Ischemic burden assessment of myocardial perfusion CT, compared with SPECT using semi-quantitative and quantitative approaches

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A R T I C L E   I N F O

A B S T R A C T

Background: We aimed to compare the myocardial ischemic burden assessed using semi-quantitative and quantitative analysis of computed tomography-myocardial perfusion imaging (CT-MPI) with that of single-photon emission computed tomography (SPECT).
Methods: From 2011 to 2013, 97 patients who underwent CT-MPI and SPECT were evaluated. The extent and severity of perfusion defects were assessed on a 5-point scale using a standard 16-segment model, and were expressed as summed stress score (SSS) and summed difference score (SDS). Receiver operating characteristic (ROC) curves for quantitative parameters were generated for the diagnosis of abnormal perfusion defect (SSS ≥ 4) and presence of ischemia (SDS ≥ 2) on SPECT.
Results: On CT-MPI, 298 (19.2%) of the 1552 segments showed perfusion abnormalities during stress, whereas perfusion abnormalities were shown in 179 (11.5%) segments on SPECT-MPI. On a per-person basis, there was good agreement, with intraclass correlation coefficients of 0.78 for SSS and 0.72 for SDS. A significant reduction of attenuation in stress and myocardial perfusion reserve index, along with an increase in % defect volume of CT-MPI, were demonstrated as the degree of perfusion defect or ischemia on SPECT increased. On the ROC curves, % defect volume on CT-MPI demonstrated the highest area under the curve: 0.91 for abnormal perfusion defect and 0.89 (all p < 0.001) for the presence of ischemia on SPECT.
Conclusions: Semi-quantitative analysis of CT-MPI showed good accordance with SPECT. A quantitative approach for CT-MPI, especially % defect volume, may provide additional value in the identification of myocardial perfusion abnormalities.
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1. Introduction

In the treatment of coronary artery disease (CAD), aside from the presence or absence of ischemia, the importance of the extent of ischemic burden has been emphasized, as it provides substantial information for risk stratification and prognosis prediction [1,2]. Recent studies show that the risk of clinical events is inversely proportional to the value of the fractional flow reserve (FFR), which has been termed "a risk continuum for FFR" [3]. As such, the identification and quantification of total ischemic burden has become a mainstay for evaluation of CAD before revascularization therapy. Continuous advances in cardiac computed tomography (CT) technology have enabled assessment of the hemodynamic significance of coronary stenosis on CT-myocardial perfusion imaging (MPI) in conjunction with anatomical assessment

of coronary CT angiography (CTA) [4]. The diagnostic accuracy and feasibility of several modes of CT-MPI have been compared with those of various reference standard modalities for CAD diagnosis [5–7]. However, still, there are only limited data available on the use of semi-quantitative or quantitative analysis for the assessment of ischemic burden on CT-MPI [8,9]. Thus, we aimed to compare ischemic burden measured on CT-MPI using semi-quantitative and quantitative approaches with that measured on SPECT-MPI, to evaluate the diagnostic value of quantitative parameters of static CT-MPI.

2. Method

2.1. Study design and population

From December 2011 to March 2013, 262 consecutive patients suspected of having CAD and having undergone CT-MPI were enrolled in a myocardial perfusion CT registry (NCT 01696006, ClinicalTrials.gov). Those patients aged 18 years or older with angina or angina-equivalent symptoms were included. Of these patients, 97 who underwent SPECT-MPI during the same period, without revascularization, were retrieved for the present study. Our institutional review board approved the study, and all patients provided written informed consent.

2.2. Cardiac CT protocol

The details of the cardiac CT protocol and the assessment of CT-MPI have been described previously [7]. Briefly, stress-rest myocardial perfusion CT protocols were performed using a second-generation dual-source CT scanner (Definition Flash; Siemens, Forchheim, Germany), with a "stress-first protocol" to avoid late contrast enhancement during the stress phase acquisition. Stress CT-MPIs were obtained during adenosine (Denosine; BCWP, Seoul, Korea) infusion (140 mg per kilogram of body weight per minute for 5 min) using a retrospective electrocardiographically gated acquisition (Supplemental Table 1). A 60–70 mL bolus of iodinated contrast material (iomeprol, Iomeron 400; Bracco, Milan, Italy) was injected at a rate of 4.0 mL/s, followed by 40 mL of a saline chaser. Rest myocardial perfusion CT was performed 10 min after adenosine was discontinued. Rest myocardial perfusion CT data were reconstructed using a standard cardiac filter (B26f) for CTA analysis. Two independent observers (J.W.K. and D.H.Y., with 9 and 5 years of experience with cardiac CT, respectively) interpreted the data using a dedicated workstation (Syngo Via; Siemens).

2.3. Assessment of CT-MPI

The two readers (J.W.K. and D.H.Y.) performed visual assessment of CT perfusion using commercial workstations (Aquarius Net; TeraRecon, Foster City, Calif), and determined the extent of perfusion defect by consensus. Visual assessments were performed using 10-mm-thick multi-planar reformatted images with a narrow window (200 HU) and a level setting of 100 HU. The two readers were blinded to the results of CTA. From the multiphase images acquired, the stress myocardial perfusion CT images were used to identify the ischemia-producing perfusion defects. An ischemia-producing perfusion defect was defined as a low-attenuation lesion that persisted throughout the cardiac cycle, and its location was classified according to the 16-segment model of the American Heart Association excluding the apex [10]. For stress and rest images, each of the 16 segments was scored according to the absence or presence of a perfusion defect and its severity. Perfusion defect severity was scored on a scale of 0 (normal) to 4 (abnormal) in a similar manner to previous literature [8]. Representative cases showing the determination of perfusion defect severity are demonstrated in Supplemental Fig. 1. The segmental scores were then summed into global scores to reflect the total ischemia burden and scar in the left ventricle. A summed stress score (SSS) within the normal range indicates a lack of significant abnormality, while a higher SSS reflects a greater extent and severity of perfusion defects [11]. The summed rest score (SRS) is the summed total of each individual segment score obtained during the rest study. The summed difference score (SDS), which indicates the amount of ischemia and the degree of defect reversibility, is the difference between the SSS and the SRS: SSS − SRS = SDS [11,12]. A SSS or SRS of ≥4 was considered to be a perfusion abnormality, while a SDS ≥2 was defined as an abnormality: an ischemia-producing perfusion defect [11,12]. Interobserver agreement was excellent, with intraclass correlation coefficients (ICCs) of approximately 0.9 for per-person or per-vessel analysis.

After visual assessment, a software-based quantification of the perfusion defect was performed using custom software (A-view Cardiac; Asan Medical Center, Seoul, Korea). This software was developed for the classification of myocardial attenuation in the 16 segments and three myocardial layers. Myocardial CT attenuation (HU) was measured in both the stress phase (A-stress) and the rest phase (A-rest). Endo- and epicardial borders of the left ventricle were drawn semi-automatically, and the total left ventricular myocardial volume was calculated. Regions of decreased myocardial perfusion were defined in all short-axis images, according to visual assessment. In cases of disagreement between readers, myocardium with CT attenuation <1 standard deviation compared to normal myocardium was considered to represent a perfusion defect [9]. The percent perfusion defect volume (% defect volume) was defined as the perfusion defect volume divided by the total left ventricular volume × 100. Fig. 1 shows a representative case.

The transmural perfusion ratio (TPR) was calculated as the ratio of the segment-specific subendocardial attenuation to the mean subepicardial attenuation on all of the short-axis images [13]. The myocardial perfusion reserve index (MPRI) was defined as the percentage difference in attenuation between the stress myocardial perfusion CT and the rest myocardial perfusion CT images in each myocardial segment as follows: (A-stress − A-rest)/A-rest × 100%. The myocardial segment with the lowest value for each quantitative parameter was chosen to represent the perfusion of each vascular territory [14]. CTA images were reviewed to confirm the correct assignment of the myocardial segment to the coronary artery territories using a previously described method [15]. Myocardial segments were thereby reassigned in 16 of the 97 patients, according to coronary artery anatomy.

2.4. Thallium SPECT

Details of the SPECT-MPI protocol and assessment methods have been described previously [16]. Gated thallium chloride (Tl-201) SPECT images were acquired after adenosine stress testing (post-stress SPECT), and again 4 h after the injection of Tl-201 chloride (redistribution SPECT). Three minutes after the initiation of the adenosine infusion, a dose of Tl-201 (range, 92.5 to 148 MBq; as determined by the subject's body weight) was injected intravenously. Six minutes after the adenosine infusion, post-stress myocardial perfusion images were acquired with a 2-head gamma camera (Ecam; Siemens, Munich, Germany) equipped with low-energy all-purpose collimators (64 × 64 matrix, 32 projections over 180°, 8 frames per cardiac cycle, 50 s per projection). A 16-segment model excluding the apex [10] was used, and SSS, SRS, and SDS were assessed in the same way as described above [11,12]. The images were evaluated by an experienced nuclear medicine physician (D.H.M).

2.5. Statistical analysis

Differences in continuous variables between groups were evaluated using Student's t-test for normally distributed data and the Wilcoxon rank test for non-normally distributed data. Using SSS, SRS, and SDS, the CT-MPI and SPECT-MPI acquisitions were compared, to determine positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA) for detection of myocardial perfusion defect. PPA was calculated as the number of true-positive results divided by the total number of true-positive and false-negative results, and NPA as the number of true-negative results divided by the total number of true-negative and false-positive results, using SPECT as the reference standard. OPA was defined as the number of true-positive and true-negative results divided by the total number of subjects. Inter-observer variability for per-segment analysis of CTP was assessed using kappa statistics treated as dichotomized variables on 28 randomly selected patients including 84 vessel territories. Inter-observer variability for per-vessel and per-patient analysis were evaluated using intra-class correlation coefficient. Spearman's correlation analysis was used to test linear correlations between quantitative parameters and the degree of perfusion defect abnormality (SSS) or ischemia (SDS). For evaluating the diagnostic performance of the CT-MPI quantitative parameters, receiver operating characteristic (ROC) plots were constructed for abnormal perfusion defect (SSS ≥ 4) and the presence of ischemia (SDS ≥ 2) on SPECT-MPI [12]. The area under the curve (AUC) and the associated 95% confidence interval (CI) were calculated, and the optimal cutoff points were determined according to the maximum sum of the sensitivity and specificity. The AUCs were compared using the approach of Delong et al. [17]. A two-tailed p value of <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc software (MedCalc Software, Mariakerke, Belgium) and R software version 3.2.2 13 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

3. Results

3.1. Baseline characteristics

The mean patient age was 62.2 ± 10.8 years, 73.2% of patients were male, and 34.0% had diabetes, as shown in Supplemental Table 2. The prevalence of previous myocardial infarction, percutaneous intervention, and coronary artery bypass grafting was 9.3%, 32.0%, and 5.2%, respectively.

3.2. Comparison of SSS and SDS between CT perfusion (CTP) and SPECT

On CT-MPI, 298 (19.2%) of the 1552 segments showed perfusion abnormalities during the stress state, while 43 (2.9%) segments showed perfusion abnormalities during rest. On SPECT-MPI, perfusion abnormalities were observed in 179 (11.5%) segments during stress and 52 (3.4%) segments during rest (Supplemental Table 3).

Table 1 summarizes the agreement rates between CT-MPI and SPECT-MPI, with SPECT-MPI being considered the reference standard. On a per-person basis, the agreement rates for SSS, PPA, NPA, and OPA
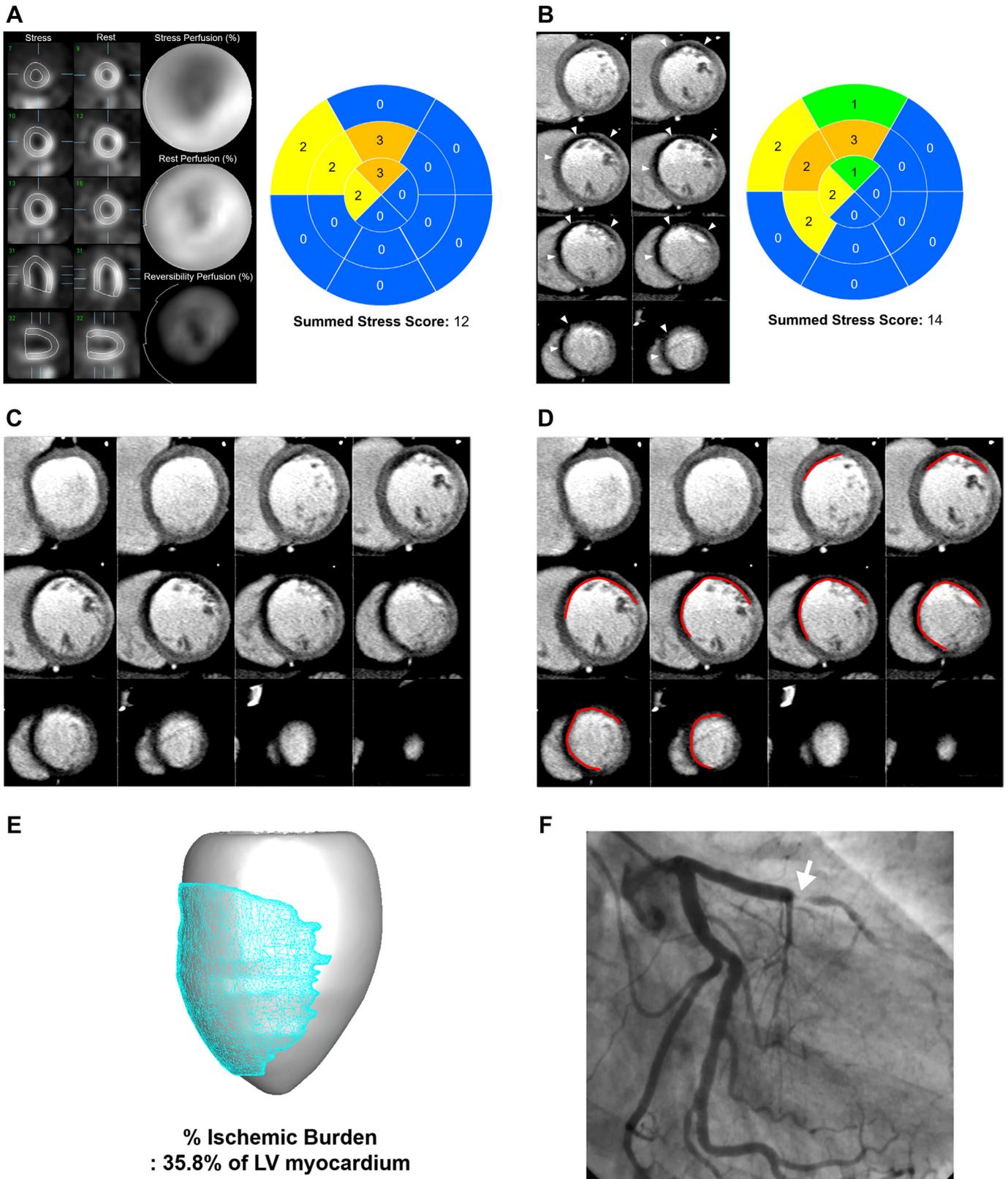
Fig. 1. A representative case of a 42-year-old male with stable angina. A: The summed stress score (SSS) of the thallium scan was 12. B: Stress perfusion CT demonstrated a perfusion defect corresponding with the left anterior descending artery (LAD) territory (white arrows) and the SSS of the stress perfusion CT was 14. C: D: Regions of decreased myocardial perfusion were defined in all short-axis images, according to visual assessment. Endo- and epicardial borders of the left ventricle were drawn semi-automatically. E: The total left ventricular myocardial volume was calculated with the dedicated software and the percent defect volume was 35.8%. F: Invasive coronary angiography showed a total occlusion of the proximal LAD. LV, left ventricle.

were 0.97, 0.74, and 0.82, respectively. For the SRS, CT-MPI showed values of 0.94 for PPA, 0.46 for NPA, and 0.88 for OPA. For the SDS, CT-MPI demonstrated values of 0.90 for PPA, 0.75 for NPA, and 0.81 for OPA. The agreements evaluated according to the ICCs were rated as good: 0.78 for SSS, 0.81 for SRS, and 0.72 for SDS (all p < 0.001). Among 52 patients identified SSS ≥1 on CTP, 42 (81%) patients underwent invasive coronary angiography and the findings were summarized in Supplemental Table 4.

3.3. Assessment of quantitative CTP parameters

Quantitative analysis of CT-MPI was completed for 96 patients, with the analysis failing in one patient because of considerable image artifacts. On a per-person basis, as the degree of perfusion defect in SPECT increased, the attenuation in the stress-state MPRI of the CT-MPI significantly decreased (p < 0.001) (Fig. 2A). In addition, the % defect volume was positively correlated with the degree of perfusion defect (p < 0.001). However, no significant association was shown between TPR and the degree of perfusion defect (p = 0.48). Similar results were revealed for the degree of ischemia assessed by SDS (Fig. 2B). Attenuation in the stress state, MPRI, and % defect volume were correlated with the degree of ischemia on SPECT (p = 0.02, p = 0.001, and p < 0.001, respectively), whereas TPR did not show a significant association (p = 0.39).

Using the ROC on a per-person basis, the cutoffs and AUCs of each quantitative CT-MPI parameter for the detection of the perfusion abnormalities found on SPECT (SSS ≥ 4) are shown in Fig. 3A. The % defect volume revealed the highest AUC, with a value of 0.91 (95% CI: 0.83 to 0.96, p < 0.001). The cutoff value was 6.8%, with a sensitivity of 97.1% and a specificity of 79.0%. In addition, attenuation in the stress state, and the MPRI, showed statistically significant values with similar AUCs: 0.69 (95% CI: 0.59 to 0.78, p < 0.001) and 0.69 (95% CI: 0.58 to 0.78, p = 0.002), respectively. However, the AUC of TPR was the lowest, and was without statistical significance (p = 0.52). The cutoffs and AUCs of the quantitative parameters for ischemia-producing defect detection on SPECT-MPI (SDS ≥ 2) were demonstrated in Fig. 3B. Similar to the results for abnormal perfusion defects (SSS ≥ 4), the AUC was the highest for the % defect volume, at 0.89 (95% CI: 0.82 to 0.94, p < 0.001). The cutoff value was 9.5%, with a sensitivity of 84.6% and a specificity of 86.0%. MPRI and attenuation in the stress state showed statistically significant AUC values (p = 0.004, and p = 0.01, respectively), whereas those of TPR were not significant (p = 0.32).

4. Discussion

This study demonstrated that 1) static CT-MPI showed good agreement with the reference standard SPECT-MPI in identifying perfusion abnormalities and determining the presence or absence of myocardial ischemia, and 2) the quantitative parameters of static CT-MPI, except for TPR, provided good accuracy for the detection of perfusion abnormalities and the presence of ischemia on SPECT-MPI, with % defect volume revealing a particularly high level of accuracy.

Previous reports based on visual assessment demonstrate favorable agreement between stress CT-MPI and the reference standard SPECT-MPI. In a study on patients presenting with chest pain, CTP demonstrated a sensitivity of 92%, specificity of 95%, positive predictive value of 80%, and negative predictive value of 98% [18]. Recently, a study showed that regadenoson-induced stress CTP was not inferior to SPECT for detecting or excluding reversible ischemia, with an agreement rate of 0.87 and sensitivity and specificity of 0.90 and 0.84, respectively [19]. Furthermore, several studies show improved diagnostic performance for a combination of CTA and CTP, compared with CTA alone in the detection of myocardial perfusion defect on SPECT-MPI [6,20].

Okada et al. investigated the agreement in the ischemic burden between CTP-MPI and SPECT-MPI with a semi-quantitative approach using the SSS and SRS [8]. Their study showed a good correlation between the two modalities, with Pearson correlation coefficients of 0.56 for SSS and 0.66 for SRS on a per-vessel basis, and 0.60 for SSS and 0.76 for SRS on a per-patient basis (all p < 0.0001). The present study, which also used SSS, SRS, and SDS, supports these previous findings indicating that CTP compares favorably with SPECT-MPI for the detection of myocardial perfusion defects and determination of their extent and severity. Moreover, the present study provided additional findings of good correlations between quantitative parameters (except TPR of static CT-MPI) and the ischemic burden assessed by SPECT-MPI.

Of note, we found that the % defect volume demonstrated excellent accuracy in the detection of perfusion abnormality and ischemia on SPECT, with AUCs of 0.91 for abnormal perfusion defect and 0.89 for the presence of ischemia on SPECT. Similarly, other recent studies revealed that the % defect volume of CTP allows objective detection of CAD with reliable accuracy [21]. In a previous study comparing CTP with SPECT, the quantitative 3D analysis of CT images showed a sensitivity of 0.79, specificity of 0.71, and accuracy of 0.76 for the detection of CAD [21]. On the other hand, the MPRI has traditionally been evaluated on cardiac MRI, where its utility for the detection of coronary microvascular and/or endothelial coronary dysfunction has been demonstrated [22]. In the present study, the MPRI of CT-MPI had a good diagnostic performance for the identification of perfusion abnormalities or ischemia, thereby suggesting its potential for use in clinical practice.

The visual-based semi-quantitative analysis showed limitations in assessment of the extent of CAD, especially in patients with multivessel disease or microvascular dysfunction [23]. However, the quantitative approach has potential benefits, including reduced intra- or inter-interpreter bias, improved detection of balanced ischemia, and objective assessment of treatment response [24]. Conventional noninvasive modalities such as positron emission tomography, MRI, or dynamic CTP are capable to do quantitative approaches, and several studies tried to demonstrate their clinical application [23,25]. However, these modalities have limited in widespread clinical application, owing to the availability of the scanners, technical issues, cost concerns, radiation hazards, and local reimbursement issues [23]. In this regard, a potential advantage of static CTP is its ability to quantify defects and perfusion reserve within a myocardial segment, and to do so with various parameters [26]. This could confer additional diagnostic value for the detection of myocardial perfusion abnormalities and ischemia. However, for a quantitative approach to CTP, technical issues involving obtaining and processing the images, as well as validation of the parameters, remain to be addressed [27]. Thus, further comprehensive research to assess the diagnostic value of quantitative parameters derived from CT-MPI is warranted.

Table 1
Comparisons between CT-MPI and SPECT-MPI as a reference standard using the semi-quantitative approach.

CT-MPI	PPA	NPA	OPA	ICC*
Per-person analysis				
SSS	0.97	0.74	0.82	0.78
SRS	0.94	0.46	0.88	0.81
SDS	0.90	075	0.81	0.72
Per-vessel analysis				
SSS	0.93	0.88	0.88	0.79
SRS	0.33	0.98	0.95	0.68
SDS	0.63	0.89	0.85	0.72

Abbreviations: CT, computed tomography; ICC, intraclass correlation coefficient; MPI, myocardial perfusion imaging; NPA, negative percent agreement; PPA, positive percent agreement; OPA, overall percent agreement; SPECT, single-photon emission computed tomography; SDS, summed difference score; SRS, summed rest score; SSS, summed stress score.
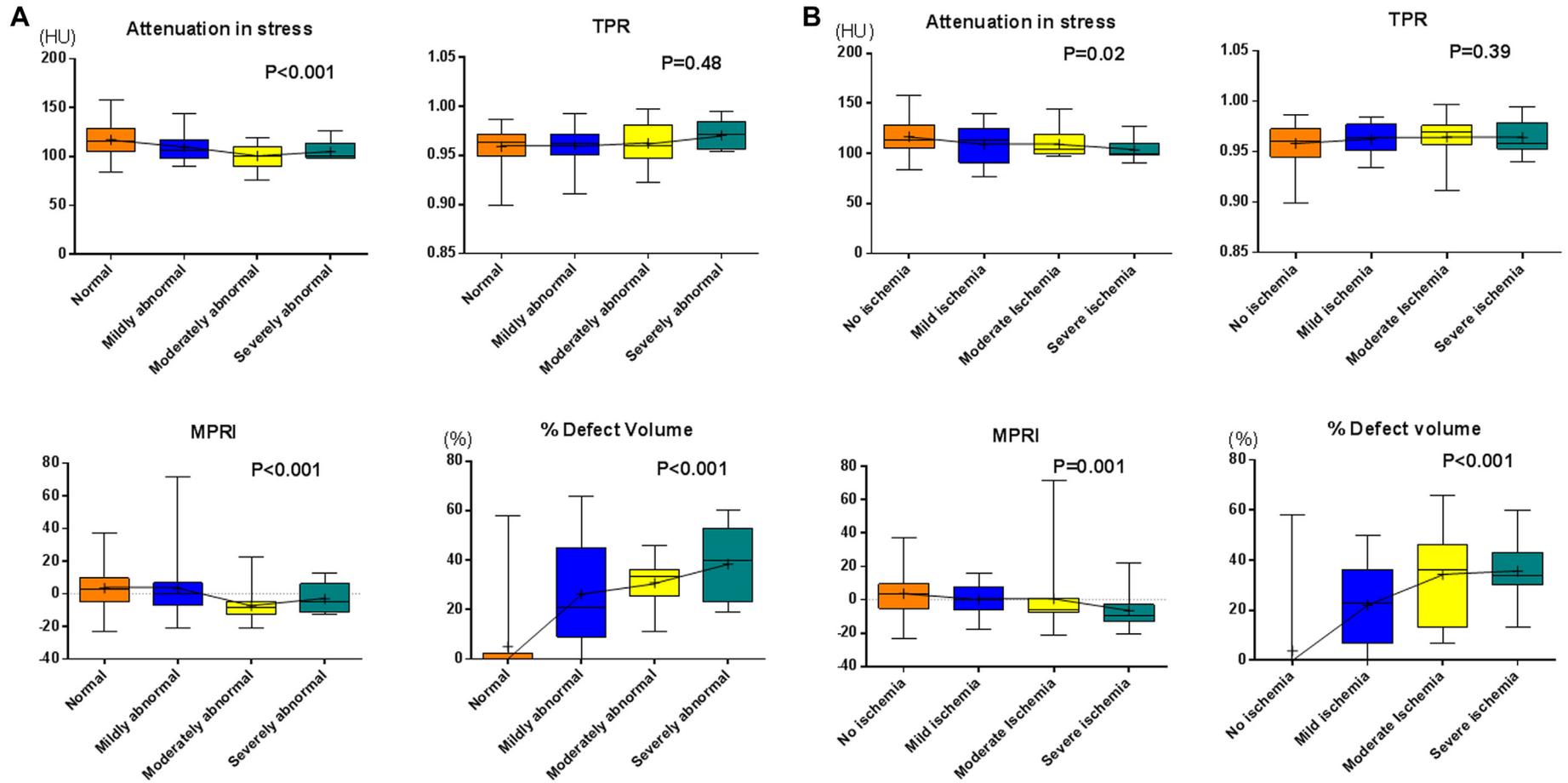 * ICC was conducted using ordinary segmental scores and all p values were <0.001.

Fig. 2. Values of quantitative parameters of CT-MPI according to the degree of perfusion defect abnormality (A) or ischemia (B) on SPECT. The p values were calculated by Spearman correlation. MPRI, myocardial perfusion reserve index; TPR, transmural perfusion ratio. A: Summed stress score (SSS). SSS <4, normal; 4–8, mildly abnormal; 9–13, moderately abnormal; and >13, severely abnormal. B: Summed difference score (SDS). SDS <2, normal; 2–4, mild ischemia; 5–8, moderate ischemia; and >8, severe ischemia. p-Values were obtained by Spearman's correlation analysis to test linear correlations between quantitative parameters and the degree of perfusion defect abnormality (SSS) or ischemia (SDS).
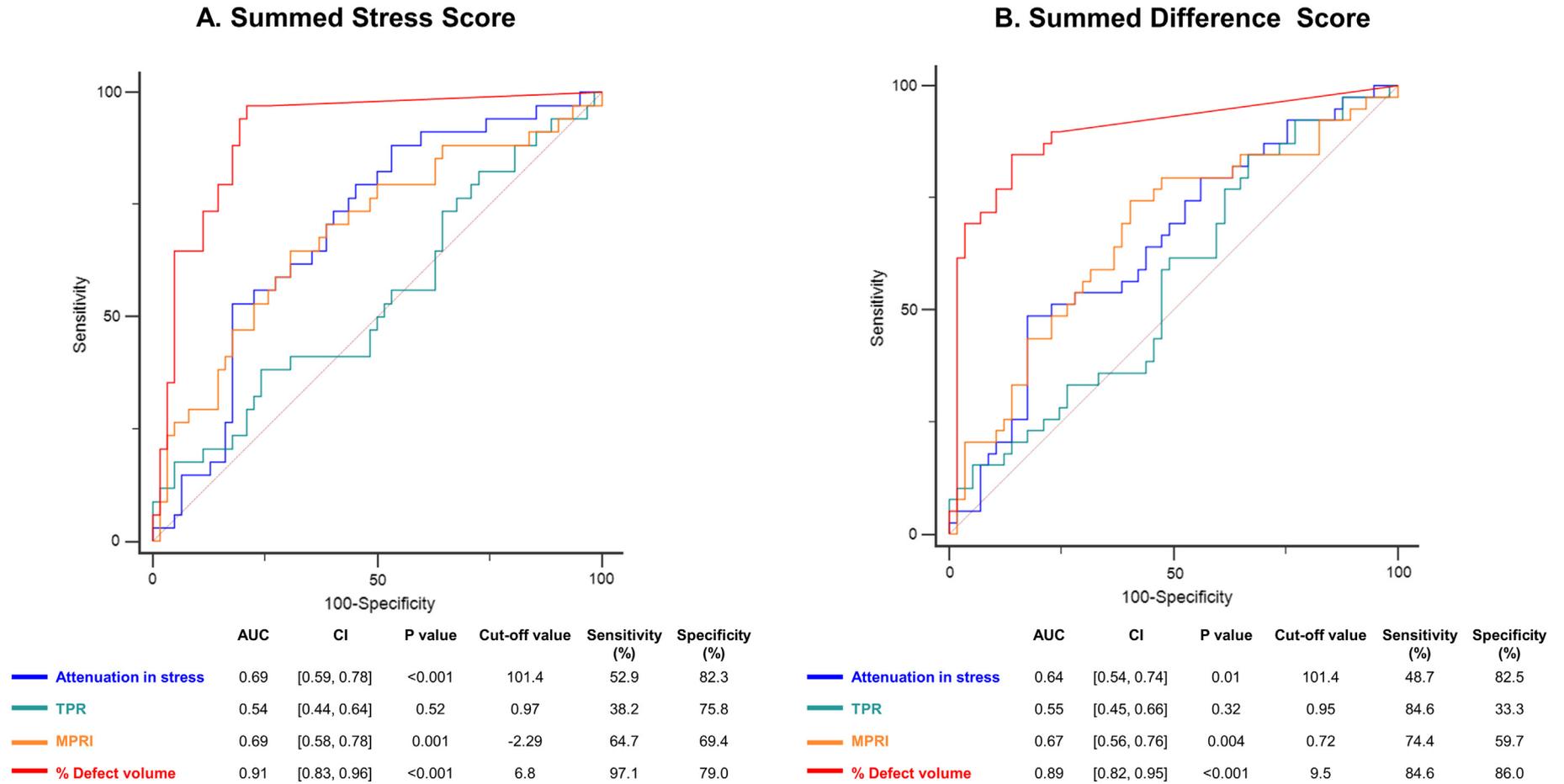
A. Summed Stress Score

B. Summed Difference Score

	AUC	CI	P value	Cut-off value	Sensitivity (%)	Specificity (%)
Attenuation in stress	0.69	[0.59, 0.78]	<0.001	101.4	52.9	82.3
TPR	0.54	[0.44, 0.64]	0.52	0.97	38.2	75.8
MPRI	0.69	[0.58, 0.78]	0.001	-2.29	64.7	69.4
% Defect volume	0.91	[0.83, 0.96]	<0.001	6.8	97.1	79.0

	AUC	CI	P value	Cut-off value	Sensitivity (%)	Specificity (%)
Attenuation in stress	0.64	[0.54, 0.74]	0.01	101.4	48.7	82.5
TPR	0.55	[0.45, 0.66]	0.32	0.95	84.6	33.3
MPRI	0.67	[0.56, 0.76]	0.004	0.72	74.4	59.7
% Defect volume	0.89	[0.82, 0.95]	<0.001	9.5	84.6	86.0

Fig. 3. Receiver operating characteristic curves of quantitative parameters of CT-MPI to detect the perfusion abnormality of SPECT. (A) Summed stress score ≥4, and (B) summed difference score ≥2. AUC, area under curve; CI, confidence interval; other abbreviations as in Fig. 2. The AUC of % defect volume for summed stress score and summed difference score were significantly higher than others.

Several limitations to this study should be noted. First, as patients with an intermediate or high probability of CAD were evaluated, the findings cannot be directly extrapolated to different populations or clinical settings. Second, like all modalities, CT has inherent technical limitations such as motion or beam-hardening artifact, which could result in false-positive myocardial perfusion deficits [27]. We tried to minimize the beam-hardening artifact using an advanced beam-hardening correction developed and implemented for this study. However, beam-hardening and other CT artifacts could have contributed to the possible false findings in some patients. Third, SPECT-MPI is limited to low sensitivity for balanced or multi-vessel ischemia and inability to accurately quantify the extent of subendocardial perfusion defects [28]. Nonetheless, SPECT is most widely used in clinical practice, and may thus serve as an appropriate clinical reference standard for evaluating the feasibility of other noninvasive functional studies. In addition, even according to a recent study using invasive FFR for the standard reference [7], CTP had good diagnostic accuracy for the detection of myocardial ischemia. Further studies comparing CT-MPI with noninvasive and invasive functional tests in various patient subsets are warranted to determine its diagnostic performance. Finally, the study population was relatively small, and of male-predominant Asian ethnicity.

5. Conclusions

In conclusions, we used semi-quantitative and quantitative approaches to evaluate the diagnostic performance of CT-MPI using a static second-generation dual-source CT scanner, making comparisons with SPECT. The study demonstrated good concordance between CT-MPI and SPECT-MPI using semi-quantitative analysis. In addition, quantitative analysis of CT-MPI, especially % defect volume, may play an additional role in the identification of myocardial perfusion abnormalities and ischemia. Further larger studies are required to validate the semi-quantitative and quantitative analysis of CT-MPI with standard modalities.

Disclosures

There are no conflicts of interest to disclose.

Sources of funding

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.12.046.

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