ORIGINAL ARTICLE

Comparison of automated quantification and semiquantitative visual analysis findings of IQ SPECT MPI with conventional coronary angiography in patients with stable angina

Konvansiyonel koroner anjiyografi ile IQ-SPECT kullanılarak yapılan otomatik ve görsel analiz yönteminin kararlı anjinalı hastalarda karşılaştırılması

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ABSTRACT

Objective: The aim of this study was to assess the validity of automated quantitative and semiquantitative visual analysis of total perfusion deficit (TPD) using the IQ SPECT gamma camera system compared to conventional coronary angiographically detected significant coronary artery disease (CAD).

Methods: The study included patients with suspected CAD who underwent myocardial perfusion single photon emission computed tomography and conventional coronary angiography. The summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) (semiquantitative visual analysis results) were assessed using a 5-point scale in a standard 17-segment model, and TPD (stress, rest, and ischemic TPD) was quantified using automated software.

Results: In all, 84 patients (Group 1, those who underwent revascularization) had significant coronary artery lesions, and 81 (Group 2) had non-significant lesions. The median interquartile range values were: stress-TPD (sTPD): 16 (3.5–33.5) vs 9.2 (2–17.9), rest-TPD: 9.4 (2.2–18.8) vs 4 (1–11), and 6.9 (1.9–14.1) vs 3.4 (1–6.1) for ischemic-TPD (iTPD) in Group 1 and Group 2, respectively. To detect ischemia, the optimal cut-off points were 9.5 (sensitivity: 75%, specificity; 60%) for sTPD, and 4.5 (sensitivity: 56%, specificity: 73%) for iTPD. There were significant correlations between quantitative and semi-quantitative methods in detection of significant coronary artery disease (sTPD-SSS: r=0.954, sTPD-SDS: r=0.746, iTPD-SSS: r=0.654, iTPD-SDS: r=0.759; p<0.05 for all).

Conclusion: The quantitative analysis and summed stress scores produced by the IQ SPECT system appear to be a useful and valid method to detect significant CAD.

ÖZET

Amaç: Bu çalışmada geleneksel koroner anjiyografi ile tespit edilen ciddi koroner arter hastalığının saptanmasında IQ SPECT gama kamera sistemi kullanılarak otomatik nicel ve yarı-nicel görsel analiz ile elde edilen toplam perfüzyon defektinin (TPD) geçerliliği değerlendirilmiştir.

Yöntemler: Çalışmaya koroner arter hastalığı şüphesi ile miyokart perfüzyon SPECT çalışması yapılan ve bu sonuca göre geleneksel koroner anjiyografi uygulanan hastalar alındı. Toplam stres skoru (SSS), toplam istirahat skoru (SRS) ve toplam fark skoru (SDS) ile yarı-nicel görsel analiz sonuçları, standart 17 segmentli bir modelde beş-puanlamalı bir ölçek üzerinde değerlendirildi ve TPD (stres, dinlenme ve iskemik TPD) otomatik nicel ölçebilen yazılım ile ölçüldü.

Bulgular: Seksen dört hastada ciddi koroner arter hastalığı saptanarak, revaskülarizasyon işlemi uygulandı (Grup 1), 81 hastada ise non-kritik koroner lezyon izlendi (Grup 2). Ortanca ve çeyrekler arası aralık (IQR) değerler; stres-TPD için 16'ya (3.5–33.5) karşı 9.2 (2–17.9), istirahat TPD için 9.4'e (2.2–18.8) karşı 4 (1–11) ve iskemik-TPD için 6.9'a (1.9–14.1) karşı 3.4 (1–6.1) idi. İskemi tespit etmek için, en uygun kestirim noktası, stres TPD 9.5 (duyarlılık %75, özgüllük %60) ve iskemik TPD için 4.5 (duyarlılık %56, özgüllük %73) idi. Ciddi koroner arter hastalığının tespitinde nicel ve yarı-nicel yöntemler arasında anlamlı korelasyon izlendi (stres TPD-SSS r=0.954, stres TPD-SDS r=0.746, iskemik TPD-SSS r=0.654, iskemik TPD-SDS r=0.759; hepsi için p<0.05).

Sonuç: IQ SPECT sistemi ile elde edilen nicel analiz ve toplam stres skoru ciddi koroner arter hastalığının tespit edilmesinde kullanışlı ve geçerli bir yöntem olarak görünmektedir.

Stable coronary artery disease (CAD) can refer to different evolutionary phases of CAD, excluding situations in which coronary artery thrombosis dominates the clinical presentation (acute coronary syndromes).[1] Myocardial perfusion imaging (MPI) using single photon emission computed tomography (SPECT) is a useful method of noninvasive risk stratification, readily identifying those patients at a great-

Received: November 10, 2018 *Accepted:* April 24, 2019

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est risk for subsequent myocardial infarction and death.[2–5] Myocardial perfusion SPECT studies using the IQ-SPECT Symbia S system with SMARTZOOM collimators and dedicated reconstruction software (Siemens Healthineers, Erlangen, Germany) have provided a shorter scan time and used less radioactivity than conventional SPECT systems.

Abbreviations:

CAD	*Coronary artery disease*
iTPD	*Ischemic TPD*
MPI	*Myocardial perfusion imaging*
rTPD	*Rest TPD*
SDS	*Summed difference score*
SPECT	*Single photon emission computed tomography*
SRS	*Summed rest score*
SSS	*Summed stress score*
sTPD	*Stress TPD*
TPD	*Total perfusion deficit*

Patients who demonstrate myocardial ischemia in 2 of 17 segments of the left ventricle or more than 10% of the myocardium in a stress test are considered to be at high risk, and revascularization is recommended.[6–9] The prognostic utility of a 10% cut-off level has been validated by previous studies, and many centers employ the summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) obtained using semiquantitative visual analysis in the assessment of ischemia. Nevertheless, this visual scoring system depends very much on the knowledge, experience, training, and interpretation skills of the physician. More objective and quantitative methods could avoid disadvantages related to dependence on the skills of individual physicians.

Total perfusion deficit (TPD), an objective parameter illustrating the severity and the area of ischemia, was calculated using Quantitative Perfusion SPECT software (QPS; Cedars-Sinai Medical Center, Los Angeles, CA, USA).[10] A close linear correlation between TPD and expert visual analysis has been reported previously by Berman and Keiichiro.[11,12] The guidelines of the American Society of Nuclear Cardiology published in 2010 identify automatic quantification as a useful technique to determine left ventricular ischemia.

The aim of this study was to assess the validity of ischemia detected based on quantitative analysis and semiquantitative analysis using the IQ-SPECT Symbia S system with dedicated reconstruction software.

METHODS

Study population

The total referral population for IQ-SPECT scan from January 20, 2015 to February 29, 2016 included 885 patients. The study group consisted of consecutive patients with suspected CAD who underwent a 2-day 99mTc-sestamibi stress/rest IQ-SPECT myocardial perfusion imaging, and a subsequent conventional coronary angiography according to the SPECT findings. Patients with a history of coronary artery bypass grafting or percutaneous coronary intervention were excluded from the study. CAD was defined as stenosis of more than 70% in a major epicardial coronary artery or 50% in the left main coronary artery according to coronary angiography.

Image acquisition and reconstruction protocol

The assessments used in this study were derived from 99mTc-sestamibi stress and 99mTc-sestamibi rest examinations performed using the 2-day protocol. Patients fasted for >6 hours before the measurements were taken. The use of beta-blockers and calcium channel antagonists was terminated 48 hours before the test, and nitrates were terminated 12 hours prior. An exercise treadmill was used for the stress study, and the participants were injected intravenously with 10 to 12 mCi (370 to 444 MBq) technetium (99mTc) sestamibi at peak exercise, followed by continued exercise for 1 minute. All of the stress testing was supervised by a qualified and appropriately trained healthcare professional. On the following day, the rest study was performed with the administration of the same dose. SPECT images were acquired 15 to 60 minutes after the tracer injection using the IQ-SPECT Symbia S gamma camera system with dedicated multifocal SMARTZOOM collimators performing cardio-centric acquisition. All of the patients were examined in the supine position. Prone positioning was applied if needed post stress imaging, but only supine images were interpreted for the study. SPECT tomograms were reconstructed and reoriented using an automatic algorithm system. The essential acquisition parameters were a matrix of 128x128 and 17 views per detector obtained at a rate of 20 seconds per view. No attenuation or scatter correction was employed. Reconstruction of the series was performed using the Flash-3D algorithm (Siemens Healthineers, Erlangen, Germany), 30 iterations, with 1 subset. Gauss filter with FWHM 14 mm was applied. Images were processed using Cedars-Sinai quantitative perfusion SPECT (QPS) software. Examples of normal and ischemic myocardia SPECT images are provided in Figure 1.

Semiquantitative visual analysis

A 5-point scale (0=normal, 1=mildly decreased, 2=moderately decreased, 3=severely decreased, and 4=absence of segmental uptake) was used with a 17-segment model to obtain summed stress scores (SSS), summed rest scores (SRS), and summed difference scores (SDS) for semiquantitative visual analysis. Images were scored using the consensus opinion of 2 nuclear medicine physicians with more than 10 years of clinical experience in nuclear cardiology. The SSS and the SRS were calculated using the sum of the 17-segment stress and rest score, respectively. The SDS was obtained by subtracting the SRS from the SSS.

Automated quantification of SPECT myocardial perfusion imaging

The TPD value was used as the automated quantification variable. The TPD measurement was computed automatically as a polar map of severities below the abnormality threshold, reflecting both the extent and severity of defects. The TPD scores were measured using stress and rest images obtained using the QPS software. The iTPD was calculated as the difference between the sTPD and rTPD values.

Coronary angiography

Coronary angiography was performed by experienced interventional cardiologists who perform at least 75 interventional procedures annually, using the femoral percutaneous approach and an Angiocore device (Siemens Healthineers, Erlangen, Germany). Coronary angiography was performed within a week of the SPECT results.

The present study was approved by the Institutional Review Board and conformed to the ethical principles described in the Declaration of Helsinki.

Statistical analysis

Statistical analyses were performed using SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±SD and categorical variables were expressed as percentages. Continuous variables were analyzed using the Kolmogorov–Smirnov to test for normal distribution. Comparisons between normally distributed data were performed with Student's t-test. The Mann-Whitney U-test was used for the data that were not normally distributed. A chi-square test was applied to compare the influence of categorical variables. The correlations between automatic quantitative parameters and semiquantitative parameters were evaluated with Pearson's r-correlation coefficients. A p value of <0.05 was considered significant. Receiver operating curves were generated to compare quantitative and semiquantitative parameters versus conventional angiography results. Cut-off values for sTPD, iTPD, SSS, and SDS were determined from the intersection of the sensitivity and specificity curves graphed by the quantification value in the entire cohort of patients to maximize both sensitivity and specificity. Sensitivity, specificity, positive and negative predictive values, and accuracy for the prediction of obstructive coronary artery disease were determined based on these curves. Areas under the curve were compared using the Delong-Clarke-Pearson method.

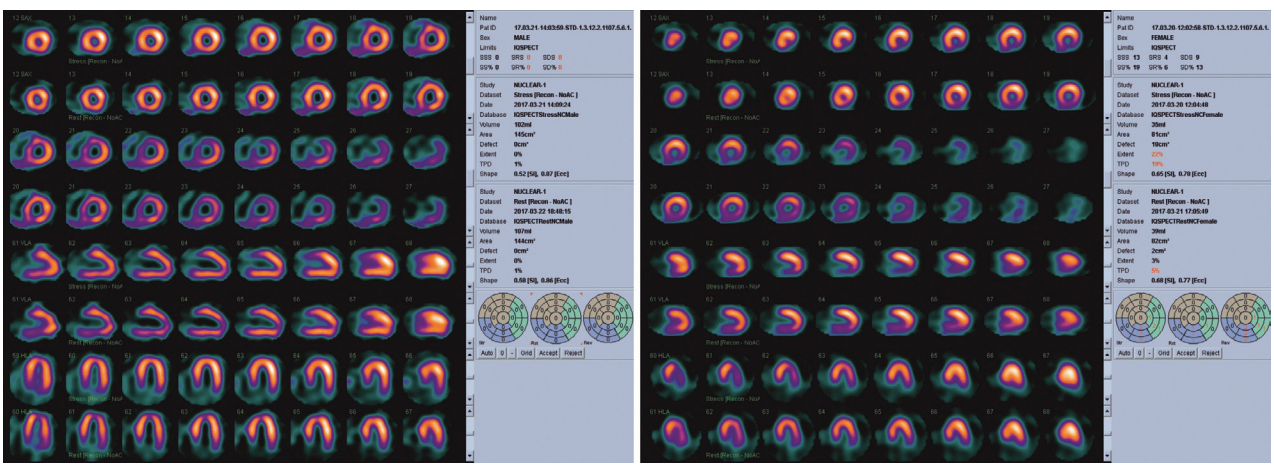

Figure 1. Examples of normal and ischemic myocardial perfusion scintigraphy.

Table 1. Baseline characteristics, risk factors, and laboratory findings of the study groups

	Group 1	Group 2	*p*
Age (years)	60±9.8	57±11	0.44
Sex, male (%)	94	52	0.001
Diabetes mellitus (%)	21	29	0.44
Hypertension (%)	50	51	0.88
Smoking (%)	52	38	0.04
Family history of CAD (%)	23	31	0.56
Glucose (mg/dL)	138±59	122±45	0.45
Urea (mg/dL)	36±13	32±10	0.23
Serum creatinine (mg/dL)	0.9±0.3	0.8±0.5	0.67
Total cholesterol (mg/dL)	224±59	210±44	0.49
LDL-cholesterol (mg/dL)	145±48	131±37	0.61
HDL-cholesterol (mg/dL)	44±10	48±10	0.63
Triglyceride (mg/dL)	177±101	149±75	0.29
WBC count ($10^3/\mu L$)	4.5±4.2	4.7±4.1	0.43
Hemoglobin (g/dL)	13±1.4	13±1.8	0.85

Group 1: patients with significant coronary lesion; Group 2: Patients without significant coronary lesion; CAD: Coronary artery disease; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; WBC: White blood cell.

RESULTS

A total of 165 patients were included in the study. Among them, 84 (Group 1: 54.9%) had significant coronary artery lesions (left anterior descending artery: 12.8%; circumflex artery: 12.8%; right coronary artery: 11.6%, and multi-vessel disease: 17.7%), and 81 patients (Group 2: 45.1%) had non-significant CAD. The demographics, risk factors for CAD and baseline biochemical parameters of the patients were presented in Table 1.

Frequency of male gender and smoking were higher in patients with significant CAD compared to those without CAD. Laboratory parameters were not different between the two groups.

SPECT results

The quantitative and visual semiquantitative SPECT values obtained during stress and rest examinations are presented in Table 2. The semiquantitative values of SSS and SDS, and quantitative TPD values were significantly higher in Group 1 patients when compared with Group 2.

Table 2. Comparison of the quantitative and semiquantitative values of the groups

	Quantitative	Semiquantitative	*p*
Summed stress score			
Group 1	10.1 (4–18.2)	8 (3.3–13.4)	0.045
Group 2	5.5 (2–7.9)	4 (2.2–6)	0.032
Summed rest score			
Group 1	5.2 (2–9.4)	4 (1.6–8.2)	0.035
Group 2	3.5 (1–7.5)	3 (1.5–6)	0.026
Summed difference score			
Group 1	5.6 (4.5–11.1)	5 (3–7)	0.043
Group 2	2.4 (1–4.5)	1.1 (1–3.5)	0.036
Stress total perfusion deficit (%)			
Group 1	16 (3.5–33.5)	13 (3–21)	0.001
Group 2	9.2 (2–17.9)	7 (2–14.5)	0.012
Rest total perfusion deficit (%)			
Group 1	9.4 (2.2–18.8)	7 (2.8–13.9)	0.026
Group 2	4 (1–11)	3.5 (2–9.7)	0.001
Ischemic total perfusion deficit (%)			
Group 1	6.9 (1.9–14.1)	6 (3–8.8)	0.034
Group 2	3.4 (1–6.1)	3 (1–4.6)	0.027

The data were presented as median (IQR). IQR: interquartile range.

Table 3. The cut-off values for detecting significant coronary artery disease

	Cut-off	AUC	Sensitivity (%)	Specifity (%)	*p*
SSS	5.5	0.706	72	67	0.001
SDS	2.5	0.740	70	65	<0.001
sTPD (%)	9.5	0.678	75	60	0.003
iTPD (%)	4.5	0.669	56	73	0.005

AUC: Area under curve; SSS: Summed stress score; SDS: Summed difference score; sTPD: Stress total perfusion deficit; iTPD: Ischemic total perfusion deficit.

The cut-off points for the quantitative and semiquantitative values that suggested the presence of significant CAD were displayed in Table 3. The values of ≥5.5 for SSS, ≥2.5 for SDS, ≥9.5 for sTPD, and ≥4.5 for iTPD were able to predict significant CAD. There were statistically significant positive correlations between quantitative and visual semiquantitative values of the whole population (between sTPD and SSS: r=0.954; sTPD and SDS: r=0.754; iTPD and SSS: r=0.654; iTPD and SDS: r=0.759). The correlations between quantitative and semiquantitative parameters are given in Figure 2.

The sensitivity, specificity, and positive and negative predictive values of the cut-off points determined

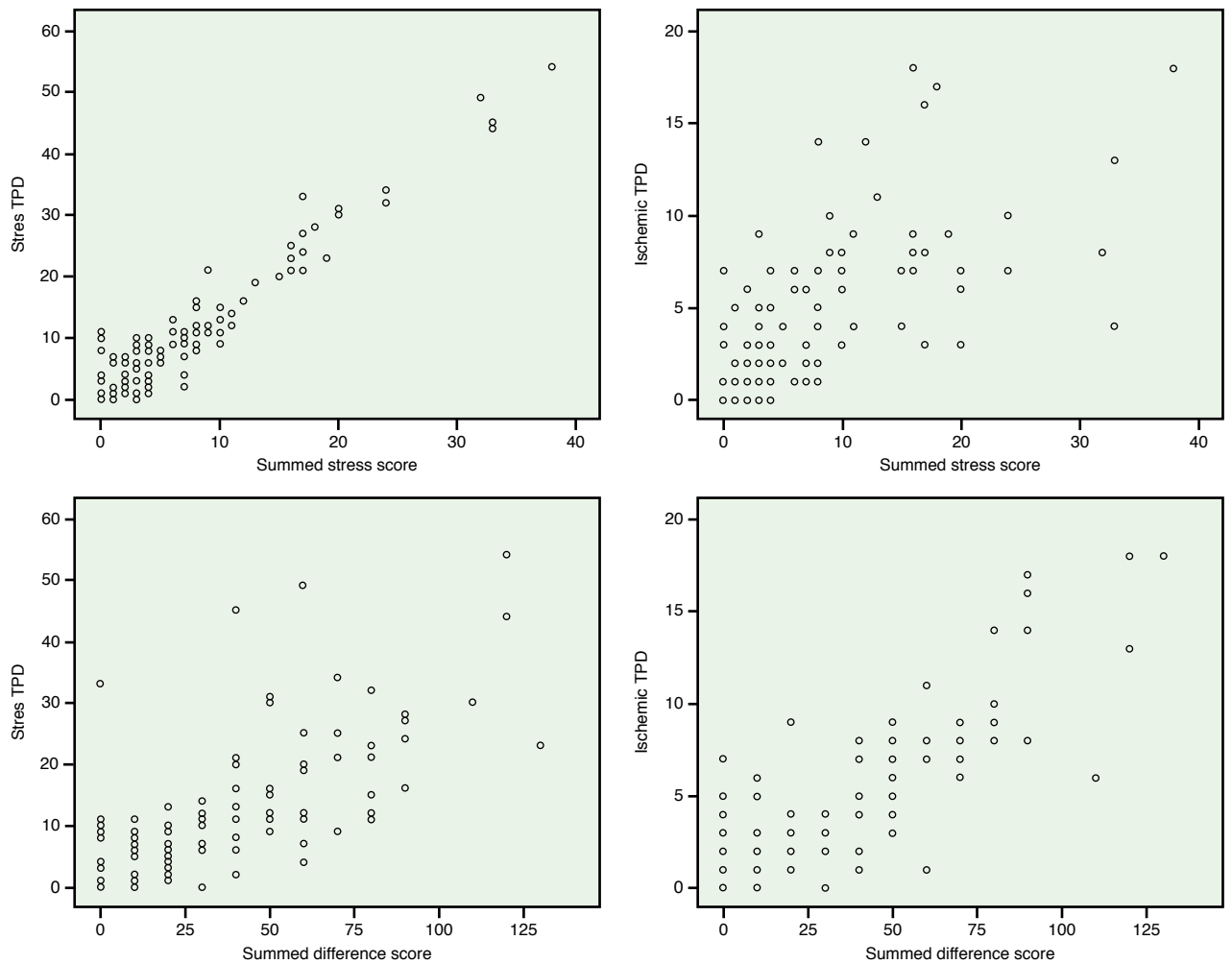

Figure 2. Correlations between quantitative and semiquantitative parameters. TPD: Total perfusion deficit.

Table 4. Diagnostic performance measures for cut-off value of SSS ≥4%, SDS ≥3DS and sTPD ≥5%

	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)
SSS ≥4%	77	47	57	68
SDS ≥3%	65	78	73	70
sTPD ≥5%	77	32	51	59

PPV: Positive predictive value; NPV: Negative predictive value; SSS: Summed stress score; SDS: Summed difference score; sTPD: Stress total perfusion deficit.

to predict significant CAD were also displayed (Table 4).

No significant difference was detected in comparisons using the Delon-Clarke method between the SSS and SDS curves (p=0.218), between SDS and sTPD (p=0.118), between SDS and iTPD (p=0.115), and between sTPD and iTPD (p=0.919). However, between SSS and sTPD (p=0.048), and between SSS and iTPD (p=0.045) found statistically significant difference.

DISCUSSION

Automated quantitative and semiquantitative values obtained with the IQ SPECT system have been shown to provide valuable information on the determination of prognosis in patients with known or suspected CAD. There are quantitative analysis programs that offer the option of assigning myocardial segments to a specific vascular territory or performing the analysis using polar maps and/or 3-dimensional displays based on pixel/voxel models. In this study, a 17-segment model and 5-point scoring were used to quantify MPI, as recommended in the guidelines.[13]

The median sTPD (16 *vs*. 9.2), rTPD (9.4 *vs*. 4) and iTPD (6.9 *vs*. 3.4) values obtained using automated quantitative analysis were higher in patients with significant CAD compared to patients without CAD. Similarly, the median SSS (8 *vs*. 4), SRS (4 *vs*. 3), and SDS (5 *vs*. 1.1) values detected using visual semiquantitative assessment were also higher. Similar to previous studies, quantitative and visual semiquantitative parameters were highly correlated to each other.[11]

Patients with stable symptoms of suspected CAD may be referred for noninvasive testing in order to determine long-term prognosis or the risk of an adverse outcome over time. These goals of testing are linked to the 2 main treatment goals for patients with suspected or known CAD: (1) amelioration of symptoms in daily life and (2) improving the outcome.[14]

The cornerstone of treatment strategy in patients with CAD is to predict the risk of major cardiac events (risk for subsequent death and myocardial infarction). MPI using IQ SPECT is a useful method to diagnose CAD and to detect the culprit lesion,[2–5] and it is also used as a noninvasive method to perform this risk stratification.[8,9]

The amount of ischemia determined by quantitative or semiquantitative methods with the IQ SPECT system in patients admitted to hospital with angina in whom a significant coronary artery lesion (≥70% stenosis) was subsequently detected by angiography (Group 1) suggests that both methods may be used to identify the clinically important lesions.

The performance characteristics of radionuclide imaging for this purpose are often based on an angiographic definition of a 50% or higher stenosis in or more in the left main artery or other main vessels or 70% stenosis in an individual epicardial vessel. This definition of CAD is founded in part on seminal studies in animal models showing that 50% stenosis begins to interfere with coronary flow. Several published studies define CAD as stenosis of 50% or more, whereas others use a threshold of 70%.[15,16] Use of the former would decrease sensitivity (as some cases of 50% to 70% stenosis are not hemodynamically significant) and increase specificity.

Use of the latter threshold, however, would increase sensitivity (as such instances of stenosis are more likely to be associated with a perfusion abnormality), but decrease specificity since any scan result with 50% to 70% stenosis would be considered a false-positive result. Over time, the view has emerged that CAD is too complex to simply be defined di-

chotomously by 50% or even 70% luminal stenosis. Despite of mentioned issues in definitions, significant lesions are accepted as those causing more than 70% luminal stenosis in this study and ischemia determination reached with IQ SPECT was found to have good sensitivity and sepcificity.

Myocardial perfusion SPECT, a valuable prognostic test in cases of CAD, is widely used to determine the need for catheterization;[16,17] however, only limited, unadjusted studies have compared survival with revascularization versus medical therapy after myocardial perfusion scintigraphy.[16,18] Previous studies have indicated that normal stress perfusion is associated with low risk, i.e., 1% per year,[7] and medical therapy is recommended for patients with normal perfusion or minimal perfusion defects, while a large stress-induced perfusion defect is associated with adverse events,[8] and revascularization is recommended for survival benefit in these patients.[3] Therefore, identification of the extent of an ischemic area is necessary for the best management of the patient.

In this study, the IQ SPECT system parameters evaluated by quantitative and semiquantitative methods at rest and during stress were higher in patients with significant luminal stenosis. We found cut-off points for ischemia detection for the SSS, SDS, and sTPD of 5.5%, 2.5%, and 9.5%, respectively. When we evaluated our patients using the cut-off points of SSS ≥4%, SDS ≥3%, and sTPD ≥5%, as reported in previous studies, we found that the values of sensitivity and specificity for our cut-off points were acceptable. These findings indicate that both of these methods may be useful as choices in the interventional treatment strategy for patients admitted with angina.[11]

At our center, as is often the case around the world, visual semiquantitative methods are usually used to quantify ischemia in the nuclear medicine department. This method is highly operator-dependent and remains semiquantitative, despite the development of SSS and SDS scores, which could reduce the disadvantages. Hence, automated quantitative analysis systems have recently been incorporated in most models of SPECT camera computer equipment. Some of the most common are Emory Cardiac Toolbox (Syntermed Inc., Atlanta, GA), QPS, and 4D-MSPECT (Michigan Medicine, University of Michigan, Ann Arbor, MI, USA). Published data do not clearly demonstrate improved sensitivity or specificity for CAD detection with these programs in comparison with visual analysis. However, these data are often produced at expert centers, many times where the quantitative software was developed, while the visual analysis data are derived from experienced readers in laboratories with excellent quality control. TPD is calculated by the QPS software as a fully automated parameter and does not require manual adjustment.[10] It allows for an objective estimation of the severity and extent of the defect.[10] In recent guidelines, "quantitative analysis" has been defined as not only a valuable aid for the visual interpretation of perfusion data, but several studies have also documented better reproducibility and less interobserver variation.[13] There is also research suggesting that automated quantitative assessment using the local normal database could be useful to detect CAD when experts in the visual interpretation of a myocardial perfusion SPECT image are not available in a clinical setting.[19] In practice, the use of contemporary quantitative programs may improve image acquisition quality as well as interpretation.[20] Moreover, the newer software programs may do better by comparing stress 1 versus stress 2 and rest 1 versus rest 2.

The positive correlation found between the quantitative TPD parameters and semi-quantitative parameters determined in this study using the IQ SPECT gamma camera system and dedicated software suggests that these parameters may be used confidently in the diagnosis and treatment plan decisions in cases of stable angina pectoris.

Conclusion

Automated quantitative parameters may be used both to determine the existence of coronary artery disease and to select the interventional therapy to be used for patients admitted with stable angina pectoris. A comparison of the quantitative and semiquantitative parameters produced by the IQ SPECT camera and the coronary angiography findings indicated that the IQ SPECT gamma camera system was valuable and that TPD assessment is a useful tool that may be helpful when incorporated into the determination of therapy choices for patients with stable angina.

Ethics Committee Approval: The study protocol was approved by Kartal Koşuyolu High Speciality Training and Research Hospital Ethics Committee (No: 2017.3/7-31).

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None.

Authorship contributions: Concept: C.D., F.Ç., Z.B., N.Ö., R.D.A.; Design: C.D., F.Ç., Z.D., Ö.K., R.D.A., E.E., A.U.; Supervision: C.K., N.Ö., A.K., S.Ç.Ö., Z.B.; Materials: A.H., Ö.Y.A., C.D., Z.B., S.Ç.Ö., E.E.; Data: C.D., F.Ç., A.K., Z.B., Ö.Y.A., A.H.; Analysis: C.D., F.Ç., A.K., C.K., N.Ö., Z.B.; Literature search: C.D., F.Ç., A.K., Z.B., S.Ç.Ö., A.H.; Writing: C.D., F.Ç., A.K., C.K., N.Ö.; Critical revision: C.D., F.Ç., A.K., C.K., N.Ö.

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Keywords: Computed tomography; coronary angiography; quantitative analysis; single photon emission computed tomography.

Anahtar sözcükler: Bilgisayarlı tomografi; koroner anjiyografi; nicel analiz; tek foton emisyon bilgisayarlı tomografisi.