ORIGINAL ARTICLE

Semi-quantitative assessment of ischemia with rubidium-82 PET myocardial perfusion imaging

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Purpose. **Semi-quantitative scores can be used as an adjunct to visual assessment in rubidium-82 positron emission tomography (^{82}Rb PET). The semi-quantitative cut-off values used in ^{82}Rb PET are derived from single-photon emission computed tomography (SPECT). It is unknown whether these cut-off values can be extrapolated to ^{82}Rb PET. We compared the semi-quantitative with the visual assessment of ischemia and determined which summed difference score (SDS) score predicts ischemia best.**

Methods. **We included 108 patients who underwent ^{82}Rb PET imaging and performed visual and semi-quantitative assessment. A scan with a SDS $\geq$ 2 and a summed stress score (SSS) $\geq$ 4 was considered to demonstrate ischemia. We compared the semi-quantitative with the visual assessment.**

Results. **41 (38%) Normal scans, and 67 (62%) scans with ischemia and/or an irreversible defect were included. The semi-quantitative assessment showed ischemia more often than the visual assessment (51% vs 29%, P < .001). Patients with a low or intermediate pre-test probability of coronary artery disease (CAD) and a SDS < 4 did not demonstrate ischemia by visual assessment.**

Conclusion. **Semi-quantitative assessment in ^{82}Rb PET imaging clearly demonstrates the presence of ischemia. Ischemia is unlikely in patients with low and intermediate pre-test probability of CAD and a SDS < 4. (J Nucl Cardiol 2022;29:3155–62.)**

Key Words: PET • MPI • image interpretation • CAD

Abbreviations

^{82}Rb PET	Rubidium-82 positron emission tomography
SPECT	Single-photon emission tomography
CAD	Coronary artery disease
SDS	Summed difference score
SSS	Summed stress score
SRS	Summed rest score
CT	Computed tomography
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting

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INTRODUCTION

Non-invasive imaging with rubidium-82 positron emission tomography (^{82}Rb PET) is increasingly used for the functional assessment of coronary artery disease (CAD).[1] PET myocardial perfusion imaging has a high sensitivity and specificity for the detection of CAD using both qualitative (visual) as well as semi-quantitative assessment (summed rest score, SRS summed stress score, SSS and summed difference scores, SDS).[2-4] Current guidelines recommend that automated semi-quantitative analysis can be used as an adjunct to visual assessment.[5,6] In ^{82}Rb PET imaging, a SSS $\geq$ 4 and a SDS $\geq$ 2 are considered abnormal and indicative for reversible and fixed perfusion defects. These cut-off values for abnormality are primarily derived from previous single-photon emission computed tomography (SPECT) studies.[7-10] Previous studies showed that semi-quantitative SPECT analysis is reproducible and provides similar diagnostic accuracy to visual assessment.[11-13] However, since ^{82}Rb PET has higher spatial resolution and a superior diagnostic performance when compared to SPECT imaging, it is unknown whether the cut-off values of semi-quantitative SPECT scanning can be extrapolated to ^{82}Rb PET imaging.[2-4,10] If the semi-quantitative approach has a high sensitivity for the assessment of ischemia and does not assess an abnormal scan as normal incorrectly, the semi-quantitative approach may be useful in the initial interpretation of ^{82}Rb PET scans. The semi-quantitative approach may possibly contribute to automatic scan assessment in the future.

Our aim was to determine the value of semi-quantitative scores in ^{82}Rb PET imaging. We compared semi-quantitative assessment of ischemia using a SDS $\geq$ 2 and SSS $\geq$ 4 as cut-off value, with visual assessment of ischemia in ^{82}Rb PET imaging. We investigated whether semi-quantitative assessment of ischemia differentiates between the presence or absence of ischemia. Furthermore, we tried to determine a semi-quantitative cut-off score that predicts ischemia.

METHODS

Study Population

We retrospectively included 108 patients with suspected stable CAD who underwent ^{82}Rb PET imaging in Isala Hospital, Zwolle, The Netherlands. All patients underwent ^{82}Rb PET between August 2017 and February 2018. We wanted to analyze the accuracy of the semi-quantitative scoring in both scans with and without perfusion defects. Hence, we included 41 (38%) consecutive patients with a normal scan and 67 (62%) consecutive patients with an abnormal scan. The abnormal scans showed either ischemia (36%), an irreversible defect (42%) or both ischemia and an irreversible defect (22%) (Table 1). All patients provided written consent for the use of their data for research purposes. Because the patients neither were subject to research procedures nor were required to follow rules of behavior, the Accredited Committee on Research Ethics of our Hospital (Isala, Zwolle) decided that the study did not fall under the scope of the Medical Research Involving Human Subjects Act in Dutch law.

Rubidium-82 PET Acquisition

All patients were asked to discontinue dipyridamole containing medications for 48 hours before the scan. They were asked to abstain from caffeine containing medication, food and drinks 24 hours before imaging. Prior to PET imaging a single low-dose computed tomography (CT) (120 kV and 20 mA) was acquired during free-breathing to provide an attenuation map of the chest. Next, 740 MBq ^{82}Rb was administered with a flow of 50 mL·min^{-1} using a ^{82}Sr/^{82}Rb generator (CardioGen-82, Bracco Diagnostics, Inc.).[14] A 7 minute acquisition was started immediately after the administration of ^{82}Rb using a Discovery 690 PET/CT scanner (GE Healthcare). Ten minutes after the start of the rest scan, stress was pharmacologically induced after injecting 400 µg regadenoson in 5 mL, which was administered over 15 seconds. After a flush with saline (5 ml NaCl 0.9%) over 10 seconds, again 740 MBq was administered for the stress scan which took 7 minutes. Attenuation correction was applied to all data on the PET system after co-registration of the CT and PET data.

Data Processing

We reconstructed the relative perfusion images using the data acquired between 2:30 and 7:00 minutes for both the rest and stress scan. The default settings as recommended by the manufacturer were used for the reconstruction: 3D iterative reconstruction with 2 iterations and 24 subsets. The reconstructed images were post-processed using Corridor4DM (INVIA Medical Imaging Solutions). After alignment of the PET images with the myocardium contours, the software automatically calculated the SSS, the SRS and the SDS, using a 17-segment bull's eye model and enabled correction of these scores by manual adjustment if required. The semi-quantitative scores were related to the Philips 4DM-PET normalcy database (INVIA Medical Imaging Solutions).[8,15] Scans were displayed in the traditional short, vertical long, and horizontal long axes and the

Table 1. Baseline characteristics and scan outcomes of all 108 included patients

Clinical characteristics	N = 108 (%)
Gender, male	74 (69%)
Age (years)	68 ± 11
Length (cm)	175 ± 9.3
Weight (kg)	88 ± 15
BMI ($kg \cdot m^{-2}$)	29 ± 5.1
Diabetes mellitus	33 (31%)
Family history positive for coronary artery disease < 60 years of age	50 (46%)
Hypercholesterolemia	71 (66%)
Hypertension	70 (65%)
Current smoking	21 (19%)
Ejection fraction in rest (mean)	54 ± 17
Left ventricle ejection fraction ≥ 50% in rest	65 (60%)
Pre-test probability coronary artery disease	
Low	13 (12%)
Intermediate	64 (59%)
High	31 (29%)
Cardiac history of ACS, PCI or CABG	
PCI	23 (21%)
CABG	26 (24%)
ACS	7 (6.5%)
Scan outcome according to original assessment	
Normal	41 (38%)
Reversible defect	39 (36%)
Irreversible defect	43 (40%)
Reversible and irreversible defect	15 (14%)

corresponding bulls eyes using the 17-segment model and reviewed using the 'Cool' color scale.[16]

Reproducibility Visual and Semi-quantitative Assessment

We assessed the intra- and inter-observer variability of the visual analysis. One pair of expert readers (a cardiologist and a nuclear medicine physician) visually interpreted the ^{82}Rb PET results of all patients twice to determine the intra-observer variability. For determination of inter-observer variability, another pair of expert readers assessed the same ^{82}Rb PET scans.

We also wanted to assess the reproducibility of the semi-quantitative ^{82}Rb PET analysis. Therefore, we performed an interim analysis of the first 51 scans that were included in the study. To evaluate the intra-technologist variability, one experienced technologist processed the scans twice ('Semi-quantitative A'). Another technologist processed the data as well in order to assess the inter-technologist variability ('Semi-quantitative B'). The technologists were blinded to the clinical condition of the patient and data sets were presented in a random order.

Visual vs Semi-quantitative Assessment

Semi-quantitative scores were compared to the visual assessment. Visual assessment was performed by consensus of one experienced nuclear medicine physician and one experienced cardiologist. All scans

Table 2. Simplified cut-off values for the semi-quantitative assessment of rubidium-82 PET scans

Normal scan	SSS ≤ 3
Abnormal scan	SSS ≥ 4
Reversible defect (ischemia)	SSS ≥ 4, SDS ≥ 2
Irreversible defect (no ischemia)	SSS ≥ 4, SDS ≤ 1

were visually interpreted using a 17-segment model, all segments were interpreted using a 5 point scoring system (0 = visually normal, 5 = visually no tracer uptake). The scans were categorized as normal or abnormal. An abnormal scan could demonstrate ischemia, an irreversible defect or both, irrespective of the segment. The semi-quantitative scores were categorized as well. For the distinction between 'normal' and 'abnormal scans', scans with a SSS $\geq$ 4 were all considered abnormal. An abnormal scan could demonstrate either ischemia, an irreversible defect, or both a reversible and irreversible defect. We considered a SDS $\geq$ 2 with a SSS $\geq$ 4 as cut-off values for the assessment of ischemia.[8-10] In this way, all scans were categorized as normal or abnormal. Abnormal scans were categorized as demonstrating ischemia or an irreversible defect or both (Table 2).

We then compared the visual assessment to the semi-quantitative assessment of ischemia. Furthermore, we determined the lowest SDS score that predicted ischemia by visual assessment.

Since most patients undergoing ^{82}Rb PET imaging are patients with a low or intermediate pre-test probability of CAD, we performed a subgroup analysis of all patients with a low or intermediate pre-test probability of CAD. We compared visual assessment with semi-quantitative assessment in this subgroup and determined what SDS score was related to a scan demonstrating ischemia by visual assessment.

Statistics

All statistical analyses were performed using IBM SPSS Statistics 24.0. Patient characteristics were computed as mean ± standard deviation or as percentage. Continuous variables were compared using an unpaired Student's *t*-test or a non-parametric Mann-Whitney *U*-test. Normal distribution was verified using the test of normality. Categorical variables were compared using Pearson's χ^2 test. Intra- and inter-observer variability were determined with Cohen's κ. A κ of 0.6-0.8 was categorized as good, a $\kappa > 0.8$ as excellent.[17] The differences in outcome between the visual assessment and semi-quantitative scores were compared using McNemar test. The level of statistical significance was set at 0.05.

RESULTS

Study Population

Of all 108 included patients, 74 (69%) were male. Mean age was 68 ± 11 years. Table 1 demonstrates the baseline characteristics and scan outcomes of all 108 patients. 56 (52%) Patients had a cardiac history of myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Some patients had a history of both a PCI and CABG or myocardial infarction.

Reproducibility Visual and Semi-quantitative Assessment

Intra- and inter-observer reproducibility of the visual assessment of a normal scan demonstrated a κ of 0.93 and 0.91 respectively. The intra- and inter-observer agreement for the qualitative assessment of a scan with ischemia (ischemia: SSS $\geq$ 4 and SDS $\geq$ 2) was 0.84 and 0.76 respectively.

The intra- and inter-technologist reproducibility of the semi-quantitative assessment of ischemia demonstrated a κ of 0.80 and 0.84, respectively. The intra- and inter-technologist reproducibility of the semi-quantitative assessment of a normal scan demonstrated a κ of 0.94 and a kappa of 0.88, respectively. As these interim analyses of the first 51 scans showed that intra- and inter-technologist reproducibility was excellent ($\kappa \geq 0.80$), an additional analysis of the reproducibility with the remaining 57 scans was considered unnecessary. One technologist (Semi-quantitative A) therefore processed the remaining 57 scans.

Visual vs Semi-quantitative Assessment

The semi-quantitative outcomes more often demonstrated ischemia, n = 55 (51%) than the visual assessment, n = 31 (29%), as shown in Table 3 ($P <$ .001). Of the 55 scans that demonstrated ischemia by semi-quantitative assessment, 25 (45%) did not demonstrate ischemia by visual assessment. Of the 53 scans that demonstrated no ischemia by semi-quantitative assessment, 1 (1.9%) scan demonstrated ischemia by visual assessment. This scan demonstrated a large irreversible defect both by visual and by semi-quantitative assessment (SSS = 8, SRS = 10, SDS = 1). In the visual assessment, the interpreters found an additional small reversible defect on this scan. Figure 1 demonstrates two examples of discordant scans.

Mean SDS was 11 ± 5.8 in all scans with ischemia by visual assessment, whereas mean SDS was 1.7 ± 2.3 in all scans without ischemia by visual assessment ($P <$ .001). Figure 2A demonstrates the SDS scores in scans with and without ischemia by visual assessment. The maximum SDS score found in a normal scan (e.g., without ischemia) was 11. The minimum SDS score that was found in a scan with ischemia by visual assessment was a SDS of 1. This scan with a SDS value of 1, was a scan with both ischemia and a large irreversible defect.

Table 3. Ischemia by visual assessment and ischemia by semi-quantitative assessment demonstrated in a cross tabulation

	Ischemia by visual assessment		
	Yes	No	Total
Ischemia by semi-quantitative assessment (SDS ≥ 2 and SSS ≥ 4)			
Yes	30	25	55
No	1*	52	53
Total	31	77	108

*SSS 8, SRS 10, SDS 1

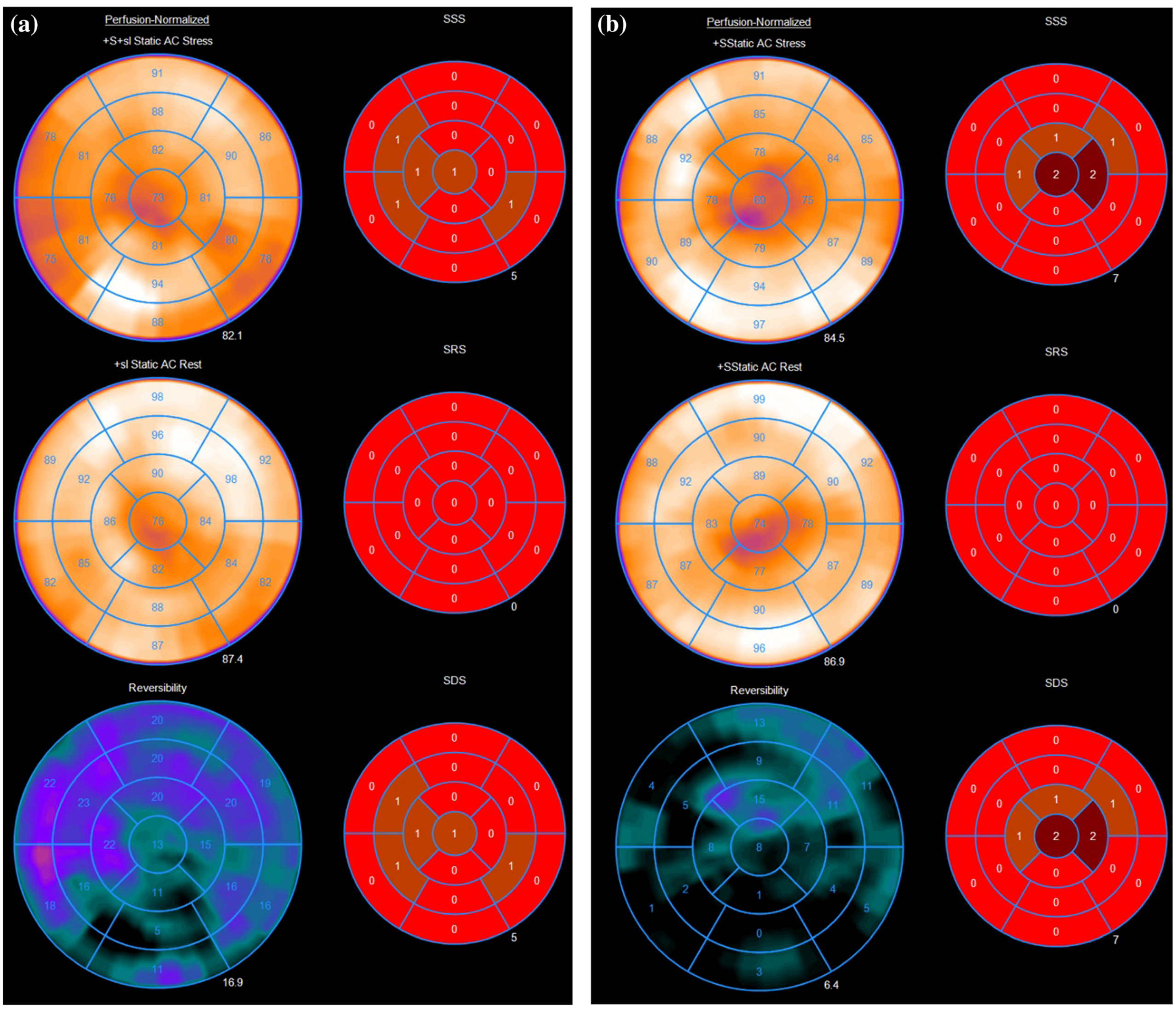

Figure 1. Examples of two discordant scans. **A** Example of a scan demonstrating no ischemia by semi-quantitative assessment (SSS 8, SRS 10, SDS 1), but ischemia on visual analysis. **B** Example of a scan demonstrating ischemia by semi-quantitative assessment (SSS 7, SRS 0, SDS 7), but no ischemia visually.

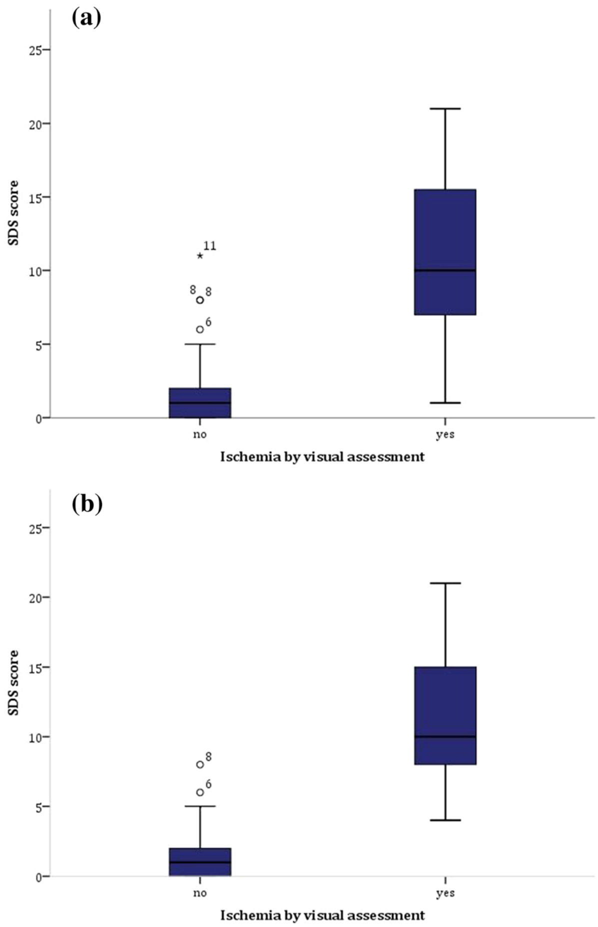

Figure 2. **A** SDS scores of patients with and without ischemia by visual assessment, n = 108. **B** SDS scores in patients with low or intermediate pre-test probability of coronary artery disease, with and without ischemia by visual assessment, n = 77.

We performed a subgroup analysis of all patients with low or intermediate pre-test probability of CAD. In this population, the minimum SDS score found in a scan demonstrating ischemia by visual assessment was a SDS score of 4. This is demonstrated in Figure 2B.

Follow-up

We assessed 1-year follow-up of death due to a possible cardiac event, invasive coronary angiography, PCI or CABG. A total of 24 patients (22%) underwent invasive coronary angiography within 1 year after PET. Of these 24 patients, 2 patients did not have obstructive CAD by invasive angiography, 3 patients underwent changes in their medication, 12 patients underwent PCI and 7 patients underwent CABG. Of all 24 patients who underwent invasive angiography within 1 year, consensus was found between visual and semi-quantitative assessment in 19 patients (79%). The 5 patients with a discrepancy in visual and semi-quantitative assessment all demonstrated ischemia by semi-quantitative assessment but were considered normal by visual assessment.

Furthermore, 4 patients (3.7%) deceased because of a possible cardiac event within 1 year of follow-up. These patients all demonstrated ischemia by semi-quantitative and visual assessment of the PET scan.

DISCUSSION

^{82}Rb PET perfusion imaging is a highly sensitive and specific non-invasive method to assess myocardial ischemia in patients with suspected significant CAD. When interpreting PET perfusion scans, it is advised to use both visual assessment of myocardial perfusion as well as semi-quantitative perfusion measures such as SSS, SRS and SDS scores. Our study showed that the use of semi-quantitative measures clearly differentiates between either the presence and the absence of ischemia. In patients with a low of intermediate pre-test probability of CAD, ischemia was not found in scans with a SDS < 4. Especially in this population, semi-quantitative scoring with ^{82}Rb PET perfusion imaging could be very valuable in the initial assessment of CAD.

Furthermore, the intra- and inter-observer variation of SDS scores in ^{82}Rb PET is excellent. This latter finding is in agreement with previous studies after the repeatability of semi-quantitative assessment of ischemia with myocardial perfusion imaging.[10,18]

Previous ^{82}Rb PET studies used cut-off values for ischemia (SSS $\geq$ 4 and SDS $\geq$ 2), which are derived from previous SPECT studies.[7-10] ^{82}Rb PET has a higher spatial resolution compared to SPECT which enables the detection of smaller and more subtle perfusion defects.[2,4,10] We reasoned that the higher spatial resolution of ^{82}Rb PET imaging might result in a lower specificity for the detection of ischemia by semi-quantitative scoring when using the same cut-off values for ischemia as in SPECT imaging. We compared the semi-quantitative assessment of ischemia with the visual assessment of ischemia in ^{82}Rb PET imaging. We demonstrated a big discrepancy when comparing our visual assessment of ischemia with our semi-quantitative assessment of ischemia using SSS $\geq$ 4 and SDS $\geq$ 2 as cut-off values. Our results show an overestimation of ischemia using these semi-quantitative cut-off values. Suggesting that semi-quantitative scoring has a low specificity for the detection of ischemia using these cut-off values. Specificity for the detection of ischemia might be higher using different semi-quantitative cut-off values. Sensitivity for the detection of ischemia with these semi-quantitative cut-off values was high, with only one scan demonstrating ischemia by semi-quantitative assessment without ischemia by visual assessment.

The consequence of selecting a different semi-quantitative cut-off value for the assessment of ischemia influences the sensitivity and the specificity. We analyzed the minimum SDS score associated with ischemia by visual assessment. In the whole cohort, a SDS of 1 was associated with ischemia by visual assessment.

In our subgroup analysis of patients with a low or intermediate pre-test probability of CAD the minimum SDS score associated with ischemia by visual assessment was a SDS of 4. Possibly, in patients with a low or intermediate pre-test probability of CAD, a SSS $\geq$ 4 and SDS $\geq$ 4 can be used as cut-off values for the detection of ischemia. This subgroup analysis is relevant, since the majority of patients referred for ^{82}Rb PET imaging are patients without a cardiac history of CAD and with a low or intermediate likelihood of obstructive CAD. It is interesting considering the possibility to assess ^{82}Rb PET scans of a relatively low risk population only by semi-quantitative assessment without further visual assessment.

We performed 1-year follow-up of death due to a possibly cardiac event, invasive angiography and PCI or CABG. A total of 24 patients underwent invasive angiography and 4 patients deceased because of a possible cardiac event. None of these patients demonstrated ischemia visually but demonstrated no ischemia by semi-quantitative assessment. In the whole population, one scan without ischemia by semi-quantitative assessment using SSS $\geq$ 4 and SDS $\geq$ 2 as cut-off value, demonstrated ischemia visually. This was a scan with a large irreversible defect (SSS 8, SDS 1, SRS 10). The ischemia found in this patient visually was clinically not relevant as no additional invasive angiography was performed nor did myocardial death occur within 1 year of follow-up. These findings suggest that the semi-quantitative assessment does not consider a scan non-ischemic incorrectly with clinical consequences.

Limitations

We wanted to assess whether the semi-quantitative scoring does not assess an abnormal scan as normal incorrectly, therefore, we selected a population with normal and abnormal scans (62%). In daily practice, mostly patients a low or intermediate pre-test probability of CAD are referred for ^{82}Rb PET imaging and we expect the percentage of patients with an abnormal scan to be much lower in comparison to our study population. Making semi-quantitative scoring even more applicable, especially in patients with a low-intermediate pre-test likelihood.

The study focused on the comparison of semi-quantitative and visual assessment of ischemia and we did not use invasive angiography as reference. Even though visual assessment has lower validity compared to invasive angiography, most laboratories use visual analysis for the assessment of ischemia. We believe that the semi-quantitative approach may be very useful in this initial assessment of ischemia by non-invasive imaging. Therefore, we compared the semi-quantitative assessment with the frequently used visual assessment. To increase the power of the results we assessed the intra- and inter-observer reproducibility of the visual assessment of ischemia, which was good and in line with previous studies.[11,13] Furthermore, we performed 1-year follow-up. In the patients with invasive angiography or death due to a possible cardiac event within 1 year of follow-up, the semi-quantitative assessment did not assess the scans as normal incorrectly.

We also did not compare semi-quantitative measurements with absolute myocardial blood flow measurements. Previous research demonstrated that myocardial blood flow analysis has an additional prognostic factor to visual assessment of myocardial perfusion imaging.[19] However, even though myocardial blood flow quantification is feasible with ^{82}Rb PET, due to intrinsic limitations of the tracer it is less reliable and not often used in clinical practice.[10]

CONCLUSION

Semi-quantitative assessment of ischemia in ^{82}Rb PET imaging differentiates between the presence and absence of ischemia in ^{82}Rb PET imaging. Overestimation of ischemia assessed by semi-quantitative assessment was found using SSS $\geq$ 4 and SDS $\geq$ 2 as cut-off values. However, our study demonstrates a high sensitivity of the semi-quantitative assessment of ischemia using SSS $\geq$ 4 and SDS $\geq$ 2 as cut-off values. In particular, in patients with a low or intermediate pre-test probability of CAD semi-quantitative scoring could be very valuable in the initial assessment of ischemia by ^{82}Rb PET. Ischemia is unlikely in this population when SSS and SDS are $<$ 4. This knowledge may be useful for trainees or inexperienced readers and may possibly contribute to automatic scan assessment in future.

NEW KNOWLEDGE GAINED

The frequently used cut-off values for the assessment of ischemia by semi-quantitative assessment with ^{82}Rb PET are a SSS $\geq$ 4 and SDS $\geq$ 2. Using these cut-off values, semi-quantitative scoring has a high sensitivity for the assessment of ischemia and a low specificity for the detection of ischemia. Overestimation of ischemia using these semi-quantitative scores is related to the cut-off values used. Especially in patients with a low or intermediate pre-test probability of CAD overestimation was demonstrated. Possibly, we should determine new-semi-quantitative cut-off values for the assessment of ischemia by ^{82}Rb PET imaging. A SDS < 4 was not associated with ischemia by visual assessment in patients with a low or intermediate pre-test probability of CAD. Maybe the cut-off value SSS $\geq$ 4 and SDS $\geq$ 4 predicts ischemia better in this population.

Disclosures

N.B. Borren, T.J. Gerritse, J.P. Ottervanger, M. Mouden, J.R. Timmer, J.A. van Dalen, P.L. Jager and J.D. van Dijk has no conflicts of interest and/or funding to declare that are relevant to the contents of this article.

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