Exercise electrocardiography combined with stress echocardiography for predicting myocardial ischemia in adults

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Abstract. Myocardial ischemia (MI) has the highest mortality rate in the world. Traditional noninvasive MI examinations include exercise electrocardiography tests (EETs) and stress echocardiography (SE). Treadmill and dobutamine tests are commonly used as stress protocols. In the present study, 278 patients with suspected MI were examined, 66 of whom were diagnosed with MI and 212 did not show evidence of MI by coronary angiography (CAG)/coronary CT angiography (CCTA). All patients underwent clinical EET and SE evaluations prior to CAG/CCTA. All groups were compared based on specific clinical parameters including age, sex, blood pressure, heart rate, blood oxygen saturation, underlying conditions and ejection fraction/fraction shortening. The data indicated superior diagnostic efficiency of the combined EET+SE method for the diagnosis of suspected MI compared with either EET or SE alone. The sensitivity/specificity/positive predictive value and negative predictive value for detecting MI were excellent compared with those of traditional examinations. The diagnostic efficiency of the combination analysis may reduce the prevalence of MI and medical costs. The present study provided novel insight for the development of methods that may be used for MI detection and prediction.

Introduction

Coronary artery disease (CAD)-induced myocardial ischemia (MI), including acute myocardial infarction (AMI), is a disease entity with the highest mortality rate in the world. Approximately 800,000 US residents experience AMI annually and 27% of these patients do not survive (1,2). Coronary angiography (CAG) is the gold standard for diagnosing CAD and MI, whereas invasive operations are high-risk treatment methods that are not easily accepted by patients, such as lack of expensive devices and experienced operators (3,4). Prior to the development of CAG, electrocardiography (ECG) was the best noninvasive technique for CAD/MI diagnosis (5). In 1979, stress echocardiography (SE) was classified as an invaluable technique that combines echocardiography and ECG with stress testing (6). Treadmill or bicycle exercise is the most frequently used type of workload stressor and dobutamine or dipyridamole may be administered as pharmacological agents (6,7). For instance, the 2015 European Society of Cardiology guidelines and the 2014 American Heart Association consensus statement recommend the use of noninvasive stress imaging for the diagnosis of stable CAD and female ischemic heart disease due to the significantly higher diagnostic accuracy of this technique (8). Douglas *et al* (9) reported that exercise ECG testing and SE may improve the diagnostic sensitivity and specificity in females with obstructive CAD. However, only a limited number of studies have combined exercise ECG testing (EET)/SE with CAG/coronary CT angiography (CCTA) in order to confirm the diagnosis of CAD (10).

SE is frequently used in i) risk stratification of patients with suspected CAD, ii) pre-operative risk assessment, iii) revascularization evaluation, iv) assessment of indications for percutaneous coronary intervention (PCI) and v) CAD/MI of unclear significance as determined by CAG or CT (6,11). A high number of studies have reported on the use of myocardial contrast echocardiography (MCE) perfusion imaging to improve the wall motion sensitivity of SE (12,13). MCE allows for simultaneous evaluation of myocardial perfusion and regional function and has a potential role in viability assessment (6,7). Furthermore, excessive elevation of systolic blood pressure during physical exercise is associated with an increased left ventricular mass in pre-hypertensive individuals (14). This result suggests that exercise blood pressure and EET are not only useful tools for screening indications and contraindications but also assistant diagnostic techniques for CAD/MI. An arterial segment that is dysfunctional or exhibits recession at the resting or loading state reflects the contracting wall response of ischemia/necrosis/viability (6).

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In the present study, analysis of EET ST-segments combined with SE wall motion abnormalities (WMA) was used to predict MI in adults with unknown MI status and was subsequently compared with CAG/CCTA results to assess the sensitivity/specificity/positive-predictive value (PPV) and negative-predictive value (NPV) in detecting CAD/MI. Therefore, the present study was performed to address the aforementioned issues and assess a possible association of the diagnostic accuracy between invasive and noninvasive CAD/MI. The present study provided an improved strategy for the noninvasive imaging diagnosis of CAD/MI.

Materials and methods

Study population. The Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, China) approved the present study and all patients provided written informed consent (approval no. SRFA-048). A total of 278 patients were enrolled between August 2018 and August 2019 at The First Affiliated Hospital of Nanjing Medical University (Nanjing, China). Certain patients had undergone PCI at least 6 months previously, whereas others did not undergo PCI. None of the patients had a previous history of heart failure or severe symptoms of atypical chest pain, severe dyspnea or an echocardiograph indicative of ischemic WMA. Prior to EET/SE, all patients underwent resting ECG/echocardiography, which was independently interpreted as negative for MI by three cardiologists. The patients who were diagnosed with pulmonary disease, including chronic obstructive pulmonary disease and asthma, as well as severe bundle-branch blocking/cardiac insufficiency, which may affect the safety of exercise testing, were excluded. In addition, patients with more than moderate valvular dysfunction, permanent pacemaker implantation with post-PCI were not included. The patients' medical information was recorded and subsequently analyzed. Following EET/SE, all patients underwent CAG/CCTA. A total of 66 patients were diagnosed with MI (CAG vessel stenosis ≥50%) and 212 patients were diagnosed with non-MI (CAG vessel stenosis <50%).

Diagnostic criteria. All diagnoses based on SE were divided into 4 categories according to wall motion function: i) Normal response, ii) ischemic response, iii) necrotic response and iv) viability response. Categories ii, iii and iv were reported in a recent study, whereas category i was not found to be present (6). A total of three experienced cardiologists assessed the results, which were classified as positive or negative.

EET was performed and independently interpreted by three cardiologists. Resting/exercise ECG, heart rate (HR) and blood pressure (BP) were recorded during the process. In the present study, the treadmill exercise and Bruce protocol were used to evaluate the method. Severe ischemia (severe chest pain, ST segment elevated ≥2 mm horizontal or downsloping ST depression), severe hypertension [HTN; systolic blood pressure (SBP) ≥220 mmHg or diastolic blood pressure (DBP) ≥120 mmHg], hypotension (SBP ≤90 mmHg or DBP ≤60 mmHg), presyncope, or significant arrhythmia and fatigue were defined as the end-points of the test. For those patients who achieved a workload of ≥9 metabolic equivalent/dobutamine load or achieved target heart pace without any symptoms, hemodynamic compromise or ECG changes, the test was considered negative. The following symptoms were considered to indicate a positive test: Hypotension, significant chest pain, related arrhythmias, two or more leads exhibiting ST segment elevation ≥1 mm and planar or downsloping ST depression during exercise or in recovery (6,13).

Stress test/SE. All patients were treated using a treadmill protocol (GE T2100) or dobutamine infusion. Short axis and apical 4-chamber, 2-chamber and 3-chamber images were obtained (iE33 Philips Medical Systems B.V.). Imaging of rest, peak-exercise, post-exercise and recovery were evaluated as described above. Information on exercise capacity, BP, HR and rhythm changes was collected and analyzed (15). WMA analysis was also performed (15). Sonovue (Bracco), an ultrasound contrast agent, was administered by intravenous bolus injection (0.3-0.5 ml) and was flushed with saline (16). The final results were independently interpreted by three cardiologists. A 17-segment left-ventricle model was evaluated by a four-point score (1, normal; 2, hypokinetic; 3, akinetic; 4, dyskinetic motion), which was used to analyze WMA and wall thickening (6). A negative judgment was defined as normal ST segments at baseline, exercise and recovery stages. Peak-exercise was defined as patients achieving the age-predicted target HR at a workload of at least 7 METS Regional WMA at rest or randomized exercise stages were deemed as a positive SE result (6,13).

A standard dobutamine stress protocol was offered to those who were less suitable for high workload. Continuous intravenous infusion of dobutamine was performed in 3 min increments with a 5 μg/kg/min onset, which was increased to 10, 20, 30 and 40 μg/kg/min (6).

Exercise EET test. The EET results were interpreted by three expert cardiologists. The treadmill and Bruce protocols were used for evaluation (17). The parameter estimation and assessment were performed as described above.

CAG/CCTA. Standard techniques were used for performing CAG/CCTA. A visual quantitative scoring system was used to evaluate stenosis, which was defined as luminal diameter narrowing in one or more epicardial coronary arteries or major branches by ≥50%. A cutoff value of 50% was used, as this amount was previously indicated to be prognostic of stenosis (18).

Statistical analysis. SPSS 22.0 (IBM Corp.) and GraphPad Prism 5 (GraphPad Software, Inc.) were used for the statistical analyses. Values are expressed as percentages and frequencies or as the mean ± standard error of the mean. Student's unpaired two-tailed t-test and the χ^2 test were used to analyze differences between groups. A two-tailed $P<0.05$ was considered to indicate a statistically significant difference.

Receiver operating characteristic curve (ROC) analysis was used to calculate the specificity and sensitivity in the combined diagnosis of the SE+EET group or of the EET/SE groups following binary logistic regression analysis and combined factor calculation. The following equations were used: PPV=(true positives)/(true positives + false positives); NPV=(true negatives)/(true negatives + false negatives).

Results

Study population. Between August 2018 and August 2019, 278 inpatients or outpatients were enrolled from the Cardiology Department of The First Affiliated Hospital of Nanjing Medical University (Nanjing, China). All of them were suspected to have MI. CAG or CCTA was used for the diagnosis of MI according to the assessment criteria described above. All patients underwent EET and SE and the baseline characteristics were not significantly different. In the MI and the non-MI groups, the mean age was 61.6±1.05 and 60.5±0.62 years, respectively. Other baseline comparison analyses included the HR, SBP, DBP, HTN, diabetes, syncope, dyspnea, chest pain, ejection fraction (EF) and fractional shortening (FS). The demographic and clinicopathological characteristics of the patients are provided in Table I.

Diagnostic efficiency. Following EET, SE and SE+EET, positive patients and patients with typical cardiovascular symptoms underwent CAG according to the diagnostic guidelines of CAD. In this group, patients who underwent CCTA were also included. The PPV and NPV for initial EET were 30.7 and 46.9%, respectively (P<0.001). These values were used for the prediction of flow-limiting disease by angiography. The PPV and NPV values for the initial SE were 55.2 and 82.2%, respectively (P<0.001). Significant improvements were observed in the PPV and NPV values using the combination of EET and SE for diagnosis (66.7 and 89.6%, respectively; P<0.001; Table II). The sensitivity and specificity (95% CI) were also evaluated in each group (Table II). In summary, the combination of EET and SE for diagnosis had particularly good sensitivity and/or specificity. ROC curves were used to further assess the diagnostic accuracy of the EET/SE and EET+SE combination (Fig. 1). The areas under the ROC curves (AUCs) are presented in Table III. The results indicated an excellent AUC for differentiating between EET, SE and their combination (EET+SE). The AUC values for EET/SE and EET+SE were 0.612/0.681 (0.5-0.7, low prediction effect) and 0.728 (0.70-0.85, standard prediction effect), respectively. Images for a representative case with the application of the diagnostic combination are presented in Fig. 2. A markedly positive EET and dobutamine-induced SE were observed in a 77-year-old female patient. Positive ST-segment changes were observed in the ECG and were reflected in the apical 4-chamber frame of the WMA of the ventricular septum, as well as in the lateral wall of the left and right ventricles.

Table I. Clinical characteristics of the study subjects.

Parameter	MI (n=66)	Non-MI (n=121)	P-value
Age (years)	61.6±1.05	60.5±0.62	0.21
Sex (male/female)	39/27	96/116	0.05
HR (bpm)	73.6±0.64	75.1±1.29	0.29
SBP (mmHg)	130.8±0.79	132.1±1.39	0.42
DBP (mmHg)	75.0±0.77	72.3±1.24	0.08
SaO_2 (%)	97.8±0.12	98.0±0.15	0.19
Diabetes	18 (27)	36 (17)	0.07
HTN	52 (79)	101 (48)	<0.001
Syncope	2 (3)	8 (4)	0.78
Dyspnea	12 (18)	20 (9)	0.05
Chest pain	10 (15)	19 (9)	0.15
EF (%)	62.3±0.41	64.3±0.18	<0.001
FS (%)	29.4±0.31	30.6±0.16	<0.001

Values are expressed as the mean ± standard error of the mean or n(%). MI was defined as vessel stenosis on coronary angiography of ≥50% and non-MI as <50%. MI, myocardial ischemia; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SaO_2, blood oxygen saturation; HTN, hypertension; EF, ejection fraction; FS, fractional shortening.

Discussion

Interventional technology has provided a novel perspective on CAD diagnosis and therapy. In the last 30 years, a high number of patients with CAD or MI have been successfully treated due to the progress made in CAG and PCI (1,2). However, the difficulty encountered during the operation and the patients' unwillingness to accept the procedure have limited the prevalence of these methods in primary medical care and in general hospitals. Several studies confirmed that noninvasive tests, such as electrocardiography, echocardiography, myocardial perfusion imaging (MPI), cardiac magnetic resonance imaging (CMR), EET, SE and CCTA provide additional diagnostic value for CAD (19). A review from the Mayo Clinic reported that SE provided an excellent NPV in diagnosing CAD in females without a prior history of ischemic heart disease (7). Various studies illustrated that EET was a useful test for excluding CAD in suspicious patients (20). The stress test provided a physiological mimic both in male and female patients and an easy dynamic monitoring process (21). To the best of our knowledge, the present study was the first to describe the combined use of EET+SE in the diagnosis of MI and compared it with that of EET or SE.

In the present study, the treadmill test and Bruce protocol or dobutamine infusion were used to mimic the stress status in the patients (6). EET or SE is a common method used to exclude MI and a high NPV is particularly valuable for screening patients with a low cardiovascular risk (19). To analyze the predicted sensitivity and specificity of EET and SE, the results were verified by CAG/CCTA. The baseline parameters were compared to eliminate marked bias. Previous studies demonstrated that the predicted data of the SE were superior to those of EET and several follow-up studies provided optimal diagnostic accuracy and prognostic value in the SE group (22). Accordingly, the present study provided novel insight into the diagnosis of MI by EET+SE combined. These results may open new avenues of research into the improvement of the diagnostic efficiency of noninvasive MI diagnosis. The present results indicated that the PPV and NPV were 30.675 and 46.919%, respectively (P<0.001) for EET and 55.172 and 82.199%, respectively (P<0.001) for SE. However, a significant improvement in the diagnostic accuracy of MI was obtained when using EET+SE combined with a PPV and NPV of 66.667 and 89.583%, respectively (P<0.001). Similar to the NPV/PPV, the sensitivity and specificity were superior with the EET+SE method compared to those of either EET or SE alone. Furthermore, superior statistical power was

Table II. Patient number and diagnostic value of EET/SE/EET+SE in the MI/non-MI groups.

A, Patients stratified (n)

Group	EET(+)	EET(-)	SE(+)	SE(-)	EET+SE(+)	EET+SE(-)
MI	50	16	32	34	26	10
Non-MI	113	99	26	186	13	86

B, Diagnostic value

Modality	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV (%)	NPV (%)
EET	75.758 (65-86)	46.919 (40-54)	30.675	46.919
SE	48.485 (36-61)	87.736 (83-92)	55.172	82.199
EET+SE	72.222 (57-88)	86.869 (80-94)	66.667	89.583

MI, myocardial infarction; PPV, positive predictive value; NPV, negative predictive value; EET, exercise electrocardiography test; SE, stress echocardiography.

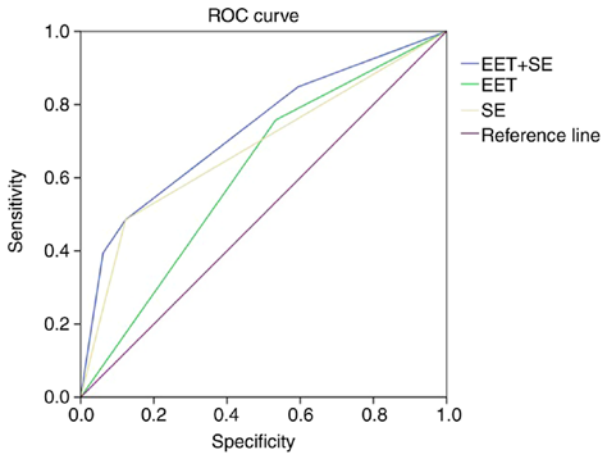

Figure 1. ROC curves for the sensitivity and specificity of the EET, SE and EET+SE combination. Areas under the ROC curve are provided in Table III. ROC, receiver operating characteristic; EET, exercise electrocardiography test; SE, stress echocardiography.

Table III. Parameters from the ROC curve analysis.

Modality	AUC (95% CI)	P-value
EET	0.612 (0.54-0.69)	<0.001
SE	0.681 (0.60-0.76)	<0.001
EET+SE	0.728 (0.65-0.80)	<0.001

EET, exercise electrocardiography test; SE, stress echocardiography; AUC, area under the ROC curve; ROC, receiver operating characteristic.

provided by the ROC curve for the EET+SE method. This initial observation suggested the usefulness of combined EET+SE for the diagnosis of patients with suspected MI, and the sex differences would not influence the results. Therefore, the traditional stress test analysis using the EET or SE requires further development, which may enhance its diagnostic value. In the clinic, the original stress test such as the treadmill or bicycle protocol has been used to exclude MI in potential cases (7,22). The first step was to perform a differential diagnosis of ischemia in patients with a low risk of CAD or those with ischemic symptoms. In both outpatients and inpatients, the total or average costs were significantly reduced and the hospitalization time was reduced (13). Previous studies have reported that compared with CCTA/MPI/CAG, the lack of radiation exposure is an important consideration for pregnant females or those at a high risk of breast cancer (23). Due to its excellent NPV, the combination of the EET and SE represents an efficient and low-cost choice for cardiologists to exclude MI.

In previous studies, EET or SE was proven beneficial for predicting coronary artery stenosis in the heart (6,17). Accordingly, CAG is considered a hallmark for MI diagnosis and prediction of artery stenosis (18). Subsequently, intravascular ultrasound/optical coherence tomography/CMR (coronary flow reserve) and other invasive examinations were used to accurately analyze stenosis of arteries based on CAG (24). These highly accurate examinations focused on microangiopathy or mesangiopathy, respectively. However, the 2020 European Society of Cardiology guidelines have pointed out that non-invasive coronary heart disease examinations are particularly valuable in low-risk patients, whereas SE and EET are particularly recommended as common examination methods (2). The unbalanced allocation of medical resources, resistance to invasive surgery, avoidance of radiation exposure and the reliability of results have led to the wide acceptance and use of CCTA for coronary ischemia examination. The study assessed SE/SEET by using CAG/CCTA or CAG as the gold standard, which is more in line with the ratio of detection methods used in the clinic. Structural or functional disorders result in flow limitations that reflect cardiovascular symptoms. However, coronary slow flow (CSF) without coronary artery stenosis was detected in patients with partial typical angina presenting at emergency departments (25). These patients exhibited vascular endothelial dysfunction or vasospasm (26). In a previous study, EET or SE was also used as a functional

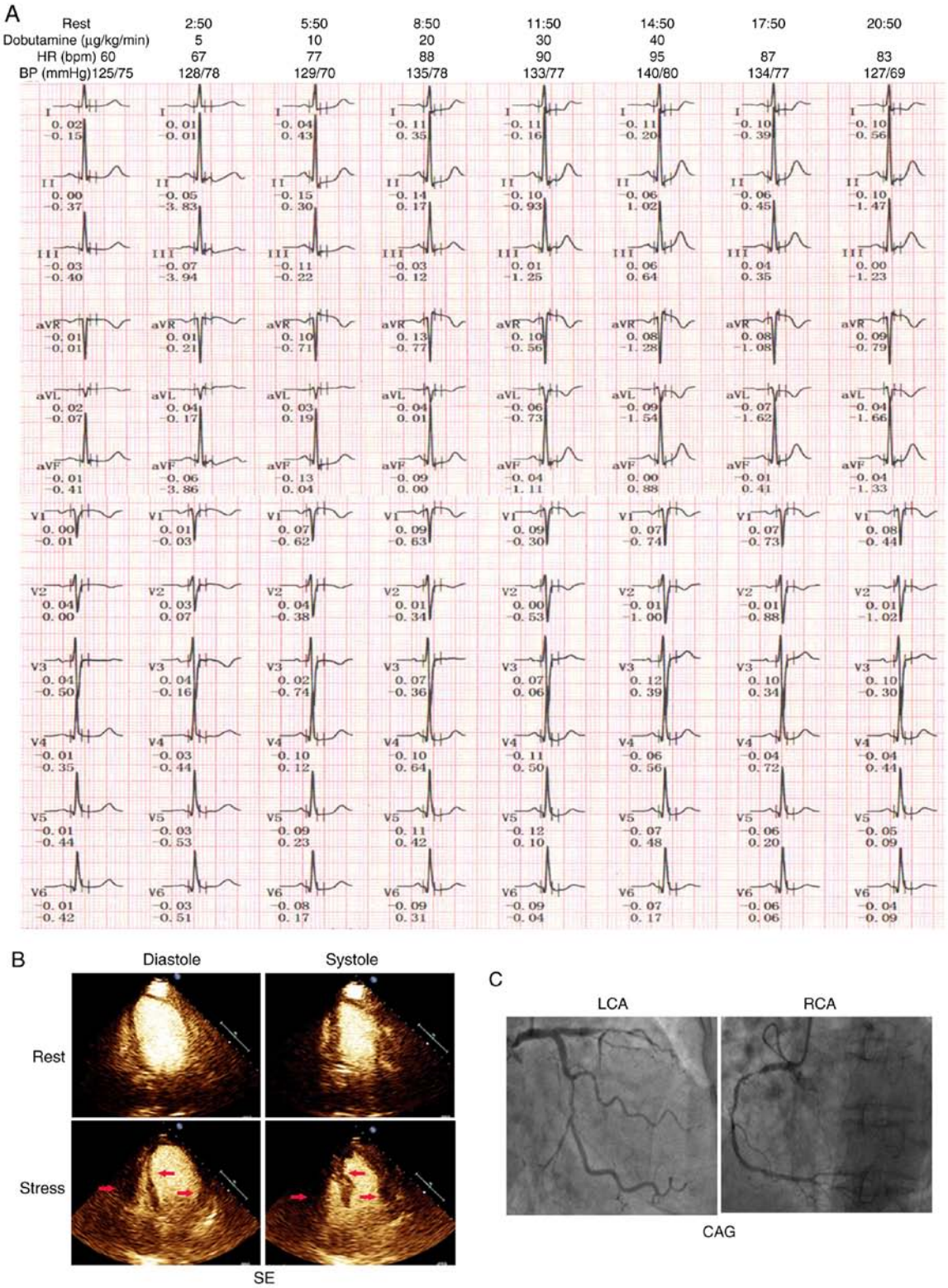

Figure 2. A sample of markedly positive EET and dobutamine SE in a 77-year-old female patient. (A) A standard dobutamine infusion was administered and the positive ST-segment changes are presented in the ECG (top panels). (B) The apical 4-chamber frame in segments of the ventricular septum as well as the lateral wall of the left and right ventricles (middle panels, red arrows). (C) The bottom panels reveal severe stenosis in left circumflex CA/left anterior descending CA and RCA by CAG. EET, exercise electrocardiography test; SE, stress echocardiography; HR, heart rate; BP, blood pressure; CAG, coronary angiography; L/RCA, left/right CA; CA, coronary artery.

test to predict MI and CSF (27). However, it was indicated that the comparatively lower diagnostic efficiency in EET or SE limited its application in the detection of these diseases.

The present study demonstrated that the combination of EET+SE produced outstanding PPV and ROC values in the diagnosis of MI. It may provide MI detection with improved

sensitivity in medical facilities that lack intravascular imaging devices. In a large meta-analysis evaluating the diagnostic accuracy of dobutamine-induced SE, the sensitivity for stenosis detection in the left circumflex coronary artery (55%) was lower than that in the left anterior descending (72%) and right coronary arteries (76%) (28). Of note, the study further indicated higher sensitivity values in detecting three-artery disease (92%) in comparison with one-artery disease (74%) and two-artery disease (86%) (28). These results suggested that the combined EET-associated ST-segment changes and the SE-associated WMA analysis provided an improvement in the detection of artery diseases thanks to the dual-localized detection method. The combined SE/EET test may improve the accuracy of diagnosis, notably in terms of the NPV. It may effectively improve the detection ability of ECG ischemic abnormality examinations in pregnant females, tumor patients and low-risk CAD groups and reduce complications, the duration of hospital stay and medical expenses.

In brief, the present study demonstrated that SE or EET were useful for diagnosing MI in potential patients. The results of the present study confirmed that the combined analysis improved the accuracy of the prediction and diagnosis of MI. This high diagnostic efficiency may provide cardiologists with novel insight into the differential diagnosis/prediction of MI.

The present study has certain limitations. First, it was a single-center study. In addition, the sample size was limited and 3 cardiologists performed EET and SE. Both workload and dobutamine infusion were used as stress protocols. The present study also lacked prognostic factor analysis for post-PCI patients. Subsequently, CCTA/CAG examinations were selected based on the cardiologist's experience and the EET/SE results.

In conclusion, EET and SE are important noninvasive examination methods that may be used for MI diagnosis. According to the present results, superior diagnostic efficiency for MI was noted when the combined EET+SE method was used; however, it may still be inferior to the gold standard. This methodological improvement may provide novel insight for cardiologists to develop strategies for MI exclusion and prediction. Therefore, the prevalence of combined EET+SE analysis may be used to optimize MI diagnosis and reduce the financial costs used for cardiac exams either in primary medical care or in general hospitals.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

NZ, XF and DL designed the study. NZ, QH, JW, JZ and DL performed the experiments. Data were collated by NZ and QH and the results were discussed by all authors. NZ, QH and JW prepared the figures. NZ, XF and QH wrote the first draft of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This research was approved by the Committee of Ethics in Human Research at The First Affiliated Hospital of Nanjing Medical University (Nanjing, China; no. SRFA-048). All of the volunteers were aware of the risks and provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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