Intra-Interobserver Variability in Myocardial Perfusion and Function Interpretation and Reproducibility of QGS/QPS Software

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Abstract

Aim: To assess three different level experienced nuclear medicine specialists' intra- and interobserver variability of semiquantitative visual interpretations of left ventricular (LV) myocardial perfusion, wall motion (WM), and wall thickening (WT) in gated myocardial perfusion single- photon emission tomography (gMPS), and to compare the compatibility between the observers' and coronary angiography (CAG) reports.

Methods: A 5-point perfusion scale, a 6-point scale for WM, and a 4-point scale for WT were used to score each segment. The images were interpreted 3 times at least one-month intervals separately by 3 observers. Subsequently, the visual semiquantitative summed scores for stress (SSS) and rest (SRS) were calculated by summing the respective segmental perfusion scores. Summed difference score (SDS) was also calculated as the difference between SSS and SRS. Both visual semiquantitative WM and WT scores were calculated from the stress images by summing all corresponding segmental scores.

Results: Intraobserver agreement in the evaluation of global perfusion was statistically significant (71.9-100 %). There was a significant agreement in all LAD-SSS, Cx-SSS, ve RCA-SSS interpretations. There was good agreement between 3 readings of 3 observers' ($p=0.0$). Due to the high interobserver agreement levels in the global evaluation, the mean values of the 1. and the 2. interpretations (mean 1.-2. int.) were calculated and regional comparisons were made with this new value and the 3. interpretation. There was a significant agreement in 3 of the regional SSS interpretations. Although lowest agreement rates were calculated in LAD artery territory, the agreement levels were statistically, and highly significant in all territories. In both Cx and RCA territories, the agreement levels were statistically significant ($p<0.05$).

Conclusion: The interobserver and intraobserver agreement levels of perfusion interpretations were significant both in the global and regional base. There was a significant agreement between the visual interpretations and CAG results, especially in the Cx and RCA artery territories. The interobserver and intraobserver agreements were higher in WM scores than wall thickness scores.

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QPS/QGS software quantitative perfusion and left ventricular ejection fraction (LVEF) values showed high repeatability.

Keywords: *Gated myocardial perfusion single-photon emission tomography; left ventricular myocardial perfusion, wall motion, wall thickening.*

INTRODUCTION

Early diagnosis and appropriate treatment are very important in coronary artery diseases (CAD) since it is possible to decrease the CAD-related mortality rates. The most and effectively used method in nuclear cardiology to diagnose CAD and to determine its prognosis is gated myocardial perfusion single- photon emission tomography (gMPS) [1]. Real defects, certain artifacts, and some normal variations are well known to decrease the specificity of the exam. To avoid false negative/positive interpretations, it is better to include functional parameters like left ventricular (LV) wall motion (WM), wall thickening (WT) and ejection fraction (EF) data in the evaluation process. Semiquantitative segmental scoring systems and multiple quantitative gMPS software programs have been developed because visual interpretation is subjective and highly observer dependent [2, 3].

The aim of this study was to assess three different experienced nuclear medicine specialists' intra and interobserver variability of semiquantitative visual interpretations of LV myocardial perfusion, WM, and WT in gMPS, and to compare the compatibility between the observers' and coronary angiography (CAG) reports and to compare the visual semiquantitative results and QPS/QGS software quantitative scores, and to determine the reproducibility of the calculated LV volumes.

MATERIAL AND METHODS

Study design

The images of 139 patients who underwent one-day rest- stress Tc-99m sestamibi (Mon.MIBI kit, Eczacıbaşı-Monrol Nuclear Products Inc., Gebze, Turkey) gMPS with a dual detector SPECT gamma camera (Millennium MG; GE Healthcare, Haifa, Israel) were retrospectively evaluated. All patients drank 200 ml milk 10 minutes after the radiopharmaceutical injection to stabilize the clearance of the gallbladder activity and drank 200 ml soda 45 minutes after the radiopharmaceutical injection to benefit from the volume effect. Image processing was performed by the observers themselves in each interpretation, and visual semiquantitative interpretation of the images was based on short axis and vertical long-axis tomograms divided into 20 segments.

Outcome parameters

A 5-point perfusion scale (0, normal; 1, equivocal; 2, moderate; 3, severe reduction of radioactivity; and 4, absence of detectable tracer uptake in a segment), a 6-point scale for WM (0, normal; 1, mild hypokinesia; 2, moderate hypokinesia; 3, severe hypokinesia; 4, akinesia; 5, dyskinesia), and a 4-point scale for WT (0, normal; 1, mild; 2, moderate to severe; 3, absent) were used to score each segment. The images were interpreted 3 times (2 times by the observers blinded to clinical data, type of stress, CAG reports, and 1 time with the patients' clinical data) at least one-month intervals separately by 3 observers. Subsequently, the visual semiquantitative summed scores for stress (SSS) and rest (SRS) were calculated by summing the respective segmental perfusion scores. Summed difference score (SDS) was also calculated as the difference between SSS and SRS. Both visual semiquantitative WM and WT scores were calculated from the stress images by summing all corresponding segmental scores. Myocardial perfusion was considered as normal in case of SSS ≤3, and as abnormal in the case of SSS>3. According to the SDS, 2 subgroups were maintained as non-reversible (SDS=0) and reversible (SDS>1). Besides this global LV data, the same subgrouping of 3 coronary vascular territories were done by summing the appropriate segment scores (segment nos. 1, 2, 7, 8, 13, 14, 15, 19, 20 for LAD; segment nos. 5, 6, 11, 12, 17, 18 for Cx and segment nos. 3, 4, 9, 10, 16 for RCA).

For the quantitative analysis, the same parameters as used in semiquantitative interpretation were obtained from the Quantitative Gated SPECT (QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, CA) software program in 2 different processing. The data were not considered as normal/abnormal, but the SSS, SRS, SDS, rest and stress SMS and STS values themselves have been compared with the corresponding scores in global LV and vascular territory. Furthermore, LV rest-stress EF and end-diastolic and end- systolic volumes (EDV, ESV) were noted to calculate the reproducibility of software.

One hundred and fourteen patients' CAG reports, which had been obtained within 3 months of gMPS were maintained. A level of 70% stenosis was accepted significant and compared with the visual semiquantitative interpretations of the perfusion by the observers.

Statistical analyses

Data were analyzed using the IBM Statistical Package for Social Sciences v21 (SPSS Inc., Chicago, IL, USA). Kappa analyses were used to determine the intra- interobserver agreements between observers. The significance of the difference between the mean values of SSS, SRS and SDS, rest and stress SMS and STS maintained from the quantitative program was calculated by Wilcoxon and Paired T-Test. The reproducibility of LV volumes was evaluated by Friedman test. Continuous data were presented as mean ± standard deviation or median [minimum-maximum], as appropriate. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

RESULTS

Among 139 patients (M/F 72/67; age 59.7 ± 11.7 years; body mass index 28.8 ± 4.9 kg/m2) presence of CAD was known in 79 (MI;30, PTCA;34, CABG;29) patients, and 60 patients were referred for the establishment of CAD diagnosis. Ninety patients underwent treadmill exercise tests (64.7 %), 22 patients (15.8 %) received oral dipyridamole, 21 patients (15.1 %) I.V. adenosine and 6 patients (4.3 %) underwent dobutamine stress pharmacological exercise. Among 114 patients who underwent CAG, the number of patients who had 50-70 % and > 70 % stenosis were 17 and 22 in LAD, 12 and 18 in Cx, and 8 and 20 in RCA respectively.

Intraobserver agreement; Intraobserver agreement in the evaluation of global perfusion was statistically significant (71.9-100 %) (Table 1).

Table 1. Intraobserver Agreement of global perfusion evaluatin with the most and the least kappa values

	1./2. interpretation	1./3. interpretation	2./3. interpretation

	%(k)	%(k)	%(k)
1. **Observer**	72,7	75,5	72,7
2. **Observer**	77	71,9(0.458)	74,8
3. **Observer**	100(1.0)	85,6(0.732)	85,6

(k; kappa value, p =0,000)

Due to the high intraobserver agreement levels in global, the mean values related to the 1. and the 2. interpretations (mean 1.-2. int.) were calculated and regional comparisons were made with this new value and the 3. interpretation. There was a significant agreement in all LAD-SSS, Cx-SSS, ve RCA-SSS interpretations (Table 2).

Table 2. Regional intraobserver agreement between perfusion interpretations

		3. interpretation			%	Kappa	P
1.observer		SSS	<4	≥4			
LAD-SSS	mean 1.-2. int..	<4	89	11	83,5	0,587	***0,000***
		≥4	12	27			
Cx-SSS	mean 1.-2. int..	<4	110	9	89,2	0,588	***0,000***
		≥4	6	14			
RCA-SSS	mean 1.-2. int.	<4	91	11	85,6	0,638	***0,000***
		≥4	9	28			
		3. interpretation			**%**	**Kappa**	**P**
2.observer		SSS	<4	≥4			
LAD-SSS	mean 1.-2. int.	<4	107	6	89,9	0,659	***0,000***
		≥4	8	18			
Cx-SSS	mean 1.-2. int.	<4	114	5	92,8	0,708	***0,000***
		≥4	5	15			
RCA-SSS	mean 1.-2. int.	<4	109	5	92,1	0,727	***0,000***
		≥4	6	19			
		3. interpretation			**%**	**Kappa**	**P**
3.observer		SSS	<4	≥4			

LAD-SSS	mean 1.-2. int.	<4	90	3	91,4	0,798	***0,000***
		≥4	9	37			
Cx-SSS	mean 1.-2. int.	<4	106	6	88,5	0,610	***0,000***
		≥4	10	17			
RCA-SSS	mean 1.-2. int.	<4	97	5	91,4	0,775	***0,000***
		≥4	7	30			

Interobserver agreement; There was good agreement between 3 readings of 3 observers' (p=0.0) (Table 3).

Table 3. Inter-observer agreement between global perfusion interpretations

1.Interpretation		**1. Observer**			**%**	**Kappa**	***P***
		Normal	Fixed	Reversible			
3. Observer	Normal	39	4	10	73,4	0,521	***0,000***
	Fixed	0	4	3			
	Reversible	14	6	59			
		2. Observer					
		Normal	Fixed	Reversible			
3. Observer	Normal	47	0	6	67,6	0,427	***0,000***
	Fixed	0	4	3			
	Reversible	33	3	43			
		2. Observer					
		Normal	Fixed	Reversible			
1. Observer	Normal	46	0	7	64,7	0,394	***0,000***
	Fixed	5	4	5			
	Reversible	29	3	40			
2.Interpretation		**1. Observer**			**%**	**Kappa**	***P***
		Normal	Fixed	Reversible			

3. Observer	Normal	52	0	1	74,1	0,545	***0,000***
	Fixed	0	4	3			
	Reversible	28	4	47			
		2. Observer					
		Normal	Fixed	Reversible			
3. Observer	Normal	49	0	4	67,6	0,438	***0,000***
	Fixed	2	3	2			
	Reversible	31	6	42			
		2. Observer					
		Normal	Fixed	Reversible			
1. Observer	Normal	65	0	15	70,5	0,444	***0,000***
	Fixed	2	3	3			
	Reversible	15	6	30			
3.Interpretation		**1. Observer**					
		Normal	Fixed	Reversible	**%**	**Kappa**	***P***
3. Observer	Normal	50	2	10	78,4	*0,600*	***0,000***
	Fixed	1	3	2			
	Reversible	14	1	56			
		2. Observer					
		Normal	Fixed	Reversible			
3. Observer	Normal	53	0	9	68,3	*0,414*	***0,000***
	Fixed	1	1	4			
	Reversible	27	3	41			
		2. Observer					
		Normal	Fixed	Reversible			

1. Observer	Normal	58	0	7	74,1	*0,517*	***0,000***
	Fixed	2	1	3			
	Reversible	21	3	44			

Due to the high interobserver agreement levels in the global evaluation, the mean values of the 1. and the 2. interpretations (mean 1.-2. int.) were calculated and regional comparisons were made with this new value and the 3. interpretation. There was a significant agreement in 3 of the regional SSS interpretations (Table 4).

Table 4. Regional **i**nterobserver agreement between perfusion interpretations with the most and the least kappa values.

Observers		**LAD-SSS** %(k)	**Cx-SSS** %(k)	**RCA-SSS** %(k)
1/2	Mean 1-2 int	82	89,9(0,591)	87,1
	3.	87.1(0,630)	89.2	83.5
1/3	Mean 1-2 int	82	86,3(0,516)	92,8 (0,816)
	3.	85.6	92.8	91.4 (0,779)
2/3	Mean 1-2 int	81,3	86,3	85,6
	3.	81.3(0,482)	90.6	84.9

***P=0,000**

Although lowest agreement rates were calculated in LAD artery territory (81.3 %, k=0.482; p=0.000), the agreement levels were statistically, and highly significant in all territories.

When we compared 114 CAG reports with the observers' interpretations in the normal/abnormal base; there was no significant agreement between any one of the observers, and CAG reports in LAD territory (p>0,05). However, in both Cx and RCA territories, the agreement levels were statistically significant (p<0.05) (Table 5).

Table 5. Detailed data and agreement levels between the observers and CAG reports

Observer and Interpretation	**CAG** **<70% ≥70%** (Mean 1.-2 int./3.int)	**%**	**Kappa**	**p**

LAD-SSS	1.	N	68/71	14/13	66,7/70.2	0,038/0,069	0,335/0,084
		Ab	24/21	8/9			
	2.	N	79/79	15/15	75,4/75,4	0,082/0,082	<u>0,05/0,05</u>
		Ab	13/13	7/7			
	3.	N	63/69	14/15	62,3/66,7	0,017/0,026	0,663/0,514
		Ab	29/23	8/7			
Cx-SSS	1.	N	86/87	11/10	81,6/83,3	0,134/0,0164	***0,002/0,000***
		Ab	10/9	7/8			
	2.	N	88/88	11/10	83,3/84,2	0,0151/0,174	***0,000/0,000***
		Ab	8/8	7/8			
	3.	N	83/88	8/8	81,6/86	0,17/0,216	***0,000/0,000***
		Ab	13/8	10/10			
RCA-SSS	1.	N	77/73	11/7	77,2/75,4	0,141/0,146	***0,000/0,000***
		Ab	17/21	7/13			
	2.	N	82/85	11/10	79,8/83,3	0,0142/0,187	***0,001/0,001***
		Ab	12/9	9/10			
	3.	N	76/76	10/8	75,4/77,2	0,118/0,151	**0,004/0,000**
		Ab	18/18	10/12			

(N:Normal (SSS<3); Ab; Abnormal (SSS**≥4)**, mean 1.-2.;the mean value of the 1. and the 2. interpretations)

Comparison of observers' interpretations and QPS: There was no significant difference in Cx-SRS either in the 1. or the 2. interpretation in all 3 observers. There were differences between other scores, but the highest agreement remained in the SRS ($p<0.01$).

Reproducibility of QPS software scores: There was no significant difference between both the global and regional scores of the QPS software from 2 different processing that performed by 3 observers. There was negligible difference in global SSS and RCA-SDS between the 1. observer and the software ($p<0.05$)

Intra and interobserver variability of the LV wall function interpretation: In general, there were common intraobserver variances in rest and stress Cx- STS and common agreements in Cx-SMS. There wasn't any significant interobserver difference as for rest and stress Cx-SMS and rest RCA-SMS values (p=0,000). However, there were significant interobserver differences between rest and stress global and LAD-STS values (p<0,05).

Comparison of visual semiquantitative and quantitative wall function scores: There were common differences in rest and stress LAD- SMS (p=0,00), common agreements in rest and stress Cx-SMS among 3 observers' visual semiquantitative scores and the quantitative scores (p>0,01). There were no significant differences in quantitative SMS and STS scores (p>0.01).

The reproducibility of the QGS software: There were significant differences in rest and stress EDV and ESV volumes, but no significant difference was seen in EF values (p>0,05).

DISCUSSION

Results of this study suggest that there is a significant agreement in both intra- and interobserver perfusion interpretations. Interobserver perfusion agreement was higher in vascular territories than global interpretations with the least agreement in the LAD territory. There was a significant agreement between observers and CAG results in Cx and RCA territories rather than LAD territory. Clinical knowledge had no impact on interpretations of 3 different level experienced nuclear medicine specialists. In general, there were significant but not clinically specific interobserver variabilities in functional scores. When we compared the visual scores with the QGS scores, there were significant differences between parameters, except rest and stress SMS in Cx territory. There was no impact of the processing procedure on QPS/QGS software; software's EF values were highly reproducible contrary to volumes.

There are several previous studies that compared the observers' variabilities. However, this is the first study that evaluates intra- and interobserver variabilities and compares the semiquantitative interpretations with CAG reports and quantitative values in a wide range of patients and exercise types.

Golub et al. reported moderate to excellent interpretative reproducibility with CAG proven 101 abnormal and 37 normal patients in the interpretations of 3 experienced, 3 less-experienced cardiologists in the global and regional territories [4]. Although, they have excluded some possible false negative interpretations (such as 84 % of the patients were male, regional interpretations were made in the LAD and non-LAD base, all patients were non-obese and underwent treadmill exercise) our results were in concordance with theirs'. On the other hand, the diagnostic accuracies of the vasodilator and physical exercise were reportedly similar, but their effects on the coronary blood flow may differ [5, 6]

Xu et al. reported high global and regional repeatability of perfusion interpretations of an observer [7]. In contrast with us, the lowest rate was related to RCA territory. The intraobserver agreements of the regional base were similar in our study. In our opinion, this is due to the study protocol that we perform; as our patients drank soda before the imaging procedure which increased the accuracy of inferior wall interpretation [6]. That is also the only study that evaluated the agreement rates of both perfusion and functional parameters. Among global functional parameters, they reported high repeatability with the highest rate belonged to WT. These results have some incompatibilities with our study, which was comprised of a larger and more heterogeneous group of patients. Although we did not find any significant inter and intraobserver variabilities in both WM and WT scores; global and WT scores of Cx artery territory showed the difference. Interobserver and intraobserver agreements were higher in the WM scores than WT scores in our study [7].

There are very few studies that compare the semiquantitative visual function scores with the quantitative scores, and they are mostly compatible with our results. Konno et al. studied 42 patients with known CAD on 9 segments. They reported an excellent correlation between semiquantitative and quantitative global WM, and a good correlation between WT parameters. However, they obtained variable results in the segment base. The lowest and highest correlations in the WM/WT evaluation belonged to the septum and inferolateral wall/septum and apex respectively [8]. We also determined significant variances in WM in LAD territory and, significant agreement in WM in Cx artery territory. Germano et al. reported agreement rates of visual and quantitative WM and WT scores as 72.6% and 74.7%, respectively [9]. We did not subgroup functional parameters as normal/abnormal, but our results were compatible with the results of this study.

Hendel et al. evaluated TI-201 and Tc99m-Tetrafosmin rest-stress images of 216 patients and reported low interobserver variability especially as for the interpretations of the lateral wall in the tetrafosmin group which corroborated with our results [10]. They also estimated the diagnostic accuracies of 4 observers from the 115 patients' CAG reports. They accepted 75 % as the threshold of a significant coronary stenosis, the areas under ROC curves of all 4 observers' in both radiopharmaceutical groups were considered similar. However, the diagnostic accuracy in the RCA territory was higher in tetrafosmin images than in TI-201 images. There are a few studies that compare the gMPS interpretations of different observers with the CAG reports. In our study, we accepted the 70 % threshold of the significant coronary stenosis; the highest agreement rates were obtained in the last interpretation based on the information obtained from patient anamnesis, in the Cx artery territory. However, there was no agreement in the LAD territory.

It is important to evaluate the accuracy and repeatability of LV volumes estimated in MPS by QGS software since it is highly used in clinical practice. In the studies evaluating this issue, the serial estimations of LVEF demonstrated high repeatability of either rest [11, 12] or dobutamine stress imaging [13]. We observed that the LVEF values were not affected by different processing methods made by the observers. There are a limited number of studies evaluating the repeatability of EDV and ESV values. Hedeer et al. reported low variability of EF value but, high variabilities in EDV and ESV in both MPS and MRI [14] which is compatible with our results.

There were some limitations of our study. Our study group comprised of a very heterogenous patient profile with multiple risk factors, with MI, CABG, PTCA and stent anamnesis, administration of both treadmill and pharmacological exercise (with dipyridamole, adenosine, dobutamine) tests. We anticipate that, in a more specific the study group, the inter/intraobserver agreement rates would be higher. The high mean body mass index value (28.8 ± 4.4 kg/m2) caused attenuations which could have affected the agreement levels, especially in the LAD region. On the other hand, although CAG is still the gold-standard in comparisons, it is known to have some limitations firstly due to the low transition characteristics of X-ray, which leads to low image quality. Secondly, it is a highly operator-dependent technique. Thirdly, it cannot assess the microvascular circulation disorders caused by systemic diseases, and cannot determine exercise-induced vasospasm. Miernik et al. evaluated the prognostic values of MPS and CAG in a female patient group with a positive exercise test and reported higher sensitivity and specificity of MPS than CAG. The accuracy rate of MPS was also reported to be higher in predicting the cardiovascular events [15]. When Cale et al. accepted IVUS as a gold-standard in

CAD diagnosis, the sensitivity, specificity, positive and negative predictive values of CAG were % 27, 89, 75 and 50 respectively in the LAD region [16].

Conclusion

In conclusion, the interobserver and intraobserver agreement levels of perfusion interpretations were significant both in the global and regional base. There was a significant agreement between the visual interpretations and CAG results, especially in the Cx and RCA artery territories. The interobserver and intraobserver agreements were higher in WM scores than wall thickness scores. QPS/QGS software quantitative perfusion and LVEF values showed high repeatability. There was no significant difference between different experienced observers' interpretations and if they interpret the images with or without knowing the patients' clinical data.

Disclosure

Dr. Kuslu, Dr. Ozturk, and Dr. Erim have nothing to disclose.

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Authorship Contributions

Concept: D.K., **Design:** D.K., **Supervision:** D.K., E.O., I.E., **Data Collection and/or Processing** D.K., E.O., I.E., **Analysis and/or Interpretation:** D.K., E.O., I.E., **Literature Review:** D.K., **Writer:** D.K.

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