Original Article
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Comparison of the Diagnostic Performance of Myocardial Perfusion Scintigraphy with and Without Attenuation Correction

Atenüasyon Düzeltmeli ve Düzeltmesiz Miyokard Perfüzyon Sintigrafisinin Tanısal Performansının Karşılaştırılması

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Abstract

Objectives: Myocardial perfusion scintigraphy (MPS) is an important diagnostic test for detecting of coronary artery stenosis (CAS); however, tissue attenuation can lead to a difference in accuracy. We evaluated the diagnostic accuracy of attenuation-corrected (AC) and non-attenuation-corrected (NC) MPS for the detection of CAS.

Methods: We retrospectively recruited patients who underwent invasive coronary angiography within 10 months after Tc-99m sestamibi MPS. The AC and NC perfusion images were analyzed separately, and each myocardial segment was scored based on relative uptake from 0 to 4. The summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were calculated. The diagnostic performances were analyzed using the area under the curve (AUC) of the receiver operating characteristic curve.

Results: From 117 patients, significant coronary stenosis was present in 66 patients (56%). The SSS and SRS obtained from NC-images were higher than those from AC, supporting the presence of attenuation artifacts in NC images. The AUC of SSS and SDS were significantly higher than those of SRS in both AC- and NC-images, but no significant difference was found between the AUC of SSS, and those of SDS. The optimal cut-offs were >12 for AC-SSS, >15 for NC-SSS, >4 for AC-SDS and >3 for NC-SDS. There was no statistically significant difference in the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy among AC-SSS, NC-SSS, AC-SDS, and NC-SDS.

Conclusion: NC-based Tc-99m-sestamibi MPS promised comparable accuracy to AC images by using different cut-off values for diagnosis.

Keywords: Coronary artery disease, myocardial perfusion imaging, single photon emission computed tomography, attenuation correction, diagnostic performance, accuracy

Öz

Amaç: Miyokardiyal perfüzyon sintigrafisi (MPS), koroner arter darlığının (CAS) saptanması için önemli bir tanı testidir; ancak doku atenüasyonu doğrulukta bir farklılığa yol açabilir. Atenüasyon düzeltmeli (AC) ve düzeltmesiz (NC) MPS'nin CAS tespiti için tanısal doğruluğunu değerlendirmeyi amaçladık.

Yöntem: Tc-99m-sestamibi MPS'den sonraki 10 ay içinde invaziv koroner anjiyografi yapılan hastaları geriye dönük olarak inceledik. AC ve NC perfüzyon görüntüleri ayrı ayrı analiz edildi ve her bir miyokardiyal segment, 0 ila 4 arasındaki rölatif tutuluma dayalı olarak puanlandı. Toplam stres skoru (SSS), toplam dinlenme skoru (SRS) ve toplam fark skoru (SDS) hesaplandı. Tanılama performansları, alıcı işlem karakteristiği eğrisinin eğri altındaki alanı (AUC) kullanılarak analiz edildi.

Bulgular: Yüz on yedi hastadan 66 hastada (%56) belirgin koroner darlık mevcuttu. NC görüntülerinden elde edilen SSS ve SRS, AC'den elde edilenlerden daha yüksekti ve NC görüntülerinde atenüasyon artefaktlarının varlığını destekledi. Hem AC hem de NC görüntülerinde SSS ve SDS'nin AUC'si SRS'ninkinden önemli ölçüde daha yüksekti, ancak SSS'nin AUC'si ile SDS'ninkiler arasında anlamlı bir fark bulunmadı. Optimum kesim değerler AC-SSS için >12, NC-SSS için >15, AC-SDS için >4 ve NC-SDS için >3 idi. AC-SSS, NC-SSS, AC-SDS ve NC-SDS arasında duyarlılık, özgüllük, pozitif öngörü değeri, negatif tahmini değer ve doğruluk açısından istatistiksel olarak anlamlı bir fark yoktu.

Sonuç: NC tabanlı Tc-99m-sestamibi MPS, tanı için farklı kesim değerleri kullanarak AC görüntülerle karşılaştırılabilir doğruluk vaat etti.

Anahtar kelimeler: Koroner arter hastalığı, miyokardiyal perfüzyon görüntüleme, tek foton emisyonlu bilgisayarlı tomografi, atenüasyon düzeltmesi, tanısal performans, doğruluk

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Introduction

Non-invasive cardiac tests are crucial steps for the diagnosis of coronary artery stenosis in patients with an intermediate pretest probability of coronary artery disease (CAD) to optimize the use of invasive coronary angiography (ICA) (1). One of the commonly used non-invasive tests is the stress/rest Tc-99m-sestamibi myocardial perfusion scintigraphy (MPS) which can be safely performed in patients with limited physical activities, or impaired renal function (2,3,4).

Several myocardial perfusion scanning techniques and image processing protocols have been used to enhance the diagnostic performance of MPS. Attenuation correction, commonly performed using computed tomography (CT), promises to reduce attenuation artifacts caused by radiation absorption of the overlying tissue and thus significantly improve the specificity of the test (5). Semiquantitative interpretation has been proposed to reduce inter-observer variability and to standardize the method of interpretation. Seventeen-segment model of left ventricular myocardium is generally suggested owing to good representation of myocardial volume and vascular territories (6). A five-point scale for scoring of each segment based on perceived abnormality compared to either normal subject or maximum myocardial uptake is commonly performed (7,8).

In this study, we aimed to compare the diagnostic accuracy of attenuation-corrected (AC) and non-attenuation-corrected (NC) MPS for the diagnosis of coronary artery stenosis using ICA as a reference standard, and define the appropriate cut-off scoring values in both types of image interpretation.

Materials and Methods

Study Design and Subjects

Patients who were suspected of CAD and had indications for MPS were sent to the division of nuclear medicine to perform 2-day adenosine-stress/rest Tc-99m-sestamibi MPS. Patients who underwent those scans from January 2013 to December 2016 and underwent ICA within 10 months after MPS were retrospectively included. Patients who had prior coronary artery bypass graft were excluded because it altered the normal distribution of vascular supply, which may affect the image interpretation. Patients who had no CT attenuation for MPS for any reason were also excluded. A body mass index greater than 25 was used as the cut-off for obesity in our protocol. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved and the requirement for informed consent was waived by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (COA no: 611/2017, IRB no: 366/60).

Imaging Procedures

On the first day, the patient was injected with Tc-99m-sestamibi 21-30 mCi at the 4th minute of total six-minute infusion of adenosine rate 140 mg/kg/min. After that, the patient took a high fat diet reduced interfering tracer activity in the liver. Then, the single photon emission computed tomography (SPECT) images were acquired approximately 1 h after radiotracer injection using a dual-head gamma camera SPECT/CT system (Symbia T6, Siemens, Erlangen, Germany) with low-energy ultra-high-resolution collimator. The data was acquired in 50 seconds/projections for 64 projections with matrix size 64x64 and zoom factor of 1.45. Low-dose CT centered at the heart was performed for attenuation correction. On the second day, the resting SPECT and CT images were acquired using the same amount of radiotracer activity and the same scanning protocol.

Image Processing

Emission data were reconstructed into short axis, horizontal long axis, vertical long axis and 17-segment polar map images with iterative reconstruction protocol using commercially available QPS (Cedar-Sinai medical center, Los Angeles, California) software. For AC images, the co-registration was properly checked by the researcher in every case before image processing. Processed SPECT images were displayed in GE multichrome color scale (9).

Semiquantitative Interpretation

AC and NC images were interpreted in a random order by the consensus of 2 experienced nuclear medicine physicians blinded to patients' medical history and ICA results. If there was disagreement between the two readers even after the discussion, a third nuclear medicine physician will give an additional comment/opinion, and a consensus was formed. The third interpreter was also blinded to the ICA results and the clinical information about the patients. Each myocardium segment was scored from 0 to 4 based on relative uptake compared to the segment of maximum uptake; score 0 represented maximum uptake while score 4 represented no uptake. For per-person analysis, the sum of scores in all segments of stress images represented summed stress score (SSS) and the sum of scores in all segments of rest images represented summed rest score (SRS). The summed difference score (SDS) was calculated by subtracting SRS from SSS. For vascular territory analysis, the summed scores are the sum of scores in all segments corresponding to the territory of each of the 3 major coronary arteries.

Invasive Coronary Angiography

The ICA was performed and interpreted by experienced board-certified interventional cardiologists using visual assessment as a routine clinical practice. The presence of significant CAD was defined when there was a stenosis of the left main coronary artery ≥50%, and/or any other coronary artery ≥70%. In patients who had previous percutaneous coronary intervention (PCI) with or without stent, the cut-off to define the diseased vessel was ≥50% re-stenosis in left main coronary artery, or ≥70% re-stenosis in other coronary arteries.

Statistical Analysis

Diagnostic performances were assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Comparison of AUC was performed by Delong's non-parametric methods (10). UL index, a statistical method for defining cut-offs using the shortest distance from the upper left corner to the ROC curve, was used to determine optimum cut-offs. These cut-off values were further used for the calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, positive and negative likelihood ratios (LR+ and LR-). Proportions and likelihood ratios were compared using chi-square tests and agreement between AC and NC scores was determined by intraclass correlation coefficient (ICC). Territories of each main coronary artery for per-vascular-territory analyses were in accordance with the American Society of Nuclear Cardiology (ASNC) Guidelines (11). The analysis was performed by SPSS for Windows version 22 and the Compbdt R package (12). P value <0.05 was considered statistically significant.

Results

Clinical Characteristics

One hundred and seventeen subjects were eligible (63 men and 54 women; mean age 69.5 years). Clinical characteristics are displayed in Table 1. CAD was present in 66 patients (56%). Most of the patients had a single vessel territory (45%) and the detailed pattern of coronary artery stenosis is shown in Table 2. Most of the patients with CAD had hypertension (n=57, 86%), and dyslipidemia (n= 91, 78%). Thirty-two patients received prior PCI (27%), and most of them had recent CAD in the current analysis (n=25, 78%). The median interval between MPS and ICA was 2 months (interquartile range 1-3 months), and the maximum interval was 10 months in 1 patient.

Per-person Analysis of The Diagnostic Performance of MPS and Optimal Cut-offs

ROC curves comparing the diagnostic performance between AC and NC scores are provided in Figure 1. There were no statistically significant differences between AC-SSS (AUC: 0.765) and NC-SSS (AUC: 0.780, p value=0.624), AC-SRS (AUC: 0.664) and NC-SRS (AUC: 0.659, p value=0.866), and AC-SDS (AUC: 0.690) and NC-SDS (AUC: 0.702, p value=0.771). For subgroup analysis based on sex, and obesity status, there was no statistically significant difference between AC-SSS (AUC: 0.801) and NC-SSS (AUC: 0.780) in the female subgroup (p value=0.668),

Table 1. Baseline patient characteristics

Characteristic	All patients, n (%)	Patients with CAD, n (%)	Patients without CAD, n (%)	p value
Disease status	117	66 (56)	51 (44)	-
Age (mean ± SD), year	69.5±12.0	69.8±13.4	69.2±10.1	0.806
Interval between MPS and ICA (mean ± SD), month	2.2±2.1	2.2±2.0	2.1±2.2	0.799
Sex				
Male	63 (54)	41 (62)	22 (43)	0.042
Female	54 (46)	25 (38)	29 (57)	0.042
Co-morbidity				
Hypertension	98 (84)	57 (86)	41 (80)	0.538
Diabetes	48 (41)	31 (47)	17 (33)	0.194
Dyslipidemia	91 (78)	58 (88)	33 (65)	0.006
Obesity	15 (13)	7 (11)	8 (16)	0.592
End-stage renal disease	4 (3)	2 (3)	2 (4)	1.000
Smoking	10 (9)	9 (14)	1 (2)	0.057

CAD: Coronary artery disease, MPS: Myocardial perfusion scan, ICA: Invasive coronary angiography, SD: Standard deviation as well as those parameters in the male subgroup (AUC: 0.742 vs. 0.764, p value=0.588). There was also no statistically significant difference between AC-SSS (AUC: 0.764) and NC-SSS (AUC: 0.797) in non-obese subgroup (p value=0.284), as well as those parameters in the obese subgroup (AUC: 0.866 vs. 0.688, p value=0.228).

Each pair of AUCs was compared, aiming to determine the best AUC for CAD diagnosis. In the AC group, the AUC of AC-SSS was significantly higher than that of AC-SRS (p value=0.005), while there was no statistically significant difference between the AUC of AC-SSS and those of AC-SDS (p value=0.057). In the NC group, the AUC of NC-SSS was also significantly higher than that of NC-SRS (p value <0.001), while there was no statistically significant difference between the AUC of NC-SSS and that of NC-SDS (p value=0.107).

Due to the high AUC of SSS and SDS in both AC and NC images, the diagnostic performance of MPS was analyzed based on those data. The optimum cut-off values were more than 12 for AC-SSS, >15 for NC-SSS, >4 for AC-SDS and >3 for NC-SDS. The sensitivity, specificity, PPV, NPV and accuracy of AC-SSS were 61%, 82%, 82%, 62%, and 70%, respectively, and the parameters for NC-SSS were 79%, 67%, 75%, 71%, and 74%, accordingly. The diagnostic parameters of AC-SDS, and NC-SDS are demonstrated in Table 3. There were no statistically significant differences among the diagnostic parameters of AC-SSS vs. NC-SSS, AC-SDS vs. NC-SDS, AC-SSS vs. AC-SDS, or NC-SSS vs. NC-SDS as detailed in Table 3.

The LR+ and LR- of AC-SSS, NC-SSS, AC-SDS, and NC-SDS were 3.39, 0.48, 2.39, 0.31, 2.26, 0.52, and 1.96 and 0.60, respectively. There were no statistically significant differences in LR+ and LR- of AC-SSS vs. NC-SSS (p=0.200 for LR+ and p=0.060 for LR-), AC-SDS vs. NC-SDS (p=0.878 for LR+ and p=0.517 for LR-), AC-SSS vs. AC-SDS (p=0.145 for LR+ and p=0.624 for LR-), and NC-SSS vs. NC-SDS (p=0.676 for LR+ and p=0.141 for LR-).

Table 2. Pattern of coronary artery stenosis

Disease involvement	Subjects	
	Number	Percentage
Single vessel territory	30	46%
Double vessels territories	12	18%
Triple vessels territories	24	36%

Per-vascular Territory Analysis of the Diagnostic Performance of MPS and Optimal Cut-offs

In the left anterior descending territory, there is no statistical significance between AC-SSS (AUC: 0.782) and NC-SSS (AUC: 0.760). The optimum cut-off values are SSS >7 for AC (sensitivity 63%, specificity 87%, PPV 81%, NPV 73%, accuracy 76%) and SSS>6 for NC (sensitivity 70%, specificity 78%, PPV 73%, NPV 75%, accuracy 74%).

In the left circumflex (LCX) territory, there was no statistical significance between AC-SSS (AUC: 0.745) and NC-SSS (AUC: 0.713). The optimum cut-off values are SSS >2 for AC (sensitivity 67%, specificity 68%, PPV 42%, NPV 86%, accuracy 68%) and SSS >5 for NC (sensitivity 70%, specificity 59%, PPV 37%, NPV 85%, accuracy 62%).

In the right coronary (RCA) territory, there is no statistical significance between AC-SSS (AUC: 0.776) and NC-SSS (AUC: 0.774). The optimum cut-off values are SSS >2 for AC (sensitivity 69%, specificity 77%, PPV 60%, NPV 83%, accuracy 74%) and SSS >8 for NC (sensitivity 64%, specificity 86%, PPV 69%, NPV 83%, accuracy 79%).

Agreements of Each Score Obtained From AC and NC Images

There was significant difference between SSS obtained from NC and AC images, with a mean difference of 5.8 (NC-SSS was higher than AC-SSS, p value <0.001), and a significant difference between SRS obtained from NC and AC images was also observed (mean difference of 5.8, NC-SRS was higher than AC-SRS, p value <0.001). This resulted in no difference between SDS obtained from the NC and AC images (p value=0.952).

On the per-vascular-territory basis, there was a significant difference in SSS obtained from NC and AC images in LCX, and RCA territories (mean difference of 2.4, and 3.3,

Table 3. Diagnostic parameters of Tc-99m sestamibi MPS based on different criteria

Criteria	Sensitivity	Specificity	Accuracy	PPV	NPV
AC-SSS >12	61% (49-72)	82% (72-93)	70% (62-78)	82% (71-92)	62% (50-73)
NC-SSS >15	79% (69-89)	67% (54-80)	74% (66-82)	75% (65-86)	71% (58-84)
AC-SDS >4	62% (50-74)	73% (60-85)	67% (58-75)	75% (63-86)	60% (47-72)
NC-SDS >3	68% (57-79)	69% (56-81)	68% (60-77)	74% (63-85)	62% (50-75)

Data in parentheses are 95% confidence intervals. There was no statistical significance between each pair of the parameters (p value >0.05). AC: Attenuation-corrected, NC: Non-attenuation-corrected, MPS: Myocardial perfusion scan, PPV: Positive predictive value, NPV: Negative predictive value, SSS: Summed stress score, SDS: Summed difference score

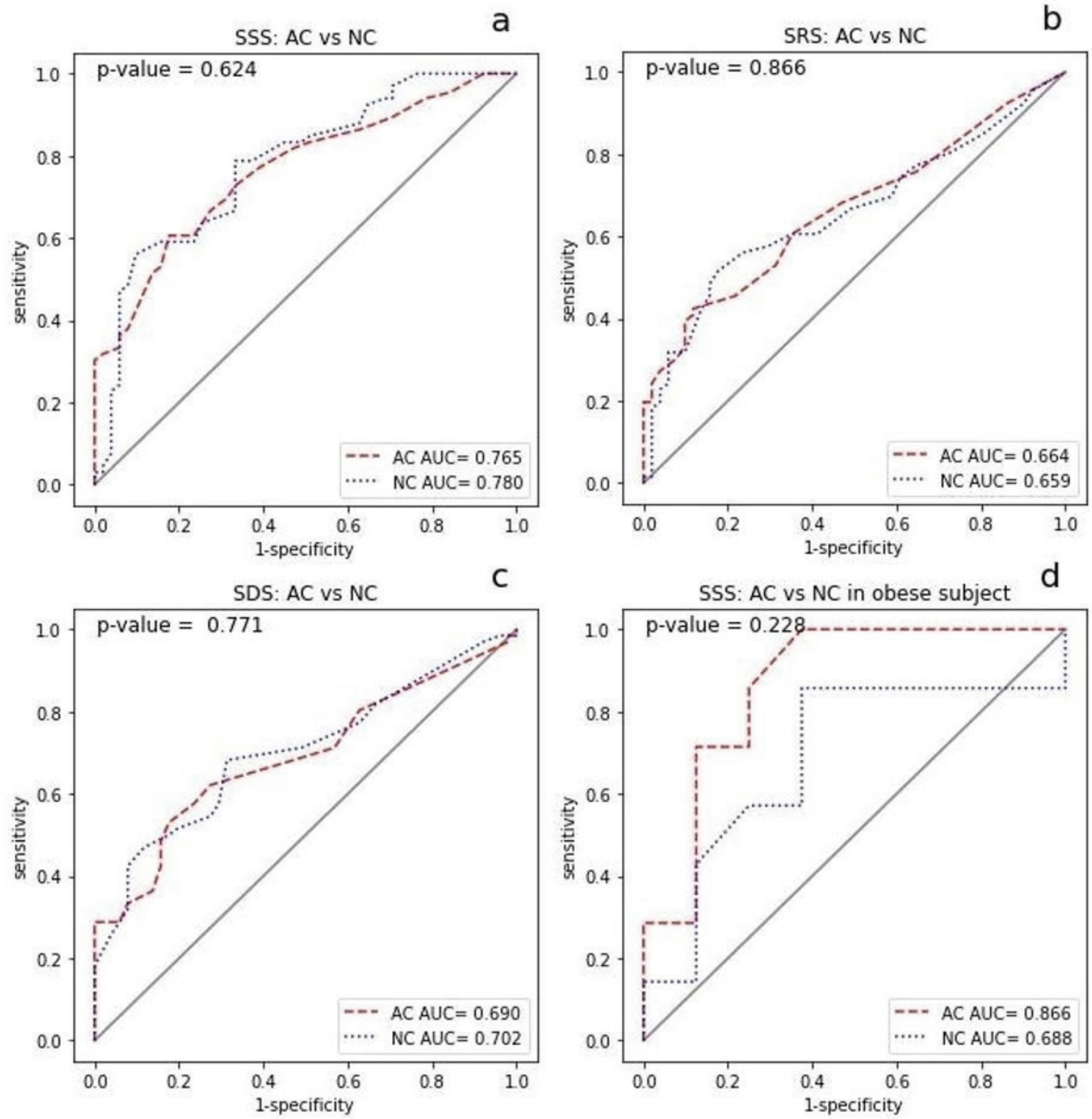

Figure 1. ROC curves comparing diagnostic performance between AC and NC scores of SSS (a), SRS (b), SDS (c) and SSS in obesity subgroup (d). (Created using Matplotlib version 3.3.3, https: matplotlib.org)

ROC: Receiver operating characteristic, AC: Attenuation-corrected, NC: Non-attenuation-corrected, SSS: Summed stress score, SRS: Summed rest score, SDS: Summed difference score

respectively, p value <0.001, Figure 2). These differences were also observed when interpreted by NC-SRS, and AC-SRS in both LCX and RCA territories (mean difference of 2.2, and 3.3, respectively, p value <0.001, Figure 3), which was not proved, but probably due to the breast and the diaphragmatic attenuation, respectively. There was no statistically significant difference between NC-SDS, and AC-SDS on per-vascular-territory basis (Figure 4).

Excellent agreements between AC-SSS, and NC-SSS (ICC: 0.9), AC-SRS, and NC-SRS (ICC: 0.9), and AC-SDS, and NC-SDS (ICC: 0.8) were observed.

Discussion

Our results demonstrated good diagnostic performance of Tc-99m-sestamibi stress-rest protocol either with or without

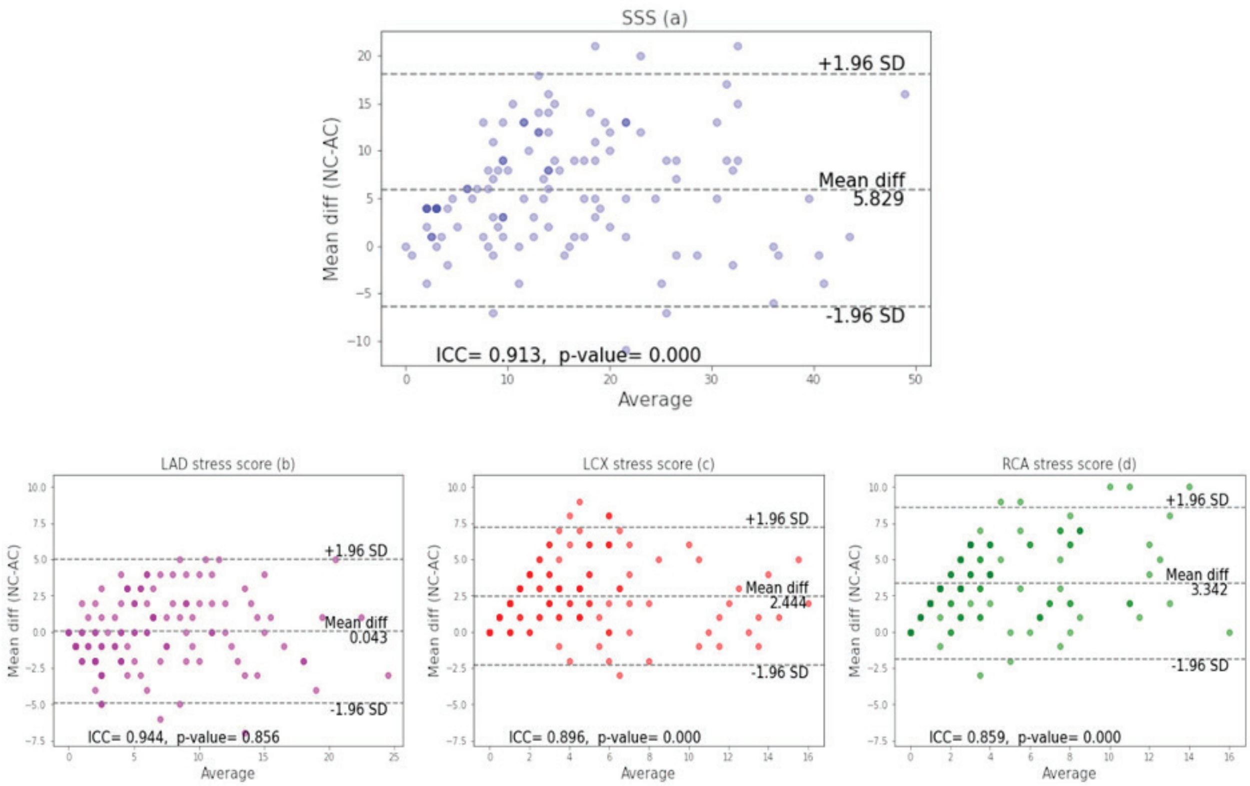

Figure 2. Agreements between stress scores. There were significant differences between AC and NC of SSS (a) and stress scores in LCX (c) and RCA (d) territories. No significant difference in seen in LAD territory (b)
AC: Attenuation-corrected, NC: Non-attenuation-corrected, SSS: Summed stress score, LCX: Left circumflex, LAD: Left anterior descending, RCA: Right coronary

attenuation correction for the diagnosis of coronary artery stenosis using ICA as a gold standard. The previously reported accuracy of MPS in several studies ranged from 63 to 94% (13,14,15). Our protocol provided good accuracy of MPS in both AC-SSS (70%) and NC-SSS images (74%). The reported superiority of AUC of SSS and SDS over SRS reaffirmed the significance of stress myocardial perfusion imaging for the diagnosis of coronary artery stenosis.

In subgroup analysis, we found no significant difference between the diagnostic performance of AC-, and NC-images in both male, and female subgroups, which concordant with the prior study by Wolak et al. (16). The difference cut-off values were due to difference interpretation methods as we defined all scores based on the relative uptake of one segment to the area of maximum uptake in the individual image. In our study, the AUC of AC-images of obese patients was notably higher than those of NC-images (AUC: 0.866 vs. 0.688), even without a statistically significant (p value=0.228). This might be consistent with Thompson et al.'s (17) conclusion that AC was particularly helpful in obese patients, but the failure to reach statistical significance in our study might be due to the small number of obese patients (n=15).

Even without a statistically significant difference, our results showed that AC-SSS offered slightly higher specificity (82%) compared to NC-SSS (67%). This was concordant with several prior studies (6,11,17). Recent meta-analysis by Huang et al. (5) revealed the pooled sensitivity and specificity of MPS using AC images of 84% and 80% and those from NC were 80% and 68%, respectively. The lower specificity of NC images was potentially caused by attenuation artifacts, which were more obvious without the correction process. The mean difference of 5.8 between AC-SSS and NC-SSS, as well as between AC-SRS, and NC-SRS found in the current study supported the presence of attenuation artifacts in NC images on both stress and rest images, especially in LCX, and RCA territories, when analyzed on per-vascular-territory basis. The presence of an attenuation artifact could also explain the larger difference between AC and NC cut-off values on per-vascular territory analysis in LCX and RCA territories.

We did not find inferior diagnostic performance of NC MPS in the diagnosis of CAD within the RCA territory, which

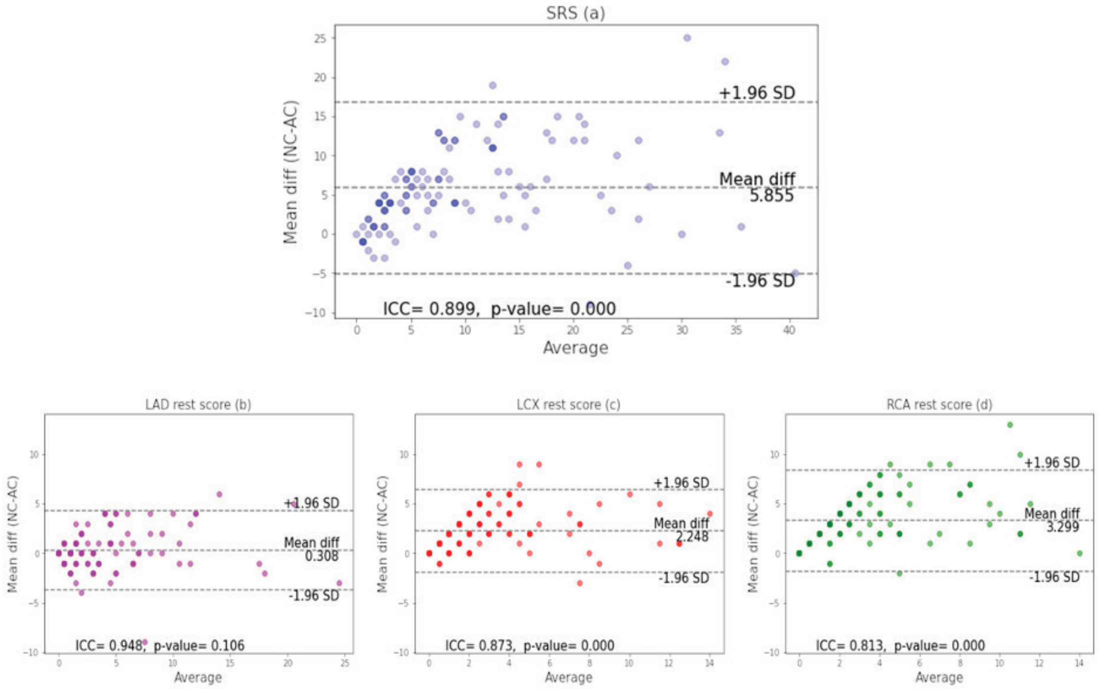

Figure 3. Agreements between rest scores. Similar to stress scores, there were significant differences between AC and NC of SRS (a) and rest scores in LCX (c) and RCA (d) territories. No significant difference in seen in LAD territory (b)

AC: Attenuation-corrected, NC: Non-attenuation-corrected, SRS: Summed rest score, LCX: Left circumflex, RCA: Right coronary, LAD: Left anterior descending

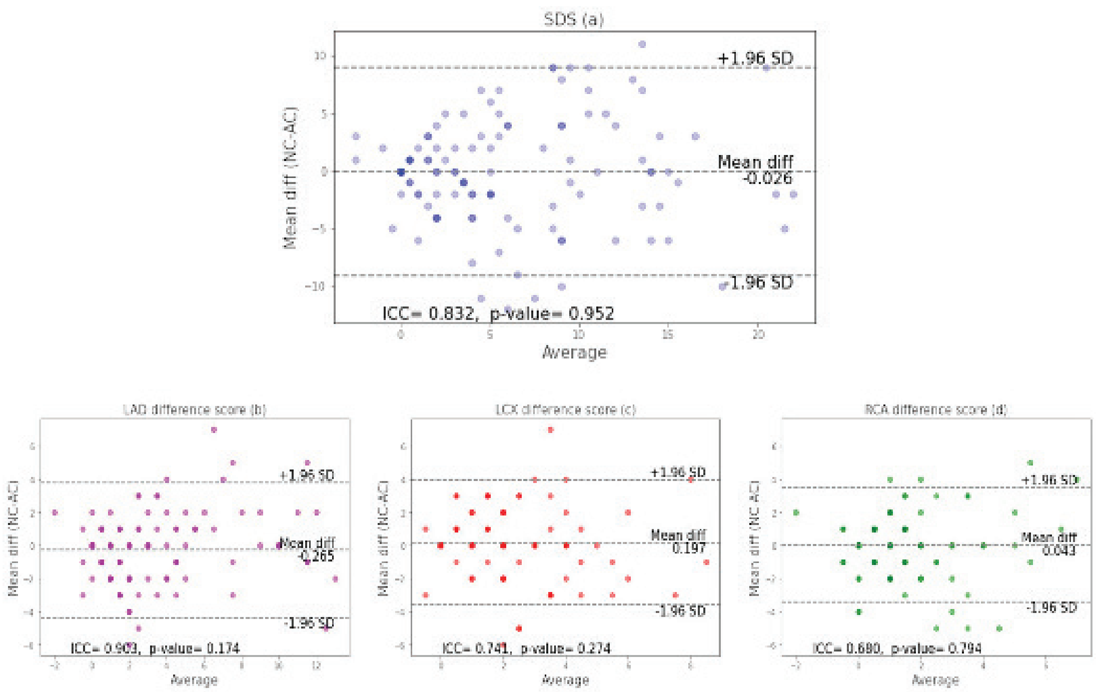

Figure 4. Agreements between difference scores. Contrary to stress and rest scores. No significant difference in either SDS (a) or territories of LAD (b), LCX (c) and RCA (d)

SDS: Summed difference score, LCX: Left circumflex, RCA: Right coronary, LAD: Left anterior descending had been reported in past studies. This absence could be a result of using standardized criteria based on tracer uptake, difference cut-offs used, interpreters being experienced, or a combination of the aforementioned factors (18). It should also be noted that the current study population had a notably high rate of RCA stenosis (38/66 patients, 58% of the study population). It is widely accepted that the detection of RCA stenosis is a problematic for MPS. A diagnosis based on either AC-SDS or NC-SDS could eliminate the interference from attenuation artifacts. Some prior data also showed higher false positive rates in NC images, however, masking of true defects by attenuation correction in AC could lead to lower sensitivity when using AC images (7,19,20). Generally, the ASNC recommends the use of attenuation correction when available to optimize image quality and improve the diagnostic utility of MPS (11).

Study Limitations

Limitation of our study was a slightly long interval between MPS and ICA in 1 patient. Nevertheless, the progression of coronary stenosis was generally insidious (21). Our method using the semi-quantitative assessment might have limitation in the assessment of multi-vessel diseases, however, the dynamic Tc-99m-sestamibi MPS for quantitative assessment of myocardial blood flow was not widely performed because of the low count sensitivity of the conventional SPECT scanner (22). Another potential weakness in our study was MPS may exhibit defects in the absence of stenoses when MPS was performed after angioplasty or stenting thus the specificity of MPS following PCI might be limited (23). Apart from CAD diagnosis, the parameters from the MPS were found to have prognostic value in the long-term period in patients having CAD regardless of ICA findings; for examples, abnormal MPS, especially in AC images, was associated with higher number of cardiac events, worsening survival rate and increased rate of hospital admission (24,25,26). Our studies still lacked of long term follow up to assess those outcomes, which could be the topic of interest for further research.

Conclusion

In conclusion, using a semiquantitative method based on relative tracer uptake with a standard 17-segment model, NC-images based Tc-99m-sestamibi MPS either by SSS, or SDS promised fairly good diagnostic accuracy comparable to AC images with different cut-off values.

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Ethics

Ethics Committee Approval: Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (COA no: 611/2017, IRB no: 366/60).

Informed Consent: The informed consent are waived by the ethic committee.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.V., Concept: S.S., S.V., Design: S.V., M.C., Data Collection or Processing: S.S., M.C., Analysis or Interpretation: S.S., M.C., Literature Search: S.V., Writing: S.V., M.C.

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