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Observational Study Comparing Visual and Automatic Semi-Quantification in Myocardial Ischemia Evaluation (SPECT MPI)

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ABBREVIATIONS

AC	Attenuation correction	**MI**	Myocardial infarction
APX	Apex of left ventricle	**NAC**	Non attenuation correction
BMI	Body mass index	**NPI**	No-prior infarction
CABG	Coronary artery bypass graft surgery	**PCI**	Percutaneous coronary intervention
CAD	Coronary artery disease	**PI**	Prior Infarction
CT	Computed tomography	**RCA**	Right Coronary Artery
LCX	Circumflex coronary artery	**SD**	Standard deviation
LDA	Left descendent artery	**SPECT-MPI**	Single photon emission computed tomography myocardial perfusion imaging
LV	Left ventricle	**WHO**	World Health Organisation

ABSTRACT

INTRODUCTION: Several software packages are available for automated evaluation of SPECT-MPI data, used as an aiding tool to standard visual analysis.

PURPOSE: The aim of this study was to compare the visual analysis versus the automated perfusion scores of SPECT-MPI, globally and according to several factors and to test their agreement.

METHODS: We included 117 consecutive patients who performed 99mTc-tetrafosmin SPECT-MPI with stress-rest 1 day protocol. The visual scoring was performed by 2 experienced Nuclear Cardiology experts and the automated scoring by *Emmory Toolbox*® software, according to the 17 segments model.

RESULTS: We found significant differences between the 2 methods, with a consistent perfusion score overestimation by the automated analysis in the stress images, mainly in the anterior and lateral walls and the apex of the left ventricle. This difference was more evident in patients without prior infarction history. When partitioned as normal or abnormal, the visual and automated score results were coincident in 56% of the cases. Statistical significant differences were found in males, but not in females. CT attenuation correction influenced the agreement significantly, with overestimation of automated scores in attenuation correction, and underestimation in non-attenuation corrected images.

CONCLUSION: In this study we found high disagreement between the visual and the automated analysis, in the anterior and lateral walls and the apex of the left ventricle, especially in males. Attenuation correction significantly influenced the performance of automated analysis.

KEYWORDS: SPECT-MPI, automated analysis;

RESUMO

INTRODUÇÃO: Vários *softwares* estão hoje disponíveis para uma avaliação automática das imagens da cintigrafia de perfusão miocárdica (SPECT-MPI), que hoje em dia são usados como ferramenta auxiliar na análise visual.

OBJETIVOS: Com este estudo pretendemos comparar a análise visual com a automática, através dos scores de perfusão do SPECT-MPI, de uma forma global e de acordo com vários fatores e testar a sua concordância.

MÉTODOS: Foram incluídos os exames de 117 doentes consecutivos que realizaram SPECT-MPI através do protocolo de um dia esforço-repouso com 99mTc-tetrafosmina. A análise visual foi realizada por 2 médicos experientes em cardiologia nuclear e a análise automática pelo *software Emmory Toolbox®,* de acordo com o modelo de 17 segmentos do ventrículo esquerdo.

RESULTADOS: Foram encontradas diferenças significativas entre os dois métodos, com uma sobrestimação consistente na análise automática em imagens de esforço, principalmente na área correspondente à parede anterior e lateral e ápex do ventrículo esquerdo. Esta diferença foi mais evidente em doentes sem história prévia de enfarte. Quando divididos em normal ou anormal, os resultados visuais e automáticos foram coincidentes em 56% dos casos. Diferenças significativas foram encontradas em homens, mas não em mulheres. A realização da correção de atenuação influenciou significativamente a concordância, com sobrestimação dos resultados automáticos nos estudos realizados com correção da atenuação por TC, contra subestimação nas imagens não corrigidas.

CONCLUSÃO: Neste estudo, encontramos elevada discordância entre a análise visual e automatizada, principalmente nas áreas correspondentes às paredes anterior e lateral e no ápex do ventrículo esquerdo, especialmente no sexo masculino. Executar correção de atenuação por TC influencia o desempenho da análise automatizada.

INTRODUCTION

Several technologic advancements in nuclear cardiology techniques has made earlier diagnosis and treatment of ischaemic heart disease possible with a significant impact on survival.[1,2] Despite this progress, this disease remains as the leading cause of death in the world, according to the WHO 2015 report.[3]

Single photon emission computed tomography myocardial perfusion imaging (SPECT MPI) is a well-established modality for the assessment of coronary artery disease (CAD).[2,4] It is useful in the diagnosis[5] and prognostication of CAD.[6–9] CAD plays a major, but not unique role in the pathophysiological process that leads to ischaemic heart disease, meaning that not all abnormalities in myocardial perfusion are caused by obstructive CAD.[10,11] For this reason, although widely used, coronary angiography is not a perfect reflection of the myocardial perfusion pattern.[10,12–15] SPECT MPI, by simultaneously assessing both perfusion and function[8] in a non-invasive manner, can reduce the number of angiographies or other invasive procedures.[16]

SPECT MPI relies on the flow and metabolism dependent uptake of a radioactive tracer by viable myocardium,[2] during stress and rest conditions. Comparing both datasets - stress and rest - allows the identification and localization of normal, ischaemic and necrotic myocardial tissue.[17] Abnormal rest images are also highly predictive of patient outcome.[6]

Perfusion scores are calculated according to a 17 segment scoring method.[11,18] Each segment is classified from 0 (normal perfusion) to 4 (absent perfusion),[1,11,18] and a final score is calculated through the sum of the scores of all 17 segments. This approach provides a reproducible semi-quantitative measurement of perfusion defect severity and extent.[11] In clinical practice this process is performed, visually, by experienced nuclear cardiology physicians, however several automated software packages are available.

Despite the high accuracy of the visual semi-quantification,[19–21] it remains dependent on various factors, such as observer experience, technical issues, artifacts, intra and inter-observer variability,[7,14,15,22] and others.

Automated software packages, if reliable, could have a significant impact on clinical practice, chiefly by simplifying the image processing workflow, decreasing the reviewing and reporting time burden and rendering the results less operator dependent.[23] To date, these software packages are recommended only to be of assistance to visual analysis.[1,8,11]

The aim of this study was to compare the visual versus the automated SPECT-MPI perfusion scores, overall and according to several factors and to test their agreement.

MATERIALS AND METHODS

Patient data

This was an observational, cohort study that included one hundred and seventeen consecutive patients that underwent SPECT MPI on the Nuclear Medicine Department of the Centro Hospitalar e Universitário de Coimbra, from June 20th to September 11th of 2018. All patients were accurately informed about the procedure and agreed to enter the study by signing an informed consent. SPECT MPI data was retrospectively analysed from an anonymised database complying with all the ethics committee regulations.

Imaging Protocol

A stress-rest [^{99m}Tc] Tc-tetrofosfomin 1 day protocol was used.[11] Stress images were acquired in exercise conditions or pharmacology induced stress using adenosine or regadenoson (Table I). Stress imaging was performed 45 minutes after injection of 10-15 mCi of the tracer. Attenuation correction by Computed Tomography (CT) was performed in 91 (78%) patients. Whenever a stress perfusion defect was identified rest images were performed,[24] 3 to 4 hours after stress images by injecting 20-30mCi of the tracer according to international recommendations (maximum of 30mCi/day). MPI images were scored by 2 experienced physicians using a 5-point scoring system (0, normal; 1, mildly decreased; 2, moderately decreased; 3, severely decreased; and 4, absence of segmental uptake), according to a 17-segments scoring model.[18] Subsequently, summed stress scores (SSS), summed rest scores (SRS) and summed difference scores (SDS) were obtained.[11]

Local summed scores for each vascular territory were also calculated and compared, according to the 17-segments polar map model.[11] Left Descendent Artery (LDA) corresponds to anterior wall of the left ventricle (LV), septum and Apex; Right Coronary Artery (RCA) corresponds to the inferior wall of the LV and Circumflex Artery (LCX) region corresponds to the lateral wall of the LV. The apex (APX) was also analysed single-handedly.

The automated perfusion score was achieved applying the *Emmory Cardiac Toolbox®* software.[4] This version of the software does not include an attenuation corrected database.

Statistical Analysis

Categorical variables were described through their frequency and percentage relative to the total, and continuous variables were represented by their mean±1 standard deviation (M±SD). Comparisons between categorical variables were performed using the Pearson Chi Square test, Fisher-exact test and the K Cohen test. Continuous variables were compared, according to their normality, using the t-test or the non-parametric corresponding test. A two-sided p value

<0.05 was considered statistically significant. Data analysis was performed with Excel 2016® plus the RealStatistics2010® supplement package.

RESULTS

Patients' characteristics are summarized in Table I. There were 73 male and 44 female patients, with a mean age of 67±11 years. Forty-four patients had prior history of infarction, 30 were submitted to percutaneous coronary intervention and 2 to bypass coronary surgery (Table I).

Table I. Patients' characteristics *(n=117)*	**Values**
Gender	
Male	73 (62%)
Female	44 (38%)
Age (M±SD)	67±11
Body Mass Index (BMI)	
M±SD	27,7±4
Normal weight	33 (28%)
Overweight	53 (45%)
Obese	31 (27%)
Stress	
Pharmacologic	26 (22%)
Exercise	91 (78%)
Attenuation Correction	
AC	91 (78%)
NAC	26 (22%)
Rest Test	60 (51%)
Indication	
Previous MI	44 (36%)
MI/PCI/CABG	*12/30/2 (27/68/5%)*
Suspected Ischemia	50 (44%)
Organ Transplantation[α]	23 (21%)

[α] Liver/Kidney transplantation

AC, Attenuation correction by Computed Tomography; BMI, Body mass index; CABG, Coronary artery bypass graft surgery; MI, Myocardial infarction; NAC, No attenuation correction; PCI, Percutaneous coronary intervention; M±SD, mean ± standard deviation.

Patients were divided into 2 groups according to the clinical information, PI - Prior Infarction, and NPI - No Prior Infarction. NPI group includes patients with known CAD or with clinical suspicion of ischemia and pre-renal and hepatic transplant patients who performed the test for risk stratification purposes. Rest images were acquired in 60 (51%) patients and therefore SRS and SDS were obtained (Table I).

Overall, automated SSS were significantly higher than their visual counterpart ($p<0,01$) (Table II and Figure 1). There were no statistically significant differences in SRS and SDS (Table II).

An abnormal stress test, defined as SSS>3, was attained by visual analysis in 40 (34%) patients versus 78 (67%) patients on automated score (Table III).

As shown in Table III, when considering this classification, visual and automated analysis agreed in 56% of the patients' stress test. This agreement was found to be weak, according to the k Cohen test, which removes the agreement by chance (K=0,20; p<0.01).

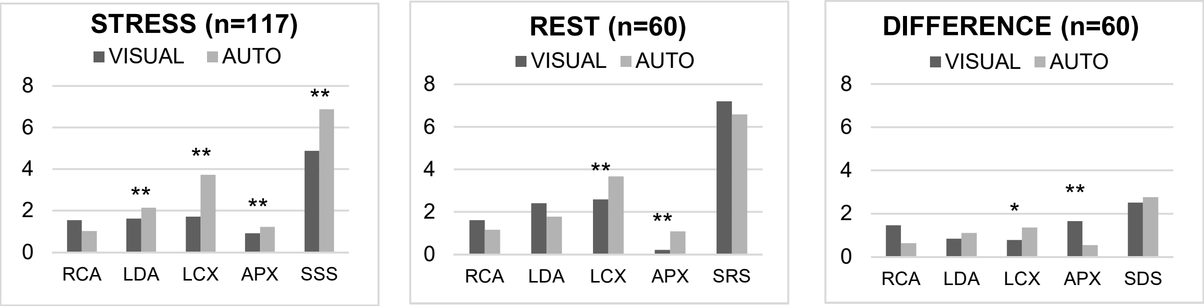
Vascular regions: Automated regional scores were significantly higher in the LDA and LCX areas and in the apex of the LV in stress images. During rest, automated scores were also significantly higher in the LCX area and the apex. Significant differences in LCX and APX persisted in SDS (Table IV and Fig.1).

Indication to perform the exam: Automated SSS were significantly higher in NPI patients. This result was not found in PI patients (Table V). No significant difference was found on SRS or SDS.

Gender: Automated SSS scores were significantly higher in males, but not in females. (Table VI). No significant difference was found in SRS or SDS.

Attenuation correction: Attenuation correction by CT (AC) was available in 91 patients. Automated SSS and SDS scores were consistently higher in AC patients. (Table VII). In patients without attenuation correction (NAC), visual scores were significantly higher both in SSS and SRS.

Figure 1. Summed and regional scores in Stress, Rest and Difference.


STRESS (n=117)

REST (n=60)

DIFFERENCE (n=60)

Figure 1. APX, Apex region of left ventricle; LDA, Left descendent artery; LCX, Circumflex coronary Artery; RCA, Right Coronary Artery; SDS, Summed difference score; SSS, Summed stress score; SRS, Summed rest score.* p<0,05 **p<0,01

Table II. Overall summed scores comparison

	Visual analysis			Automated analysis			p
	M ± SD	***M***	**IQR**	**M ± SD**	***M***	**IQR**	
SSS (n=117)	4,9 ± 8,7	0,0	6,0	6,9 ± 5,5	6,0	0,0	<0,01
SRS (n=60)	7,2 ± 11,0	3,0	9,5	6,6 ± 6,1	5,0	8,3	0,70
SDS (n=60)	2,5 ± 3,3	1,0	4,0	2,8 ± 3,4	1,5	4,0	0,56

SSS summed stress score; SRS summed rest score and SDS summed difference score. IQR interquartile range. SD standard deviation. *M*, median M±SD, mean ± standard deviation

Table III. Agreement according to stress test result: normal vs abnormal

			Visual			Agreement (%)	k
			Normal	**Abnormal**			
Automated	**Total**	**Normal**	32	7	**(39)**	56%	0,20
	(n=117)	**Abnormal**	45	33	**(78)**		
			(77)	**(40)**			
	PI	**Normal**	7	1		67%	-0,57
	(n=42)	**Abnormal**	13	21			
	NPI	**Normal**	25	6		49%	-0,25
	(n=75)	**Abnormal**	32	12			

Abnormal test defined by SSS>3.PI, previous infarction; NPI, non-previous infarct, refers to prior infarction and no prior infarction patient' groups. K (Cohen's K)

Table IV. Vascular regional scores

	Visual analysis			Automated analysis			*p*
	M±SD	***M***	**IQR**	**M±SD**	***M***	**IQR**	
Stress (n=117)							
RCA	1,5 ± 3,7	0,0	0,0	1,0 ± 1,7	0,0	1,0	0,50
LDA	1,6 ± 2,9	0,0	2,0	2,1 ± 1,9	2,0	2,0	<0,01
LCX	1,7 ± 3,7	0,0	2,0	3,7 ± 3,2	1,0	5,0	<0,01
APX	0,9 ± 1,3	0,0	2,0	1,2 ± 0,9	1,0	1,0	<0,01
Rest (n=60)							
RCA	1,6 ± 3,4	0,0	2,0	1,2 ± 2,1	0,0	1,3	0,26
LDA	2,4 ± 3,8	1,0	3,0	1,8 ± 2,1	0,0	3,0	0,17
LCX	2,6 ± 4,5	0,0	2,3	3,7 ±3,6	3,0	4,3	<0,01
APX	0,2 ± 0,5	0,0	0,0	1,1 ± 1,0	1,0	2,0	<0,01
Diference (n=60)							
RCA	1,5 ± 2,7	0,0	2,3	0,6 ± 1,0	0,0	1,0	0,08
LDA	0,8 ± 1,3	0,0	1,0	1,1 ± 1,4	1,1	2,0	0,23
LCX	0,8 ± 1,3	0,0	1,3	1,4 ± 1,8	0,0	2,0	<0,05
APX	1,7 ± 1,3	2,0	3,0	0,6 ± 0,7	0,0	1,0	<0,01

APX, Apex region; LCX, Circumflex coronary artery; LDA, Left descendent artery; M±SD, mean ± standard deviation; *M*, median; RCA, Right coronary artery.

Table VI. Summed scores according to gender

	MALES							FEMALES						
	Visual			Automated			p	Visual			Automated			p
	M±SD	*M*	IQR	M±SD	*M*	IQR		M±SD	*M*	IQR	M±SD	*M*	IQR	
SSS (n=117)	5,9 ± 9,6	1,0	7,0	8,7 ± 5,6	8,0	7,0	p<0,01	3,6 ± 6,8	0,0	4,3	3,9 ± 3,7	3,0	5,3	0,06
SRS (n=60)	8,3 ± 12,0	3,0	11,0	7,9 ± 6,6	5,5	9,5	0,59	5,1 ± 8,4	1,0	6,0	4,0 ± 3,9	6,0	8,0	0,89
SDS (n=60)	2,3 ± 3,3	1,0	3,0	2,7 ± 3,4	2,0	4,0	0,43	2,9 ± 3,2	2,5	4,0	2,9 ± 3,5	1,0	4,5	0,93

SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; IQR interquartile range. *M*, median; M±SD, mean ± standard deviation.

Table V. Summed scores according to the indications to perform the exam

	PRIOR INFARCTION							NO PRIOR INFARCTION						
	Visual			Automated			p	Visual			Automated			p
	M±SD	*M*	IQR	M±SD	*M*	IQR		M±SD	*M*	IQR	M±SD	*M*	IQR	
SSS (n=117)	9,6 ± 12,0	4,0	18,5	9,0 ± 6,4	8,5	8,5	0,83	2,0 ± 3,6	0,0	2,0	5,6 ± 4,3	5,0	6,0	p<0,01
SRS (n=60)	6,8 ± 9,3	2,5	11,3	6,7 ± 5,0	6,0	6,5	0,67	7,5 ± 12,1	3,0	9,0	6,5 ± 6,8	4,5	9,0	0,99
SDS (n=60)	2,9 ± 4,1	1,5	3,3	1,8 ± 2,9	1,0	3,3	0,34	1,9 ± 3,6	1,0	4,0	2,8 ± 4,4	2,0	4,3	0,44

SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; IQR, interquartile range; *M*, median; M±SD, mean ± standard deviation.

Table VII. Summed scores according to the performance of attenuation correction by CT (AC)

	ATTENUATION CORRECTION							NO ATTENUATION CORRECTION						
	Visual			Automated			p	Visual			Automated			p
	M±SD	*M*	IQR	M±SD	*M*	IQR		M±SD	*M*	IQR	M±SD	*M*	IQR	
SSS (n=117)	4,3 ± 8,9	0,0	4,0	7,7 ± 5,4	7,0	7,0	p<0,01	6,9 ± 7,6	5,0	11,5	4,0 ± 4,8	2,0	3,8	p<0,05
SRS (n=60)	7,5 ± 12,0	2,5	7,5	7,9 ± 6,2	7,0	6,3	0,16	6,4 ± 7,7	4,0	11,3	3,1 ± 4,2	1,0	3,5	p<0,05
SDS (n=60)	1,7 ± 2,2	1,0	3,0	2,8 ± 3,5	1,5	4,0	p<0,05	4,8 ± 4,6	3,0	6,3	2,8 ± 3,2	1,5	5,3	0,14

SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; IQR, interquartile range; *M*, median; M±SD, mean ± standard deviation.

DISCUSSION

The agreement between visual and automated analysis in MPI was investigated in previous studies with very good results.[14,25,26] Some studies even displayed a small advantage of the automated methods, in terms of intra and inter-observer reproducibility.[14,27]

In the present study, however, there was significant disagreement between the visual analysis and the automated method, mainly on the SSS, due to overestimation by the automated analysis. We can be quite confident on the overall accuracy of the visual analysis, due to the excellent diagnostic and prognostic value of MPI SPECT, achieved in several international studies[1,28] and in a large local research paper.[29]

When considering the different vascular regions, automated SSS were significantly higher in the LDA, LCX and APX regions, but not in the RCA, which corresponds, roughly, to the inferior wall. This result might be due to the high prevalence of male patients and attenuation corrected images in our sample, and to the fact that the normal database, used for the automated scoring, was not corrected for attenuation artifacts. This factor might also explain, at least partially, the differences found in the other vascular territories.

Also, fewer and less pronounced statistically significant differences were found in SRS and SDS, probably due to the smaller sample size (only 60 patients performed the rest test), a trend that is present in all other sub-group analysis.

Automated SSS were significantly higher in males, but not in females, probably due to the smaller sample size (73 males versus 44 females). No statistically significant differences among demographic variables were found between groups. As for the vascular regions analysis, the smaller sample size may explain for the absence of statistically significant differences in SRS and SDS.

When considering the different clinical indications for MPI, the SSS agreement was higher in patients with prior infarction than in those with no history of infarction, probably due to the higher heterogeneity of the latter group. Also, according to published literature,[19,30] the automated scoring accuracy seems to be high in patients with a high probability or known to have CAD and perfusion defects.

Attenuation correction had the most significant impact, namely it completely reversed the results. Automated SSS and SRS were lower than the respective visual scores in non-attenuated corrected images while automated SSS and SDS were higher than their visual counter-part in attenuated corrected images. Meaning that on the one hand when AC images were compared with a NAC database automated perfusion scores were falsely amplified (false positives, low specificity) in all territories, with the exception of the inferior wall, as previously discussed. On the other hand when NAC images were compared with a NAC database automated perfusion scores were underestimated (false negatives, low sensitivity). The absence of an attenuation corrected database represents a major drawback and should serve as a warning for those trying to implement automated scoring in clinical practice.[31–33] The effect of an appropriated AC database was recently shown by Kennedy, *et al*,[34] by improving automated analysis accuracy. Additionally, attenuation correction is just one of many other acquisition parameters, and, ideally, the database should be developed in the local Nuclear Medicine Department, with the same acquisition parameters, and with volunteers from the same population as the patients.

On a different note, multivessel disease might cause some differences between the visual and the automated analysis,[32] since the software might recognise a spread perfusion defect, also known as “balanced ischemia”, that may escape the human eye. However, due to the holistic nature of the visual analysis, this issue should be reasonably small.

Finally, when comparing three different automated software packages, Johansson, *et al,*[15] found that the *Emmory Cardiac Toolbox* performance was inferior, with higher SSS than visual analysis and the other automated software.

These pros and cons of the automated analysis should always be taken into consideration when applied in clinical practice.

Limitations: Sample size is an important limitation, restraining statistical power. Also, as previously stated, the absence of an AC database, when the majority of patients underwent attenuation correction with computed tomography is a critical limitation. As this was an observational study our results were dependent of routine clinical practice, which imposes some limitations, namely not performing attenuation correction when necessary was not an option, and rest images were only obtained when clinically required.

CONCLUSION

Despite the high agreement in SPECT-MPI analysis between visual and automated methods found in the literature, the present study suggests statistically significant differences between both methods, mainly on stress, in the anterior and lateral wall and the apex of the left ventricle in males.

Out of all variables, attenuation correction had the highest impact, with overestimation of the automated method when attenuation correction was performed and underestimated when not. This was, probably, due to the absence of an AC database, a major limitation of the present study.

Visual analysis is the method of choice for SPECT-MPI assessment, however it might benefit from the aid of semi-quantitative automated software. Particular care must be taken to ensure that the available software databases are adequate for the technical capability of the center. Development of local databases might be expensive but represents the optimal option.

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