Incremental Diagnostic Performance of Combined Parameters in the Detection of Severe Coronary Artery Disease Using Exercise Gated Myocardial Perfusion Imaging

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Abstract

Purpose

Myocardial perfusion imaging (MPI) using gated single-photon emission tomography (gSPECT) may underestimate the severity of coronary artery disease (CAD). This study aimed to evaluate the significance of combined parameters derived from gSPECT, as well as treadmill stress test parameters, in the detection of severe CAD.

Methods

A total of 211 consecutive patients referred for exercise MPI between June 2011 and June 2013 (who received invasive coronary angiography within six months after MPI) were retrospectively reviewed. Exercise MPI was performed with Bruce protocol and ²⁰¹Tl injected at peak exercise. Gated SPECT was performed using a cadmium-zinc-telluride camera and processed by QPS/QGS software. Perfusion defect abnormalities such as sum stress score (SSS); sum difference score, algorithm-derived total perfusion deficits, transient ischemic dilatation ratios of end-diastolic volumes and end-systolic volumes, post-stress changes in ejection fraction, and lung/heart ratio (LHR) were calculated. Treadmill parameters, including ST depression (STD) at the 1st and 3rd minutes of recovery stage (1STD and 3STD), maximal STD corrected by heart rate increment (ST/HR), heart rate decline in 1st and 3rd minutes of recovery stage, recovery heart rate ratio (HR ratio), systolic and mean blood pressure ratios (SBP ratio and MAP ratio) during recovery phase were recorded. Diagnostic performances of these parameters were analyzed with receiver operating characteristic (ROC) analysis and logistic regression for detection of left main (≥ 50%) or 3-vessel disease (all ≥ 70% luminal stenosis) on invasive angiography.
Results
Among various MPI and treadmill parameters used for detection of severe CAD, SSS and ST/HR had the highest AUC (0.78, 0.73, $p = \text{NS}$) and best cut-off values (SSS > 6, ST/HR > 17.39 $\text{mV/bpm}$), respectively. By univariate logistic regression, all parameters except $1^\prime$HRR, $3^\prime$HRR, SBP and MAP ratios increased the odds ratio of severe CAD. Only increased $L/H$ ratio, $3^\prime$STD, and HR ratio remained significant after multivariate regression. The predicted values of combined MPI and treadmill parameters ($LHR$, $3^\prime$STD, and HR ratio) gave the best ROC (AUC: 0.91) than any individual parameter or parameter combination.

Conclusions
Of all treadmill and gSPECT parameters, the combination of MPI and treadmill parameters can offer better diagnostic performance for severe CAD.

Introduction
Myocardial perfusion imaging (MPI) using gated single-photon emission tomography (gSPECT) is a useful imaging modality for the detection and risk stratification of coronary artery disease (CAD). However, it is well known that MPI may underestimate the severity and extent of CAD due to its relative quantification of perfusion defects, particularly in cases of balanced ischemia [1]. Although the problem of balanced ischemia can be solved by calculating coronary flow reserve using dynamic positron emission tomography [2, 3] or SPECT [4], additional costs and/or an acquisition algorithm are needed.

In addition to perfusion deficits, several stress-induced abnormalities [such as transient ischemic dilation (TID) and post-stress ejection fraction (EF)] can be derived from gSPECT [5–8], and increased pulmonary uptake. These stress-induced abnormalities have shown diagnostic and prognostic importance in patients with suspected CAD [9–11]. Left ventricular TID ratio is known as a functional parameter which could increase the sensitivity of MPI for severe CAD [12–16] and may be a specific prognostic marker for cardiovascular events [17–19]. Post-stress left ventricular stunning, in cases of decreased EF, is also an indicator of poor prognosis on gSPECT [18].

In addition, previous studies have shown that a number of variables obtained from the treadmill exercise test (TET) alone can be used to estimate prognosis in patients with suspected CAD. ST depression (STD) during the recovery stage [20], STD corrected by heart rate (HR) [21, 22], and post-exercise hemodynamic abnormalities, such as post-stress systolic blood pressure (SBP) [23–27] and HR changes during the recovery stage [28–31], are associated with higher risk of cardiovascular events and mortality.

In this retrospective study, the diagnostic performance of combined parameters was compared with gSPECT and TET parameters. The aim of this study was to evaluate the significance of combined parameters derived from gSPECT using novel cadmium-zinc-telluride (CZT) detectors, as well as treadmill stress test parameters, in the detection of severe CAD.

Methods
Patients referred for exercise MPI between June 2011 and June 2013, who received invasive coronary angiography (CAG) within six months, were retrospectively reviewed. Patients were
excluded if they had a history of myocardial infarction (MI), coronary artery bypass grafting, percutaneous coronary intervention, or documented congenital heart disease or severe valvular disease. The medical records (including demographics, cardiac risk factors, and medication) were reviewed for each patient. The pretest probability of CAD was evaluated using age, sex and angina typicality-based approach [32].

Ethical statement
This study was approved by the institutional review board of National Taiwan University Hospital. Patients’ written informed consent was waived due to the retrospective nature of the study.

Treadmill MPI protocol
MPI gSPECT was performed using the one-day exercise stress-rest protocol with injection of 3 mCi (111 MBq) thallium-201 (201TI). Treadmill exercise stress was applied using the standard Bruce protocol with a 4 minute recovery stage. Endpoints of treadmill stress included achievement of 85% of age-adjusted maximal heart rate, >2 mm ST depression, systolic blood pressure (SBP) >250 mmHg, typical angina, frequent ventricular ectopy, hemodynamically compromised arrhythmia, or physical limitation.

Imaging acquisition was performed using the Discovery NM530c SPECT gamma camera (GE Healthcare, Haifa, Israel), which was equipped with solid-state CZT detectors. Projections were recorded on 32 × 32 pixelated (2.46 × 2.46 mm²) CZT elements. Maximum likelihood expectation maximization was used with a reconstructed voxel size of 4.0 × 4.0 × 4.0 mm³. A Butterworth post-processing filter was applied (order 10, cut-off frequency, 0.37) to the reconstructed slices [33].

Treadmill parameters
Maximal ST depression (STD) and ST depression corrected by maximum HR (ST/HR) [21, 22] were recorded. STDs at 1 min and 3 min of the recovery stage (1’STD, 3’STD) were also recorded. The SBP and HR dynamic changes during recovery stage were reviewed as post-stress hemodynamic changes. SBP at 3 min of recovery stage was divided by the SBP at 1 min of recovery stage to manifest the decline in SBP from target exercise level and was recorded as the SBP ratio [34]. The difference between heart rate at peak exercise and that at 1st min and 3rd min of recovery stage were also recorded (1’HRR and 3’HRR, respectively) [8, 28]. HR recovery ratio (HR ratio) was calculated as ratio of HR at 3rd min of recovery stage and that at 1st min of recovery stage.

MPI parameters
Semiquantitative interpretation of 17 segments from the short axis, vertical long axis, and horizontal long axis of each gSPECT was performed by two experienced nuclear physicians. Each segment was visually scored using a 5-point scale: 0 = normal, 1 = equivocal or mild, 2 = moderate, 3 = severe reduction of radiotracer uptake, and 4 = absence of radiotracer uptake. The scores of all 17 segments for both stress and rest images were summed to produce summed stress scores (SSS) and summed rest scores (SRS), respectively. The difference between SSS and SRS was recorded as the summed difference score (SDS). For gSPECT functional parameters, automated algorithm quantitative perfusion SPECT, and quantitative gated SPECT (QPS/QGS, Cedars-Sinai Medical Center, LA, USA) were used. Patients were excluded for functional parameter analysis if significant arrhythmia compromised the ECG gating.
The extent and severity of pixel-based cardiac perfusion defects at rest (rTPD) and post-stress (sTPD) were also compared and expressed as continuous parameters of QPS/QGS [35]. The difference between sTPD and rTPD was recorded as dTPD. The left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) and the transient dilatation ratios (TIDs) of EDV and ESV were calculated at stress and rest. TID ratios derived from hearts less than 20 ml (i.e., small hearts) were excluded from analysis. Both stress and rest left ventricular EF ratios (EF ratio) and differences (EF change), retrieved from the QGS algorithm, were calculated as manifestations of post-stress EF changes.

The same 3 × 3 cm square region of interest (ROI) was placed on the anterior wall and lung region above the anterior wall at a distance equal to two ROIs using the anterior view of maximal intensity projection (MIP). Placement of ROIs on areas with hypoperfused myocardium was avoided. The ratio of total radioactivity recorded from the ROIs of lung and myocardium were calculated as the lung/heart ratio (LHR). The post-stress LHR (sLHR) and increment in LHR (dLHR) from rest to stress were used as parameters of increased pulmonary uptake after stress.

**Coronary angiography results**

CAG results performed within 6 months served as the gold standard. CAD was defined as more than 70% stenosis in any vessel. Severe CAD was defined as (1) left main arterial stenosis more than 50%, (2) three vessel disease with luminal stenosis of each major epicardial coronary artery more than 70%, and (3) two vessel disease including left anterior descending artery (LAD) with stenosis more than 70%.

**Statistical analysis**

Continuous variables of patient groups were compared using the student t-test. Mann-Whitney test was used if normalcy of variables was rejected. Categorical variables were compared used Chi-square test. A p value < 0.05 was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of each parameter were calculated and compared. The receiver operating characteristic (ROC) curve was used to compare the diagnostic performance of parameters and to determine cut-off values for identification of severe CAD, primarily using Youden index (except for the TID ratio). The cut-off values of TID ratio were determined using the mean value + 2 standard deviations (SDs) in patients without stenotic coronary arteries, according to CAG results [12, 13]. The cut-off criteria were also calculated to determine diagnostic performance using a combination of at least two different parameters, all of which had to be fulfilled simultaneously. The performance between cut-off values was compared using McNemar test or Cochran’s Q test.

**Results**

A total of 211 patients were included for analysis. Most patients included had intermediate to high pretest cardiovascular risk and MPI was performed for risk stratification. Two hundred and five patients (97%) had interpretable ECG. Four patients (1.9%) with left bundle branch block and another two patients (0.9%) with ventricular pacing rhythms were excluded for ST-T change interpretation. MPI results of five patients (2.4%) with atrial fibrillation were still included since no rapid ventricular response was noted on baseline ECG. The exercise duration of these five patients all reached stage 2 of Bruce protocol with average METS of 4.6. Other abnormal rhythm noted on baseline ECG included eighteen patients (8.5%) with right bundle branch block, eight patients (3.8%) with first degree atrioventricular block, and six patients...
(2.8%) with left ventricular hypertrophy. Fifty-two patients (24.6%) had positive treadmill stress test indicative myocardium ischemia.

Most patients had intermediate to high pretest CAD risk (high risk: 61 patients; intermediate risk: 146 patients; and low risk: 4 patients). Among all patients, 35 (20%) patients were diagnosed with severe CAD. The demographic comparisons between patients with and without severe CAD are listed in Table 1. Patients with severe CAD had a higher prevalence of diabetes.

### Table 1. The comparison of demographic data between patient with and without severe CAD.

|                      | No severe CAD | Severe CAD | P value |
|----------------------|---------------|------------|---------|
| Patients No.         | 176           | 35         | <0.01   |
| Age                  | 59±10         | 59±9       | 0.98    |
| BMI                  | 26.4±3.7      | 25.5±3.2   | 0.21    |
| METS                 | 7.2±1.5       | 6.8±1.5    | 0.09    |
| HTN                  | 125 (71%)     | 25 (71%)   | 0.88    |
| DM                   | 44 (25%)      | 17 (49%)   | 0.01    |
| Hyperlipidemia       | 98 (57%)      | 27 (77%)   | 0.02    |
| Smoking              | 62 (35%)      | 13 (37%)   | 0.98    |
| Medication           |               |            |         |
| Aspirin/Clopidogrel  | 87 (49%)      | 21 (60%)   | 0.34    |
| Nitrate              | 33 (19%)      | 12 (34%)   | 0.07    |
| Beta-blocker         | 71 (40%)      | 14 (40%)   | 0.88    |
| ACEI/ARB             | 68 (39%)      | 17 (49%)   | 0.37    |
| Statin/Fibrate       | 35 (20%)      | 7 (20%)    | 0.83    |
| MPI parameters       |               |            |         |
| SSS                  | 5.2±5.4       | 12.6±10.1  | <0.01   |
| SDS                  | 4.1±4.0       | 8.3±5.4    | <0.01   |
| sTPD                 | 8.5±7.6       | 16.1±11.6  | <0.01   |
| dTPD                 | 4.2±6.4       | 9.0±6.6    | <0.01   |
| ESV TID              | 0.97±0.20     | 1.09±0.27  | 0.06    |
| EDV TID              | 1.0±0.11      | 1.09±0.14  | <0.01   |
| EF ratio             | 1.05±0.15     | 0.97±0.19  | 0.17    |
| EF changes           | 1.9±6.7       | 2.8±13.2   | 0.10    |
| sLH ratio            | 0.30±0.06     | 0.33±0.08  | 0.13    |
| rLH ratio            | 0.32±0.05     | 0.32±0.06  | 0.70    |
| dLH ratio            | -0.02±0.05    | 0.01±0.05  | <0.01   |
| Treadmill parameters |               |            |         |
| ST/HR                | 17.28±14.97   | 29.72±18.85| <0.01   |
| 1' STD               | 0.34±0.53     | 0.78±0.72  | <0.01   |
| 3' STD               | 0.40±0.50     | 0.92±0.73  | <0.01   |
| SBP ratio            | 0.92±0.29     | 0.99±0.28  | 0.01    |
| MAP ratio            | 0.98±0.17     | 1.01±0.23  | 0.07    |
| 1'HRR                | 23.1±9.8      | 24.3±10.4  | 0.05    |
| 3'HRR                | 43.7±12.0     | 50.4±10.3  | 0.10    |
| HR ratio             | 0.81±0.12     | 0.86±0.07  | 0.01    |

Abbreviation:
BMI, body mass index; METS, metabolic equivalents; HTN, hypertension; DM, diabetes mellitus; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; rLH ratio, the lung/heart ratio at rest.

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mellitus and hyperlipidemia, while no difference had been noticed regarding prescribed medication. Significant differences between the two groups were observed for SSS, SDS, TPD, EDV TID, dLHR, ST/HR, and recovery STD.

The ROC analysis of TET and MPI parameters are displayed in Fig 1 and Table 2. SSS and ST/HR had the highest AUC among MPI and TET parameters (AUC = 0.781 and 0.730, respectively). The mean values of EDV TID and ESV TID in patients with patent coronary arteries on CAG were 0.99 ± 0.10 and 0.93 ± 0.17, respectively. The cut-off values of EDV TID and ESV TID were, therefore, set as 1.19 and 1.27, respectively, i.e., 2 SD above the mean values. Cut-off values of parameters other than TID are listed in Table 3. Corresponding sensitivity, specificity, PPV, NPV and accuracy of each TET, MPI and combined parameters are also listed in Table 3.

Among MPI and treadmill parameters, SSS and ST/HR had the highest AUCs (0.78 and 0.73, respectively) and best cut-off values (SSS > 6 and ST/HR > 17.39 10^{-2} mV/bpm, respectively) in detection of severe CAD. SSS, as well as other perfusion deficit scores (SDS, sTPD, and dTPD) had fair sensitivity of up to 80%. EDV and ESV TID had extremely low sensitivity (both 20%) but high specificity (91%, 86%, respectively) for severe CAD.

Criteria using combined cut-off values of SSS or ST/HR, in addition to one or two other parameters, are shown in Table 3. These criteria had high specificity and accuracy in the detection of severe CAD, but sensitivity was inevitably compromised.

Upon univariate logistic regression (Table 4), all parameters significantly increased the odds ratio of severe CAD except 1’HRR, 3’HRR, and mean arterial pressure ratios in recovery stage (MAP ratio). However, only dLHR, 3’STD, and HR ratio remained significant on multivariate logistic regression (Table 5). The predicted probabilities generated from multivariate logistic regression had the highest AUC (0.91) and best detection of severe CAD (sensitivity 87%,
specificity 90%, PPV 67%, NPV 97%, and accuracy 89%) of any other individual or combination of parameters mentioned above (p < 0.01).

Discussion

The identification of severe CAD based on abnormal MPI is important for referral physicians since management is critical in these patients. MPI is a useful imaging modality for the diagnosis of CAD. However, its limitation in severe extensive CAD, the so-called balanced ischemia, has been well documented. The perfusion defects visualized on MPI may underestimate the extent of coronary artery stenosis due to the lack of quantification of absolute coronary blood flow. Even using SSS > 6 as the cut-off, below 8, the sensitivity was still only 77%.

Severe functional parameters on gSPECT MPI are associated with severe CAD. Prior studies have found that TID could be used to diagnose severe CAD in conjunction with perfusion defects. In the present study, the cut-off values for TID were similar to prior investigations [12, 13, 36], however, the sensitivity (20%) was lower than expected. Prior studies had suggested the superior performance of ESV TID over EDV TID [37], while only EDV TID remained significant in this study. Possible explanations for this discrepancy include differences in radioisotopes used (99mTc tracers vs. 201Tl), differences in stressors used (pharmacological vs. exercise), different imaging protocols, cameras, algorithms, methods of ratio calculation, or even differences in patients’ underlying disease such as diabetes or left ventricular hypertrophy [38, 39]. The significantly high prevalence of small heart size (79 patients, 37%) may have contributed to the differences in TID results. Small LV size is not uncommon in the Asian population, especially in women [40–42]. Other functional parameters, such as decreased EF or increased pulmonary uptake after stress, are associated with worse prognosis [43].

Recently introduced SPECT using solid state CZT cameras has shown better intrinsic performance compared with Anger cameras [44, 45]. The significant reduction in acquisition time allows for rapid imaging before recovery of post-stress stunning [46]. However, the differences

Table 2. The ROC analysis of MPI and TET parameters.

| Parameter | AUC  | SE  | 95% CI        | P   |
|-----------|------|-----|---------------|-----|
| SSS       | 0.781| 0.0436 | 0.720 to 0.835 | <0.01 |
| SDS       | 0.763| 0.0450 | 0.700 to 0.819 | <0.01 |
| sTPD      | 0.731| 0.0458 | 0.666 to 0.789 | <0.01 |
| dTPD      | 0.727| 0.0456 | 0.662 to 0.786 | <0.01 |
| EDV TID   | 0.707| 0.0526 | 0.622 to 0.782 | <0.01 |
| ESV TID   | 0.621| 0.0670 | 0.532 to 0.703 | 0.07 |
| EF ratio  | 0.608| 0.0696 | 0.520 to 0.691 | 0.12 |
| EF change | 0.604| 0.0691 | 0.516 to 0.688 | 0.13 |
| dLHR      | 0.673| 0.0492 | 0.605 to 0.736 | <0.01 |
| ST/HR     | 0.730| 0.0441 | 0.665 to 0.789 | <0.01 |
| 1’STD     | 0.706| 0.0500 | 0.639 to 0.767 | <0.01 |
| 3’STD     | 0.717| 0.0532 | 0.649 to 0.778 | <0.01 |
| 1’HRR     | 0.512| 0.0549 | 0.443 to 0.581 | 0.83 |
| 3’HRR     | 0.590| 0.0487 | 0.519 to 0.657 | 0.07 |
| HR ratio  | 0.650| 0.0500 | 0.582 to 0.715 | <0.01 |
| SBP ratio | 0.637| 0.0566 | 0.568 to 0.703 | 0.02 |
| MAP ratio | 0.596| 0.0576 | 0.526 to 0.664 | 0.09 |

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in prognostic value between gated functional parameters derived from different camera systems have not yet be validated. Although ventricular volume and EF obtained from CZT cameras and Anger cameras have shown good agreement based on prior studies [47, 48], the cut-off values for post-stress abnormalities may be different. For example, the upper limit of post-stress lung/heart ratio (0.41) of patients without CAD in our study was apparently lower than that previously reported [49, 50]. Furthermore, gSPECT using 201Tl is clinically feasible using CZT cameras because of higher sensitivity [44, 45, 51], but it could still contribute to differences in functional parameters on gSPECT [52, 53].

The criteria of positive TET result using significant STD was not sensitive enough for the diagnosis of CAD. Using STD >2 mm for severe CAD had poor sensitivity (46%) in this study.

| Table 3. The cutoff values of MPI, TET and combined parameters and corresponding diagnostic performance. |
|---------------------------------------------------------------|-----------------|-----------------|---------------|---------------|---------------|
| **Treadmill parameters**                                     | **Cut off values** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** |
| STD                                                          | >1*             | 46              | 80             | 31           | 88           | 74           |
| ST/HR                                                        | >17.39          | 77              | 61             | 28           | 93           | 63           |
| 3' STD                                                       | >0.6            | 63              | 79             | 39           | 91           | 76           |
| SBP ratio                                                    | >0.9            | 79              | 43             | 22           | 91           | 49           |
| MAP ratio                                                    | >1.03           | 49              | 72             | 26           | 87           | 68           |
| 3HRR                                                         | <50             | 83              | 32             | 20           | 90           | 40           |
| HR ratio                                                     | >0.87           | 37              | 83             | 30           | 97           | 75           |
| STHR + SBP                                                   | 60              | 77              | 35             | 91           | 75           |
| STHR + 3HRR                                                   | 66              | 73              | 33             | 91           | 72           |
| STHR + SBP ratio + 3HRR                                      | 54              | 85              | 43             | 90           | 80           |
| **MPI parameters**                                           | **Cut off values** | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** |
| SSS                                                          | >6              | 77              | 74             | 38           | 94           | 75           |
| SDS                                                          | >4              | 80              | 66             | 32           | 94           | 68           |
| sTPD                                                         | >8              | 80              | 63             | 30           | 94           | 65           |
| dTPD                                                         | >5              | 71              | 64             | 28           | 92           | 65           |
| EDV TID                                                      | >1.19           | 20              | 91             | 32           | 85           | 80           |
| ESV TID                                                      | >1.27           | 20              | 86             | 23           | 84           | 75           |
| EF ratio                                                     | <1.04           | 68              | 41             | 18           | 86           | 45           |
| EF change                                                    | <3              | 34              | 76             | 22           | 85           | 69           |
| sLHR                                                         | >0.37           | 32              | 90             | 38           | 87           | 80           |
| dLHR                                                         | >0.04           | 88              | 37             | 21           | 94           | 45           |
| SSS + EDV TID                                                | 20              | 97              | 54             | 86           | 84           |
| SSS + EF ratio                                               | 54              | 80              | 35             | 90           | 76           |
| SSS + dLHR                                                   | 68              | 83              | 43             | 93           | 80           |
| SSS + sLHR                                                   | 24              | 97              | 57             | 87           | 85           |
| **MPI + Treadmill parameters**                               | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** |
| SSS + ST/HR                                                   | 63              | 86              | 47             | 92           | 82           |
| SSS + SBP                                                    | 66              | 84              | 46             | 92           | 81           |
| SSS + 3HRR                                                    | 66              | 82              | 43             | 92           | 79           |
| SSS + EDV + ST/HR                                            | 20              | 97              | 58             | 86           | 84           |
| SSS + ST/HR + SBP                                            | 51              | 91              | 53             | 90           | 84           |
| SSS + ST/HR + 3HRR                                           | 51              | 90              | 51             | 90           | 84           |
| SSS + dLH + ST/HR                                            | 56              | 89              | 49             | 91           | 83           |
| Logistic predict values                                       | 87              | 90              | 67             | 97           | 89           |

* >1mm with horizontal or downsloping ST depression, >2mm with upsloping ST depression in consecutive multiple leads.

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However, the HR corrected STD or STD in the recovery stage showed better performance than the uncorrected STD. In addition, abnormal hemodynamic changes after exercise have well established prognostic relevance regarding cardiovascular events and mortality. The delayed decline of SBP during the recovery stage of TET, the so-called paradoxical SBP elevation, was shown to be associated with severe CAD in prior studies [23, 26, 34]. However, like MPI parameters, none of TET parameters rendered acceptable cut-off values.

The majority of patients included in the current study had intermediate and high pre-test cardiovascular risk. However, estimating pre-test probability of angiographically significant CAD with traditional age, sex, and angina typicality-based approach sometimes overestimates the actual prevalence of disease[54]. Therefore stress tests might provide incremental value of risk stratification. The possibility of severe CAD is increasing in patients with intermediate and high pre-test cardiovascular risk. However, estimating pre-test probability of angiographically significant CAD with traditional age, sex, and angina typicality-based approach sometimes overestimates the actual prevalence of disease[54]. Therefore stress tests might provide incremental value of risk stratification. The possibility of severe CAD is increasing in patients with intermediate and high pre-test cardiovascular risk. However, estimating pre-test probability of angiographically significant CAD with traditional age, sex, and angina typicality-based approach sometimes overestimates the actual prevalence of disease[54]. Therefore stress tests might provide incremental value of risk stratification. The possibility of severe CAD is increasing in patients with intermediate and

### Table 4. The univariate logistic regression analysis.

| Variable | Odds ratio | 95% CI       | P    |
|----------|------------|--------------|------|
| SSS      | 1.1361     | 1.0766 to 1.1989 | <0.01|
| SDS      | 1.1873     | 1.1004 to 1.2810 | <0.01|
| dTPD     | 1.0997     | 1.0440 to 1.1583 | <0.01|
| EDV TID* | 1.0603     | 1.0224 to 1.0995 | <0.01|
| ESV TID* | 1.0255     | 1.0060 to 1.0454 | 0.01 |
| EF ratio | 0.0297     | 0.0012 to 0.7579 | 0.03 |
| EF change| 0.9389     | 0.8852 to 0.9958 | 0.04 |
| dLHR*    | 1.1548     | 1.0631 to 1.2544 | <0.01|
| ST/HR    | 1.0400     | 1.0189 to 1.0614 | <0.01|
| 1'STD    | 2.8165     | 1.6280 to 4.8728 | <0.01|
| 3'STD    | 3.7164     | 2.0303 to 6.8028 | <0.01|
| 1'HRR    | 1.0122     | 0.9758 to 1.0500 | 0.52 |
| 3'HRR    | 0.9770     | 0.9478 to 1.0072 | 0.13 |
| HR ratio*| 1.0531     | 1.0048 to 1.1036 | 0.03 |
| SBP ratio*| 1.0235     | 1.0037 to 1.0436 | 0.02 |
| MAP ratio*| 1.0274     | 0.9996 to 1.0560 | 0.05 |

* Multiplied by 100 for unit correction.

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### Table 5. Multivariate logistic regression of MPI TET parameters.

| Variable  | Coefficient | Std. Error | P    |
|-----------|-------------|------------|------|
| SSS       | 0.058750    | 0.038571   | 0.13 |
| EDV TID*  | 0.056826    | 0.036858   | 0.12 |
| EF_ratio  | 1.79116     | 2.29137    | 0.43 |
| dLHR*     | 0.26390     | 0.088108   | <0.01|
| ST/HR     | -0.010108   | 0.043857   | 0.82 |
| 3'STD     | 2.21776     | 0.94335    | 0.02 |
| HR ratio* | 0.27037     | 0.083471   | <0.01|
| SBP ratio*| 0.0083895   | 0.021928   | 0.70 |
| Constant  | -34.4571    |            |      |

*Multiplied by 100 for unit correction.
high risk. The balanced ischemia on MPI might underestimate the disease severity, it is important to consider the risk factors, symptoms and prior treadmill exercise test results. The increment of diagnostic performance of combined MPI and treadmill parameters could be expected; however, previous studies mainly focused on validation of the diagnostic or prognostic significance of CAD of single test, and limited data validated the combination of treadmill ECG and MPI variables in patients with intermediate and high risk groups to our best knowledge. The majority (97%) of enrolled patients in this study had interpretable ECG and was feasible for analysis. The addition of TET to the gSPECT parameters offered better diagnostic accuracy than the individual test, primarily through an improvement in specificity. Using multivariate logistic regression, the probability of severe CAD could be predicted well by a combination of dLHR, 3'STD, and HR ratio. It is worth mentioning that LHR should be calculated despite the small field of view of the CZT camera considering its prognostic significance based on our results. Using the predicted probabilities as a cut-off had high sensitivity, specificity, and accuracy for diagnosis of severe CAD. For the few patients with non-evaluable ECG, as the other six patients (3%) in this study, the MPI parameters were still helpful with the acceptable accuracy.

The major limitations of this study included its retrospective nature and small sample size with heterogeneous characteristics. Only patients who underwent coronary angiography were included in the analysis which may have caused a selection bias. The frequency of coronary risk factors was high in the enrolled subjects, which might limit the generalization for clinical application.

In conclusion, although further prospective validation in a larger population is needed, our results encourage the wide use of treadmill as a stressor for MPI since these treadmill parameters could be easily retrieved from daily practice without additional cost or algorithm.

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Author Contributions

Conceived and designed the experiments: CJL YWW. Performed the experiments: CJL YWW KYK YCC. Analyzed the data: CJL YWW KYK. Contributed reagents/materials/analysis tools: CJL YWW KYK YCC MFC RFY KYT. Wrote the paper: CJL YWW.

References

1. Hsu PY, Lee WJ, Cheng MF, Yen RF, Tzen KY, Wu YW. The Incremental value of coronary CT angiography added to myocardial perfusion imaging in patients with intermediate-to-high cardiovascular risk. Acta Cardiol Sin. 2015; In press.
2. Wu YW, Chen YH, Wang SS, Jui HY, Yen RF, Tzen KY, et al. PET assessment of myocardial perfusion reserve inversely correlates with intravascular ultrasound findings in angiographically normal cardiac transplant recipients. J Nucl Med. 2010; 51(6):906–12. doi: 10.2967/jnumed.109.073833 PMID: 20484427
3. Schindler TH, Quercioli A, Valenta I, Ambrosio G, Wahl RL, Dilsizian V. Quantitative assessment of myocardial blood flow—clinical and research applications. Semin Nucl Med. 2014; 44(4):274–93. doi: 10.1053/j.semnuclmed.2014.04.002 PMID: 24948151
4. Hsu B, Chen FC, Wu TC, Huang WS, Hou PN, Chen CC, et al. Quantitation of myocardial blood flow and myocardial flow reserve with 99mTc-sestamibi dynamic SPECT/CT to enhance detection of coronary artery disease. Eur J Nucl Med Mol Imaging. 2014; 41(12):2294–306. doi: 10.1007/s00259-014-2881-9 PMID: 25143072
5. Sharir T, Germano G, Kavanagh PB, Lai S, Cohen I, Lewin HC, et al. Incremental prognostic value of post-stress left ventricular ejection fraction and volume by gated myocardial perfusion single photon emission computed tomography. Circulation. 1999; 100(10):1035–42. PMID: 10477527

6. Dona M, Massi L, Settimo L, Bartolini M, Gianni G, Pupi A, et al. Prognostic implications of post-stress ejection fraction decrease detected by gated SPECT in the absence of stress-induced perfusion abnormalities. Eur J Nucl Med Mol Imaging. 2011; 38(3):485–90. doi: 10.1007/s00259-010-1643-6 PMID: 21061211

7. Borges-Neto S, Javaid A, Shaw LK, Kong DF, Hanson MW, Pagnanelli RA, et al. Poststress measurements of left ventricular function with gated perfusion SPECT: comparison with resting measurements by using a same-day perfusion-function protocol. Radiology. 2000; 215(2):529–33. PMID: 10796936

8. Watanabe J, Thamilaranas M, Blackstone EH, Thomas JD, Lauer MS. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: the case of stress echocardiography. Circulation. 2001; 104(16):1911–6. PMID: 11602493

9. Higgins JP, Higgins JA, Williams G. Stress-induced abnormalities in myocardial perfusion imaging that are not related to perfusion but are of diagnostic and prognostic importance. European journal of nuclear medicine and molecular imaging. 2007; 34(4):584–95. PMID: 17103165

10. Hansen CL, Sangrigoli R, Nkadi E, Kramer M. Comparison of pulmonary uptake with transient cavity dilation after exercise thallium-201 perfusion imaging. J Am Coll Cardiol. 1999; 33(5):1323–7. PMID: 10193734

11. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. N Engl J Med. 1987; 317(24):1486–9. PMID: 3683484

12. Weiss AT, Berman DS, Lew AS, Nielsen J, Potkin B, Swan HJ, et al. Transient ischemic dilation of the left ventricle on stress thallium-201 scintigraphy: a marker of severe and extensive coronary artery disease. J Am Coll Cardiol. 1987; 9(4):752–9. PMID: 3558976

13. Mazzanti M, Germano G, Kiat H, Kavanagh PB, Alexanderson E, Friedman JD, et al. Identification of severe and extensive coronary artery disease by automatic measurement of transient ischemic dilation of the left ventricle in dual-isotope myocardial perfusion SPECT. Journal of the American College of Cardiology. 1996; 27(7):1612–20. PMID: 8696545

14. Abidov A, Bax JJ, Hayes SW, Cohen I, Nishina H, Yoda S, et al. Integration of automatically measured transient ischemic dilation ratio into interpretation of adenosine stress myocardial perfusion SPECT for detection of severe and extensive CAD. Journal of nuclear medicine: official publication, Society of Nuclear Medicine. 2004; 45(12):1999–2007.

15. Xu Y, Ansari R, Clond M, Hyun M, Lemley M Jr., Fish M, et al. Transient ischemic dilation for coronary artery disease in quantitative analysis of same-day sestamibi myocardial perfusion SPECT. J Nucl Cardiol. 2012; 19(3):465–73. doi: 10.1007/s12350-012-9527-8 PMID: 22398366

16. Kinoshita N, Sugihara H, Adachi Y, Nakamura T, Azuma A, Kohno Y, et al. Assessment of transient left ventricular dilatation on rest and exercise on Tc-99m tetrofosmin myocardial SPECT. Clin Nucl Med. 2002; 27(1):34–9. PMID: 11805482

17. Abidov A, Bax JJ, Hayes SW, Hachamovitch R, Cohen I, Gerlach J, et al. Transient ischemic dilation ratio of the left ventricle is a significant predictor of future cardiac events in patients with otherwise normal myocardial perfusion SPECT. Journal of the American College of Cardiology. 2003; 42(10):1818–25. PMID: 14642694

18. De Winter O, Velghe A, Van de Veire N, De Bondt P, De Buyzere M, Van De Wiele C, et al. Incremental prognostic value of combined perfusion and function assessment during myocardial gated SPECT in patients aged 75 years or older. Journal of nuclear medicine: official publication of the American Society of Nuclear Cardiology. 2005; 46(6):662–70.

19. uz Zaman M, Fatima N, Samad A, Ishaq M, Wali A, Rehman K, et al. Predictive and prognostic values of transient ischemic dilatation of left ventricular cavity for coronary artery disease and impact of various managements on clinical outcome using technetium-99m sestamibi gated myocardial perfusion imaging. Ann Nucl Med. 2011; 25(8):566–70. doi: 10.1007/s12149-011-0500-4 PMID: 21629988

20. Rywik TM, Zink RC, Gittings NS, Khan AA, Wright JG, O'Connor FC, et al. Independent prognostic significance of ischemic ST-segment response limited to recovery from treadmill exercise in asymptomatic subjects. Circulation. 1998; 97(21):2117–22. PMID: 9626171

21. Hamasaki S, Nakano F, Arima S, Tahara M, Kamekou M, Fukumoto N, et al. A new criterion combining ST/HR slope and deltaST/deltaHR index for detection of coronary artery disease in patients on digoxin therapy. Am J Cardiol. 1998; 81(9):1100–4. PMID: 9605049

22. Zimarino M, Barnabei L, Madonna R, Palmieri G, Radico F, Tatasciore A, et al. A comparison of the diagnostic performance of the ST/HR hysteresis with cardiopulmonary stress testing parameters in
detecting exercise-induced myocardial ischemia. Int J Cardiol. 2013; 168(2):1274–9. doi: 10.1016/j.ijcard.2012.12.007 PMID: 23260751

23. Hsu JC, Chu PS, Su TC, Lin LY, Chen WJ, Hwang JS, et al. Predictors for coronary artery disease in patients with paradoxical systolic blood pressure elevation during recovery after graded exercise. Int J Cardiol. 2007; 119(2):274–6. PMID: 17050013

24. Huang CL, Su TC, Chen WJ, Lin LY, Wang WL, Fang MH, et al. Usefulness of paradoxical systolic blood pressure increase after exercise as a predictor of cardiovascular mortality. Am J Cardiol. 2008; 102(5):518–23. doi: 10.1016/j.amjcard.2008.04.027 PMID: 18712505

25. Allison TG, Cordeiro MA, Miller TD, Squires RW, Gau GT. Prognostic significance of exercise-induced systemic hypertension in healthy subjects. Am J Cardiol. 1999; 83(3):371–5. PMID: 10072226

26. Hashimoto M, Okamoto M, Yamagata T, Yamane T, Watanabe M, Tsuchioka Y, et al. Abnormal systolic blood pressure response during exercise recovery in patients with angina pectoris. J Am Coll Cardiol. 1993; 22(3):659–64. PMID: 8354795

27. Schultz MG, Otahal P, Cleland VJ, Blizzard L, Marwick TH, Sharman JE. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. Am J Hypertens. 2013; 26(3):357–66. doi: 10.1093/ajh/hps053 PMID: 23382486

28. Cole CR, Blackstone EH, Pashkov FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med. 1999; 341(18):1351–7. PMID: 10536127

29. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med. 2000; 132(7):552–5. PMID: 10744592

30. Nishime EO, Cole CR, Blackstone EH, Pashkov FJ, Lauer MS. Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. JAMA. 2000; 284(11):1392–8. PMID: 10989401

31. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol. 2003; 42(5):831–8. PMID: 12957428

32. Ronan G, Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology. 2013; 21(1):192–220.

33. Ko CL, Wu YW, Cheng MF, Yen RF, Wu WC, Tzen KY. Data-driven respiratory motion tracking and compensation in CZT cameras: a comprehensive analysis of phantom and human images. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology. 2015; 22(2):308–18.

34. McHam SA, Marwick TH, Pashkov FJ, Lauer MS. Delayed systolic blood pressure recovery after graded exercise: an independent correlate of angiographic coronary disease. J Am Coll Cardiol. 1999; 34(3):754–9. PMID: 10483957

35. Germano G, Kavanagh PB, Slomka PJ, Van Kriekinge SD, Pollard G, Berman DS. Quantitation in gated perfusion SPECT imaging: the Cedars-Sinai approach. J Nucl Cardiol. 2007; 14(4):433–54. PMID: 17679052

36. Alfonso L, Mahajan N. Single-photon emission computed tomography myocardial perfusion imaging in the diagnosis of left main disease. Clin Cardiol. 2009; 32(12):E11–5. doi: 10.1002/clc.20534 PMID: 20014205

37. Heston TF, Sigg DM. Quantifying transient ischemic dilation using gated SPECT. J Nucl Med. 2005; 46(12):1990–6. PMID: 16330561

38. Petretta M, Acampa W, Daniele S, Petretta MP, Nappi C, Assante R, et al. Transient ischemic dilation in SPECT myocardial perfusion imaging for prediction of severe coronary artery disease in diabetic patients. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology. 2013; 20(1):45–52.

39. Emmett L, Magee M, Freedman SB, Van der Wall H, Bush V, Trieu J, et al. The role of left ventricular hypertrophy and diabetes in the presence of transient ischemic dilation of the left ventricle on myocardial perfusion SPECT images. Journal of nuclear medicine: official publication, Society of Nuclear Medicine. 2005; 46(10):1596–601.
40. Ababneh AA, Sciaccia RR, Kim B, Bergmann SR. Normal limits for left ventricular ejection fraction and volumes estimated with gated myocardial perfusion imaging in patients with normal exercise test results: influence of tracer, gender, and acquisition camera. J Nucl Cardiol. 2000; 7(6):661–8. PMID: 11144482

41. Nakajima K, Kusuoaka H, Nishimura S, Yamashina A, Nishimura T. Normal limits of ejection fraction and volumes determined by gated SPECT in clinically normal patients without cardiac events: a study based on the J-ACCESS database. Eur J Nucl Med Mol Imaging. 2007; 34(7):1088–96. PMID: 17219133

42. Nakajima K. Normal values for nuclear cardiology: Japanese databases for myocardial perfusion, fatty acid and sympathetic imaging and left ventricular function. Ann Nucl Med. 2010; 24(3):125–35. doi:10.1007/s12149-009-0337-2 PMID: 20108130

43. Romanens M, Gradel C, Saner H, Pfisterer M. Comparison of 99mTc-sestamibi lung/heart ratio, transient ischaemic dilation and perfusion defect size for the identification of severe and extensive coronary artery disease. Eur J Nucl Med. 2001; 28(7):907–10. PMID: 11504088

44. Liu CJ, Cheng JS, Chen YC, Huang YH, Yen RF. A performance comparison of novel cadmium-zinc-telluride camera and conventional SPECT/CT using anthropomorphic torso phantom and water bags to simulate soft tissue and breast attenuation. Ann Nucl Med. 2015.

45. Takahashi Y, Miyagawa M, Nishiyama H, Ishimura H, Mochizuki T. Performance of a semiconductor SPECT system: comparison with a conventional Anger-type SPECT instrument. Annals of nuclear medicine. 2013; 27(1):11–6. doi:10.1007/s12149-012-0653-9 PMID: 22956363

46. Chowdhury FU, Vaidyanathan S, Bould M, Marsh J, Trickett C, Dodds K, et al. Rapid-acquisition myocardial perfusion scintigraphy (MPS) on a novel gamma camera using multipinhole collimation and miniaturized cadmium-zinc-telluride (CZT) detectors: prognostic value and diagnostic accuracy in a ‘real-world’ nuclear cardiology service. Eur Heart J Cardiovasc Imaging. 2014; 15(3):275–83. doi:10.1093/ehjci/jet149 PMID: 23975570

47. Buechel RR, Herzog BA, Husmann L, Burger IA, Pazhenkottil AP, Treger V, et al. Ultrafast nuclear myocardial perfusion imaging on a new gamma camera with semiconductor detector technique: first clinical validation. European journal of nuclear medicine and molecular imaging. 2010; 37(4):773–8. doi:10.1007/s00259-009-1375-7 PMID: 20107783

48. Tanaka H, Chikamori T, Hida S, Uchida K, Igarashi Y, Yokoyama T, et al. Comparison of myocardial perfusion imaging between the new high-speed gamma camera and the standard anger camera. Circulation journal: official journal of the Japanese Circulation Society. 2013; 77(4):1009–17.

49. Hansen CL, Cen P, Sanchez B, Robinson R. Comparison of pulmonary uptake with transient cavity dilation after dipyridamole Ti-201 perfusion imaging. J Nucl Cardiol. 2002; 9(1):47–51. PMID: 11845129

50. Kaminek M, Myslivecek M, Skvarilova M, Husak V, Koranda P, Metelkova I, et al. Increased prognostic value of combined myocardial perfusion SPECT imaging and the quantification of lung Ti-201 uptake. Clin Nucl Med. 2002; 27(4):255–60. PMID: 11914664

51. Songy B, Lussato D, Guernou M, Queneau M, Geronazzo R. Comparison of myocardial perfusion imaging using thallium-201 between a new cadmium-zinc-telluride cardiac camera and a conventional SPECT camera. Clinical nuclear medicine. 2011; 36(9):776–80. doi:10.1097/RLU.0b013e1821a294e PMID: 21825848

52. Wang SY, Cheng MF, Hwang JJ, Hung CS, Wu YW. Sex-specific normal limits of left ventricular ejection fraction and volumes estimated by gated myocardial perfusion imaging in adult patients in Taiwan: a comparison between two quantitative methods. Nucl Med Commun. 2011; 32(2):113–20. doi:10.1097/MNM.0b013e3283422838 PMID: 21150486

53. Chien CL, Wu YW, Yang WS, Yang PC, Su HM, Wu YT. Myocardial perfusion image in asymptomatic postmenopausal women with physical inactivity and overweight. Obes Facts. 2011; 4(5):372–8. doi:10.1159/000333439 PMID: 22166757

54. Cheng VY, Berman DS, Rozanski A, Dunning AM, Achenbach S, Al-Mallah M, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation. 2011; 124(22):2423–32, 1–8. doi:10.1161/CIRCULATIONAHA.111.039235 PMID: 22025600