MSIMI. Technologic advances have introduced ECG, echocardiography, SPECT in detecting myocardial ischemia and standard criteria of MSIMI diagnosis have been used.[1] So far, we could not draw any significant relationship between coronary artery stenosis and MSIMI from our study. Furthermore, due to the important and evolving role of biomarkers, some researchers have focused on the association between biomarkers and MSIMI previously.

Cardiac troponins are currently the most sensitive and specific biochemical markers used for myocardial infarction. There are three types of troponins including, troponin-C, -I, and -T. The clinical measurement of serum hs-cTnI has become an important tool in the diagnosis of acute myocardial infarction. Hs-cTnI level was found to be higher in patients with exercise-induced myocardial ischemia (ESIMI) in Lee and his colleagues' study.[26] Hammadah *et al*[27] investigated 587 patients with CAD who underwent both mental stress and conventional stress, assessing myocardial ischemia by SPECT. They concluded that higher resting levels of hs-cTnI were associated with MSIMI or ESIMI. From the results of our study, we happen to hold the same view that patients with CAD with MSIMI have slightly higher hs-cTnI level, and exhibit higher elevations of hs-cTnI after 5-min mental stress task, and at the optimal cut-off points of post-stressor hs-cTnI $\geq$ 0.015 ng/mL have seven-fold increase in the risk of developing MSIMI. Results observed above may be a reflection of the extensive functions of hs-cTnI in cardiac muscle fibers contraction.

NT-proBNP is produced predominately by the cardiac ventricular myocytes and is released in response to myocardial stress and filling pressures, and is involved in maintaining intravascular volume homeostasis; moreover, it has been proved to be a strong and independent predictor of obstructive CAD causing myocardial ischemia.[28] An elevation of NT-proBNP gene has demonstrated the close link between NT-proBNP and chronic stable angina, which is characterized by myocardial ischemia, while the concentration of NT-proBNP could decrease after percutaneous coronary revascularization.[29] NT-proBNP is now considered to be a useful marker and has a high degree of diagnostic accuracy in clinical practice and cardiovascular research as a diagnostic tool for the occurrence and severity of heart failure and MACEs.[30] In addition, we have found a close association between NT-proBNP and MSIMI in patients with CAD. We infer that NT-proBNP is involved in the pathophysiologic process of mental stress. For example, Feinkohl *et al*[31] had done a cross-sectional analysis in 1066 diabetes patients, and they suggested that raised plasma NT-proBNP was significantly associated with poorer cognitive function and depression.

Other studies have concluded that there is more obvious elevation of DBP during mental stress when compared to SBP.[32] Krantz's study[33] showed that after controlling for baseline diastolic blood pressure and group status, there was a significantly 2.4-fold higher relative risk of cardiac events for high versus low stress-induced peak diastolic blood pressure responses compared to low. On the contrary, we found that higher levels of SBP were associated with MSIMI and increased risk of MSIMI. We infer the possible reason may be related to the age and disease history and coronary artery calcium of patients recruited in this study. Further research is needed to clarify our point.

To our knowledge, this is a rare study focused on the association between hs-cTnI, NT-proBNP, and blood pressure, and MSIMI in Chinese patients with CAD. However, we have not found any significance of CK-MB, CRP, D-dimer, myoglobin, and MSIMI, which may be related to the small sample size and biomarkers detection time. And we need more researches to prove which of the three predictors is more powerful or whether the combination is better. Furthermore, we plan to conduct a larger multicenter study involving a larger number of patients from around China, selecting more related biomarkers, exploring potential interventions of pharmacologic and behavioral approaches, and we should have a 3- to 5-year follow-up to further study the association of MSIMI and MACEs.

In conclusion, the present study shows that patients with CAD have higher hs-cTnI levels, and/or greater NT-proBNP levels and/or SBP may be at higher risk of suffering from MSIMI when compared with those without MSIMI, indicating that hs-cTnI, NT-proBNP, SBP might be potential predictors of MSIMI. We will expand our study in the future involving patients and healthy volunteers from different study centers, and further develop suitable treatments for MSIMI.

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Conflicts of interest

None.

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