Eur J Nucl Med Mol Imaging (2009) 36:1594–1602
DOI 10.1007/s00259-009-1143-8

ORIGINAL ARTICLE

Myocardial perfusion quantitation with ^{15}O-labelled water PET: high reproducibility of the new cardiac analysis software (Carimas™)

Sergey V. Nesterov · Chunlei Han · Maija Mäki · Sami Kajander · Alexandru G. Naum · Hans Helenius · Irina Lisinen · Heikki Ukkonen · Mikko Pietilä · Esa Joutsiniemi · Juhani Knuuti

Received: 19 December 2008 / Accepted: 1 April 2009 / Published online: 30 April 2009

Abstract
Purpose Carimas™ (Cardiac Image Analysis System) is a new software package developed at the Turku PET Centre for the quantitation of PET studies of the heart with a broad range of tracers. The goal of this study was to assess the reproducibility of results the package provides for myocardial perfusion (MP) quantitation using ^{15}O-labelled water.
Methods Four observers with various levels of experience in nuclear medicine independently analysed 20 MP studies (10 rest flow: "rest", 10 adenosine-induced hyperaemia: "stress"). Each study was analysed twice. The linear mixed model for repeated measures was fitted to the data to calculate intraclass correlation coefficients (ICC), differences between the repeats (the intraobserver differences) and differences between the observers (the interobserver differences). Also, Pearson correlation coefficients (r) were calculated and Bland-Altman plots were drawn. The reproducibility of MP was assessed on global, regional and segmental levels. Thereafter, this analysis was applied in 48 consecutive clinical patients with suspected coronary heart disease (CHD).
Results For the experienced observer the Pearson r for all segments was 0.974 at rest and 0.978 at stress ($p<0.0001$), and the repeatability coefficients were 0.145 ml/g per min (15.5% of the average) and 0.389 ml/g per min (14.9%), correspondingly. The ICC reflected very good overall reproducibility. The intraobserver and interobserver differences were small, and the difference between the most and the least experienced observers at stress was 8.5% for the global MP. The clinical accuracy of the perfusion in the detection of CHD was excellent (positive predictive value 91% and negative predictive value 88%) against invasive angiography.
Conclusion The results demonstrate high reproducibility of myocardial perfusion quantitation with ^{15}O-labelled water PET using Carimas™. The results support the feasibility of robust analysis and good clinical accuracy.

Keywords Myocardial perfusion imaging · Freeware · Reproducibility · Intraclass correlation coefficient · Linear mixed models · PET

S. V. Nesterov (✉) · C. Han · S. Kajander · A. G. Naum · J. Knuuti
Turku PET Centre, University of Turku,
P.O. Box 52, Turku 20521, Finland
e-mail: serge.nesterov@tyks.fi

S. V. Nesterov
IM Sechenov Institute of Evolutionary
Physiology and Biochemistry, Russian Academy of Sciences,
St. Petersburg, Russia

M. Mäki
Department of Clinical Physiology and Nuclear Medicine,
Turku University Hospital, University of Turku,
Turku, Finland

A. G. Naum
Nuclear Medicine and PET Centre,
Haukeland University Hospital, University of Bergen,
Bergen, Norway

H. Helenius
Department of Biostatistics, University of Turku,
Turku, Finland

I. Lisinen
Research Centre of Applied and Preventive Cardiovascular
Medicine, University of Turku,
Turku, Finland

H. Ukkonen · M. Pietilä · E. Joutsiniemi
Department of Internal Medicine, Turku University Hospital,
Turku, Finland

Introduction

Positron emission tomography (PET), which is increasingly used in routine clinical practice due to its superior accuracy [1–3], can absolutely quantitate myocardial perfusion (MP) both at rest and at stress [4]. At rest MP is around 0.6–1 ml/g per min [5]; at stress, when the coronaries dilate, it increases by three- to fivefold. Absolute MP quantitation in PET is performed using the tracer kinetic method, which is based on measuring the in vivo kinetics of a tracer concentration during dynamic acquisition, and this analysis can be done in the standard segmentation [6]. MP imaging has gained a strong position in clinical cardiology both in detection of coronary heart disease (CHD) and assessment of its severity.

Although PET has allowed the non-invasive absolute quantitation of global and regional MP [7], most of the PET studies are still focused on relative perfusion analysis in patients with CHD because of the considerable complexity of required acquisition and analysis protocols [8]. The studies where absolute quantitation was used typically assessed cardiac perfusion on the global level only and were usually focused either on the effect of various risk factors on early coronary dysfunction or on patients with different cardiovascular diseases [9, 10]. Therefore, large studies demonstrating the value of absolute quantitation in the detection of CHD as well as guiding therapy are still lacking, and one potential reason for this may be the limited availability of robust analysis software for this purpose.

Carimas™ (Cardiac Image Analysis System) is a free software package developed at the Turku PET Centre (downloads and information available at www.turkupetcentre.net/carimasturku) for visualising, processing and modelling of cardiac PET studies with a broad range of radiopharmaceuticals. It was developed in an "interactive data language" (IDL) and runs on IDL Virtual Machine™ (IDL VM)—a freely distributed, cross-platform utility for running compiled IDL code. In Carimas™ the process of an image analysis from loading the image to generating a report takes four sequential steps. The first, volume view, applies a subtraction method to generate a difference image (the image providing anatomical location of a left ventricle) from the dynamic sequence. The second step, reorientation, serves for spatial reorientation of the data to the standard short axis projection. In the third, ROI definition step, Carimas™ automatically searches for ventricle borders and locates initial regions of interest (ROIs) which can be modified manually to improve their quality. Based on the automatic segmentation of the left ventricle, the program performs the mathematical modelling (using the validated models [11, 12]) and generates parametric images (Fig. 1). Carimas™ recognizes ECAT and DICOM formats; also, it can output the parametric volume of the heart in DICOM format. The parametric image of the heart in DICOM generated by Carimas™ is

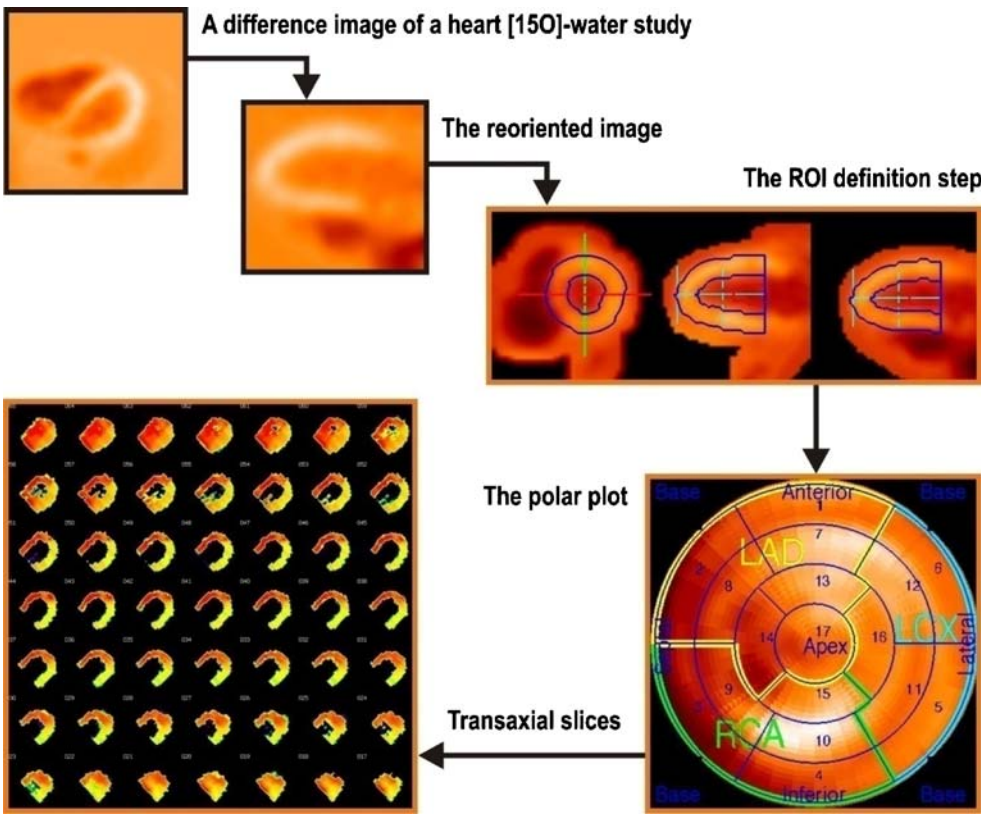

Fig. 1 Analysis workflow in Carimas™

compatible with the GE ADW (General Electric Advanced Development Workstation) analysis software.

The goal of the present study was to assess intra- and interindividual reproducibility of MP absolute quantitation in Carimas™ using ^{15}O-labelled water and PET and to assess the clinical accuracy of the results in the detection of CHD.

Materials and methods

Image acquisition

Scanning was performed using the GE Discovery STE VCT tomograph (General Electric, Waukesha, WI, USA) using a standard protocol. ^{15}O-labelled water (700–900 MBq) was injected at rest as an intravenous bolus over 20 s at an infusion rate of 10 ml/min and the venous line was then flushed for another 2 min. The 4 min 40 s dynamic acquisition was performed (14 frames at 5 s, 3 frames at 10 s, 3 frames at 20 s and 4 frames at 30 s). After decay of the ^{15}O radioactivity, the second scan was performed during adenosine-induced hyperaemia (stress). Adenosine was started 2 min before the scan start and infused for a total of 6 min 40 s at 140 μg/kg body weight per min, according to standard practice [13]. The data were reconstructed using the standard iterative reconstruction algorithm of the scanner manufacturer with a zoom of 2.0 to the 128×128 matrix (standard for MP PET imaging [14]; voxel size 2.73×2.73×3.27 mm).

Analysis of the images

Twenty randomly selected ^{15}O-labelled water PET scans (later termed "subjects") from ten patients (one "rest" and one "stress" from each patient; the patients had histories of chest pain and 30–70% pre-test likelihood of CHD) were analysed by four observers. The observers, though educated as medical doctors, differed in experience: O_I was an experienced nuclear medical physician who had performed and analysed MP studies for 10 years, O_{II} had completed his Ph.D. in MP studies, O_{III}, is a biophysicist and the developer of the Carimas™ software, and O_{IV}, a novice, having had performed the analysis of MP only once. Before the actual analysis the observers were given identical training. All of the observers were not informed of a subject's properties such as a patient's name, clinical data and a subject's type (rest or stress); also, they were blinded to results of each other. Each observer performed the analysis of each subject twice (in two sessions separated by 2 weeks time), so producing two *repeats* for each subject.

The observers analysed the images through the aforementioned consecutive steps. Volume view and reorientation were done manually; ROI definition, though performed automatically, was then usually accompanied by manual adjustment; modelling and reporting of results were automatic. The results obtained represented global MP, perfusion in the coronary artery territories and the segmental MP [6]. As the variability in anatomical myocardial blood supply occurs at the apex (segment 17) which can be supplied by any of the three arteries [6], we calculated MP in the left anterior descending coronary artery (LAD) without the apex (LADwa). Thus, the territorial division included the three coronary artery territories [right coronary artery (RCA), LADwa and left circumflex (LCx) coronary artery] and the apex. So each subject (of 20) produced eight sets (two repeats in four observers) of 22 numbers: global, 4 territorial and 17 segmental MP values.

Clinical study

The accuracy of perfusion imaging was then tested in a clinical situation in 48 consecutive symptomatic patients (Table 1) with suspected CHD who were referred for invasive angiography based on clinical justification. The patients had neither earlier diagnosis of CAD nor previous myocardial infarction, nor any other known cardiac disease. In invasive coronary angiography 50% or more luminal narrowing was considered significant. The analysis was performed using the standard quantitative coronary angiography software by Siemens. The alignment of perfusion results (the standard 17-segment model) with the coronary findings was performed individually. The cut-off value of absolute perfusion analysis for the optimal detection of coronary stenosis was assessed first, and thereafter the positive and negative predictive values (PPV, NPV) as well as accuracy were calculated.

Statistical analysis

Traditional methods such as calculating Pearson correlation coefficients (r) and drawing Bland-Altman plots were

Table 1 Characteristics of the patients in the clinical series

Parameter	Characteristics
Gender (M/F)	37/11
Age (years)	66±7
Weight (kg)	82±14
BMI (kg/m^2)	27.0±3.4
Invasive angiography (0-/1-/2-/3-vessel disease)	21/11/12/4
Risk factors for CAD	
Increased family risk	15
Smoking	9
Hypertension	26
Diabetes mellitus	7 (all type 2)
Hyperlipidaemia	23

applied first; however, the complexity of the original data demanded a more advanced method which would make comprehension of reproducibility exhaustive, yet easy, so linear mixed models for repeated measures were used [15].

An intraclass correlation coefficient (ICC) was used, since it is essential when the assessment of reliability of repeated quantitative measurements is needed [15]. In general, ICC measures consistency (or conformity) between two or more quantitative measurements. The basic idea of ICC is to compare the variability due to the repeated measurements from the same object to the total variation which is induced by all measurements and all the objects. Here, the ICC informed on intraobserver correlations between the repeats and was used to determine the intra-observer reproducibility of the analysis as such with no division into "rest" and "stress" subjects. The interpretation of the ICC values was based on the criteria proposed by Fleiss [16]: intraclass correlation coefficient values of 0.00–0.20 represented *slight* agreement, 0.21–0.40 represented *fair* agreement, 0.41–0.60 represented *moderate* agreement, 0.61–0.80 represented *substantial* agreement and >0.81 represented *very good* agreement.

The intraobserver and interobserver differences were calculated based on the aforementioned linear mixed model. These differences treated the "rest" and the "stress" subjects separately. Should the compared results be equal to each other the differences between them would equal zero; however, in practice it is enough to be sure that the 95% confidence interval of the difference includes zero, meaning the difference between them is not significant. The difference values obtained were expressed in standard MP units—ml/g per min—which would have impeded the comprehension of their significance if the rest and the stress flows were to be inspected simultaneously. So, the per cent values from the corresponding mean MP values were calculated. In the case of intraobserver difference the difference value was divided by the mean MP in the region; in the case of interobserver difference the mean MP value was calculated as an average of the two mean values in the compared observers.

Results

The mean values and the Pearson correlation coefficients for the global MP and MP in coronary artery territories are presented in Table 2. Linear regression values and Bland-Altman plots demonstrated good reproducibility. In Fig. 2 (the O_I observer) all the segmental MPs were plotted separately for "rest" and "stress" (two measurements of segment 3 are missing, basal inferoseptal wall) (the *r* values were 0.974 and 0.978, and the repeatability coefficients −0.145 ml/g per min and 0.389 ml/g per min at rest and

Table 2 Mean values of myocardial blood flow (MBF) (ml/g per min) and Pearson correlation coefficients between the replicates in the observers at rest and at stress

	O_I			O_{II}			O_{III}			O_{IV}		
	MBF-I	MBF-II	*r*	MBF-I	MBF-II	*r*	MBF-I	MBF-II	*r*	MBF-I	MBF-II	*r*
Rest												
Global	0.988±0.275	0.946±0.236	0.992	0.964±0.250	0.974±0.297	0.934	0.933±0.273	0.923±0.266	0.991	0.946±0.291	0.925±0.232	0.951
LADwa	0.915±0.217	0.867±0.175	0.986	0.914±0.156	0.928±0.222	0.890	0.872±0.208	0.844±0.192	0.974	0.907±0.228	0.900±0.191	0.868
LCx	0.976±0.316	0.962±0.309	0.992	1.007±0.352	1.037±0.330	0.978	0.973±0.354	0.955±0.334	0.995	0.949±0.367	0.941±0.312	0.977
RCA	0.864±0.276	0.829±0.237	0.982	0.838±0.266	0.836±0.299	0.927	0.805±0.237	0.794±0.248	0.984	0.872±0.304	0.803±0.228	0.966
Apex	1.276±0.346	1.209±0.302	0.956	1.209±0.334	1.194±0.466	0.853	1.163±0.368	1.120±0.365	0.973	1.106±0.314	1.125±0.261	0.917
Stress												
Global	2.653±0.900	2.669±0.868	0.994	2.804±0.921	2.837±1.008	0.881	2.810±1.081	2.679±0.832	0.940	2.754±1.018	3.043±1.029	0.888
LADwa	2.422±0.772	2.463±0.789	0.992	2.494±0.869	2.557±1.023	0.868	2.519±1.012	2.442±0.773	0.966	2.527±0.945	2.773±1.061	0.889
LCx	2.744±0.921	2.760±0.904	0.988	3.029±1.035	3.019±1.106	0.890	2.984±1.129	2.888±0.899	0.902	2.885±0.891	3.330±1.075	0.883
RCA	2.516±0.853	2.592±0.879	0.982	2.768±0.883	2.799±1.075	0.847	2.787±1.116	2.553±0.814	0.904	2.661±0.885	3.068±1.010	0.908
Apex	2.970±1.140	2.919±1.007	0.992	3.043±1.256	3.095±1.203	0.825	3.054±1.146	2.924±0.994	0.918	3.090±1.511	3.197±1.247	0.774

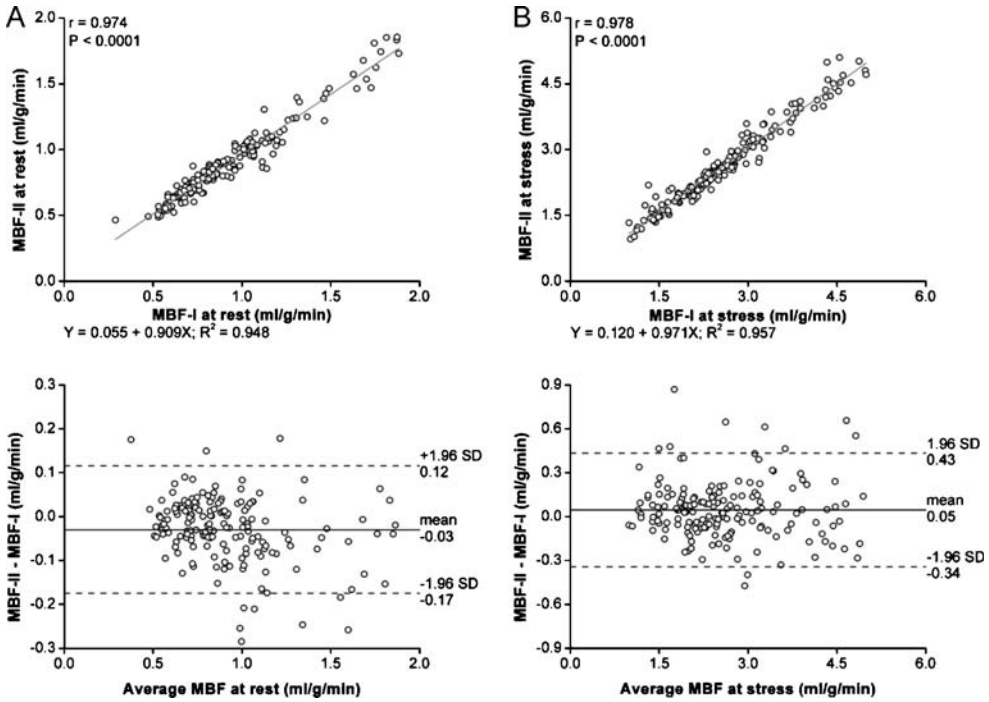

Fig. 2 Reproducibility of MBF in the first observer (O_I) at rest in 168 ROIs of ten subjects (**a**) and at stress in 170 ROIs of ten subjects (**b**). *Top* Regression lines are drawn. *Bottom* Bland-Altman plots

at stress, correspondingly). The MP values in segments belonging to the three coronary artery territories are plotted in Fig. 3.

Global perfusion

Reproducibility, both intraobserver and interobserver, was *very good* for global perfusion. ICC for the intraobserver reproducibility (Fig. 4) showed *very good* agreement. It was the highest in the most experienced observer O_I: 0.99 and the lowest in O_{II}: 0.88; in O_{III} and O_{IV} it was 0.91 and 0.89, correspondingly, all the values falling into the range of *very good* agreement. The intraobserver reproducibility (Fig. 5) was good as well, with the 95% confidence intervals of the differences between repeats including zero both at rest and at stress, indicating that the differences were not significant. So, the repeated analysis by the same observer produced nearly the same results. The absolute values of difference were close to zero. At rest the largest value was 4.3% in O_I, and at stress it was somewhat higher in the novice O_{IV} being 9.9%. The interobserver reproducibility (Fig. 6) was also good except for the difference between the most experienced (O_I) and the novice (O_{IV}) observers at stress which was significant.

Perfusion in the coronary artery territories

The highest ICC values (Fig. 4) were observed in the most experienced observer (O_I): in the three territories it was above 0.98. The lowest values were found in O_{II}: 0.86 in LADwa, 0.84 in RCA and in O_{IV}: 0.88 in LCx, all these values still falling into the category of *very good* agreement. The intraobserver reproducibility (Fig. 5) was fine except in the novice observer (O_{IV}) at stress in LCx and RCA with the absolute values of difference being 14.3 and 14.2%, correspondingly, and it was significant. As to the interobserver reproducibility (Fig. 6) the systematic difference was again found between the most and the least experienced observers O_I and O_{IV} at stress; it was significant in the territories LADwa, LCx and RCA: 8.1, 12.1 and 11.4% (the absolute values), correspondingly, all these differences being very small in practice.

Segmental perfusion

The vast majority of segmental ICC values and all the values in the most experienced observer (O_I) were above 0.81 (Fig. 4) indicating *very good* agreement for segmental results as well. The lowest segmental ICC values were observed in the basal inferoseptal segment 3. In O_{IV} the ICC for this segment was 0.72, in O_{III} 0.74 and in O_{II} 0.78. However, in the most experienced observer (O_I) it was still excellent: 0.95. The lowest ICC in this experienced observer was 0.84 in the basal anteroseptal segment (2); all the other ICCs in O_I were above 0.95.

The intraobserver differences in segmental values were also analysed in detail and no significant difference in any segment was found in the most experienced observer (Fig. 7). Neither was there any significant difference in the observer O_{II}. However, in the other two observers at stress significant differences were found between the repeats. In the observer O_{III} it was 12.0% in the 15th segment and no other

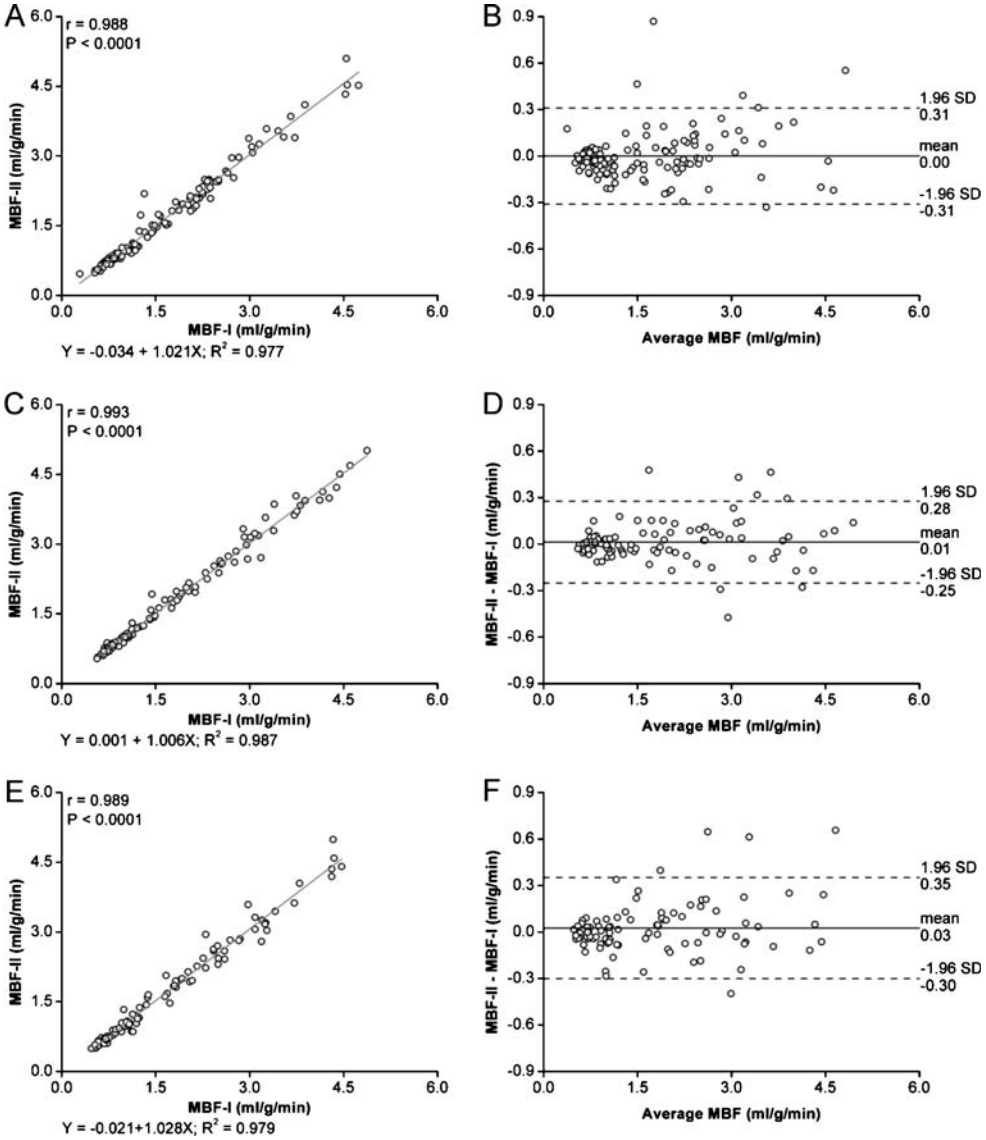

Fig. 3 Linear regression analysis and Bland-Altman plots comparing MBF measurement replicates in the observer O_I by coronary artery territories: LADwa (**a** and **b**), LCx (**c** and **d**) and RCA (**e** and **f**)

significant difference was present, and in O_{IV} the significant differences were present in lateral (6, 11, 12 and 16) and inferior segments (4, 10 and 15) and the largest one of those was 15.4% in segment 10.

The significant interobserver difference was found at rest between the most experienced observer O_I and the observer O_{II}: in basal segments 1, 5, 6 and in the 12th segment; the maximal difference was 10.2% in the 6th segment. However, it needs to be mentioned that the results of the observer O_{II} were significantly different from all the other observers as well, and the differences were mostly in the basal segments: O_{II} and O_{III}: segments 1–6, maximal difference 18.3% (the 3rd segment), O_{II} and O_{IV}: segments 5 and 6, maximal difference 12.9% (also the 12th at 9.1%).

At stress the differences were found between observers O_I and O_{II} in segments 1 and 11 (11.7 and 12.9%, correspondingly) and between observers O_I and O_{IV} in segments 1 and 14 (11.9 and 12.1%).

Clinical accuracy

The incidence of CHD in the clinical population was 56% in invasive angiography and most of the affected patients had 1–2-vessel disease (Table 1). The other clinical characteristics and risk factors for CAD are shown in Table 1. When compared against existence of >50% stenosis in invasive angiography the absolute MP of <2.5 ml/g per min was found to be the best criterion in identifying significant coronary stenosis. With this cut-off value PPV, NPV and accuracy of MP results in detecting significant CHD were 91, 88 and 90%, respectively.

Discussion

The present study assessed the reproducibility of the new free cardiac PET analysis software, Carimas™, for the

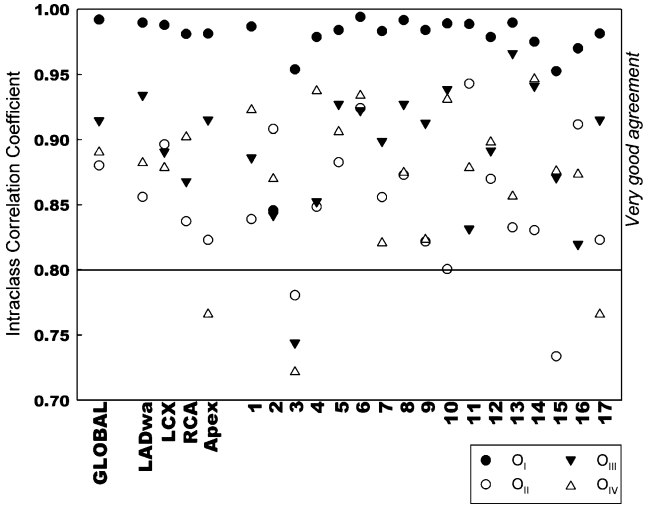

Fig. 4 Intraclass correlation coefficient (ICC) for intraobserver reproducibility. The ICC values above 0.80 (*horizontal line*) indicate very good agreement and values from 0.61 to 0.80 represent substantial agreement

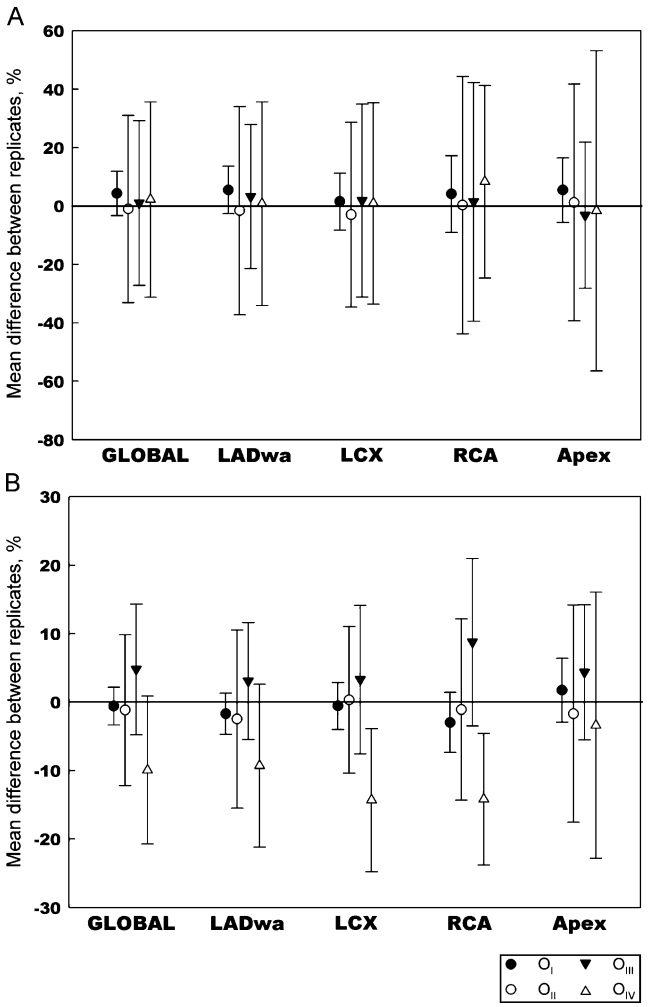

Fig. 5 Mean differences (and 95% confidence intervals) between replicates in the observers at rest (**a**) and at stress (**b**). The difference is not significant if the confidence interval crosses the zero line

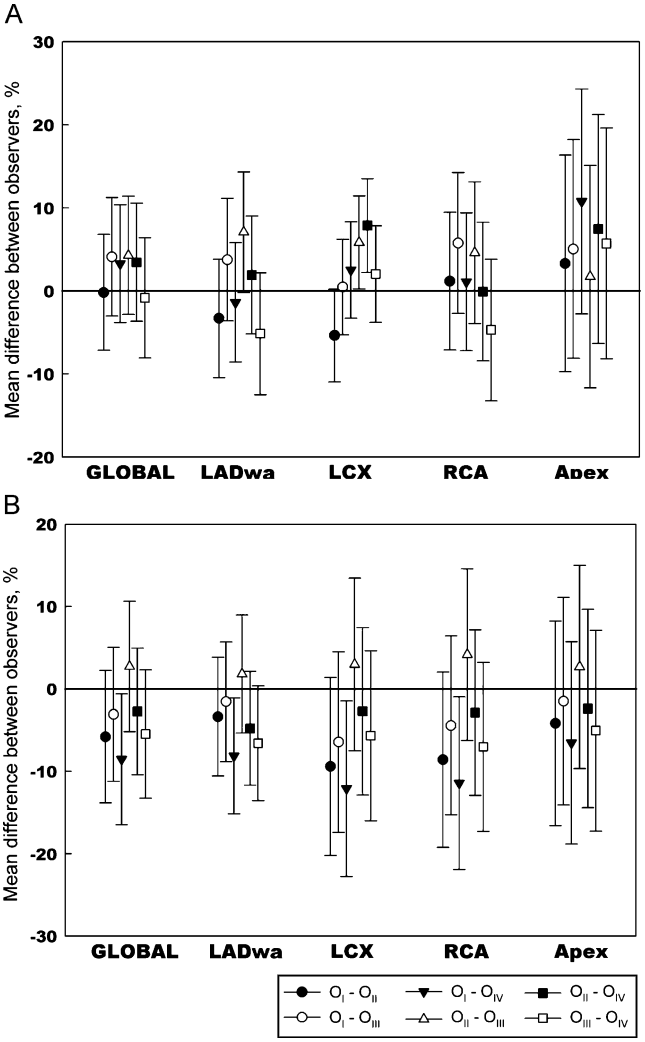

Fig. 6 Mean differences (and 95% confidence intervals) between the observers at rest (**a**) and at stress (**b**). The difference is not significant if the confidence interval crosses the zero line

analysis of ^{15}O-labelled water myocardial perfusion (MP) studies. Four observers with various levels of experience studied 20 real clinical MP studies, repeating each analysis twice. It was found that Carimas™ can reliably quantitate MP in a whole heart but also in coronary artery regions and in standardized myocardial segments. The analysis was found to be robust enough even for the less experienced observers, but the best results were obtained when analysis was done by the experienced nuclear medicine specialist. The preliminary clinical accuracy tested in a small yet reasonable patient population was also excellent.

MP reproducibility has not yet been assessed in the same methodological framework (new software—^{15}O-labelled water—several observers—linear mixed model) as has been in this study, so direct comparison is not possible; however, Katoh et al. [17] advanced "an improvement of algorithm for quantification of regional myocardial blood flow using ^{15}O-water with PET". This algorithm yielded

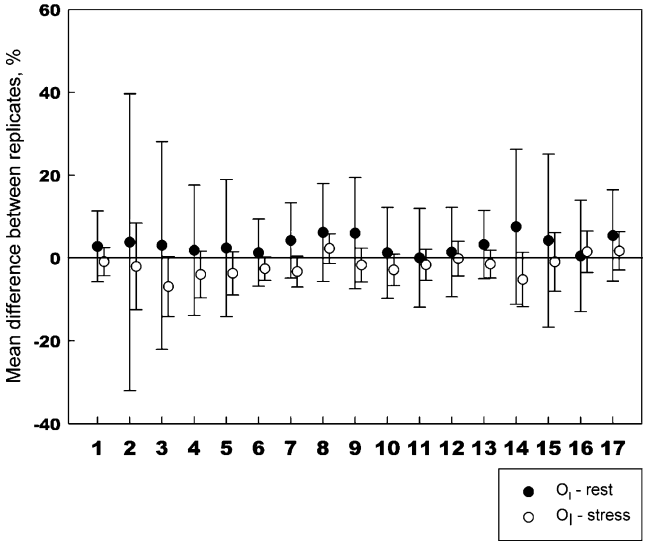

Fig. 7 Segmental mean differences (and 95% confidence intervals) between the replicates in the first observer (O_I) at rest and at stress

Pearson's *r* equal to 0.806 at rest in 576 ROIs in 36 subjects. In our study the Pearson's *r* in the experienced observer O_I at rest was 0.974 in 168 ROIs in ten subjects. As to the repeatability coefficient, which was defined as 1.96×SD of the mean in the Bland-Altman plot [18], Katoh et al. [17] reported 0.149 ml/g per min with a mean of 0.031 ml/g per min for the remaining values; in O_I we had it 0.145 ml/g per min and 0.029 ml/g per min, correspondingly. This value in a study by Kaufmann et al. [7] was 0.166 ml/g per min. The study by Katoh et al. [17] did not provide the stress values of repeatability. In the study by Kaufmann et al. [7] hyperaemic myocardial blood flow measurements with ^{15}O-labelled water showed the repeatability coefficient of 0.936 ml/g per min (25% of the average; only one observer in the study). The corresponding value in this study was 0.389 ml/g per min in observer O_I (14.9% of the average). These findings suggest that Carimas™ shows at least as good reproducibility for absolute quantitation of MP as the earlier used software packages. Of note, higher variability in stress imaging could be caused by greater variability of MP response for stressors rather than the error of measurements.

When global perfusion was analysed, an excellent reproducibility was found independently of the observer's experience. The intraobserver difference was close to zero, the most prominent being 9.9% during stress in the least experienced observer, and it can be regarded as clinically negligible. The interobserver difference was also very small (8.5%).

Analysing the reproducibility on the regional and the segmental levels, the best results were detected in the most experienced observer; in the less experienced observers the results were also very good indicated by high ICCs and non-significant differences in most segments in intra- and interobserver analysis. However, some useful information is due. The most consistent differences were found in the novice observer analysing the stress images, and even then, the intraobserver difference was at most 14.3% and the difference between the most experienced observer and the novice was at most 12.1%; these values look rather modest. The most difficult region in the heart seems to be the basal segments of the septal wall; this is comprehensible and is due to the variability of the septal length causing problems for the definition of septal ROIs. The variation in heart axis definition may also have a greater impact on the smaller sized ROIs. Despite these facts the reproducibility we found in these regions was quite good with the lowest ICC values of 0.72 and 0.84.

Traditionally, Bland-Altman plots are used to analyse reproducibility. However, due to the complexity of the current data with four observers, 20 subjects and two repeats of each subject, using only the Bland-Altman plots would have provided incomprehensible results. Also, the Bland-Altman techniques are descriptive, focusing on behaviour of the separate statistical units or more generally on indication of systematic shapes in the behaviour of different observations. The linear mixed models were used because they offered a comprehensive and a theoretically clear way to analyse both the inter- and intraobserver reproducibility with the same technique. With the mixed models it was also possible to take into account the rest/stress condition in the analysis and to run statistical tests and calculate confidence intervals. The linear mixed model techniques allowed us to display the results in a compact way at the summary statistics level.

The present analysis focused on ^{15}O-labelled water since it has been regarded as the most challenging perfusion tracer for clinical applications as it does not produce an immediate image of perfusion distribution. Since no non-invasive gold standard exists for the quantification of perfusion in humans, we tested the method in a small group of consecutive patients with moderate likelihood of disease who were referred for invasive angiography due to their chest pain symptoms. We found that the accuracy of quantitative perfusion was excellent in detection of CHD in invasive angiography when the cut-off value of 2.5 ml/g per min was used. The quantitative water model applied in the analysis has been validated against microspheres in dogs [12] and has been subsequently widely used in numerous earlier studies [9]. In Carimas™ no new modelling has been implemented, but only the image processing, segmentation and ROI definition were improved to allow more accurate regional analysis of perfusion in clinical situations. The strength of this study was also in the selection of the subjects studied—the patients with chest pain and 30–70% pre-test likelihood of CHD—those for whom the MP

imaging was clinically indicated. Obviously, further larger studies are warranted to validate the applied cut-off value of absolute perfusion. Furthermore, the comparison only against an anatomical gold standard is not ideal for the assessment of the clinical accuracy of the perfusion method.

The results of this study have several clinical implications. While there are several other software solutions for absolute MP quantitation, no studies have focused on the feasibility and reproducibility of the analysis for routine situations with observers with different levels of expertise. The analysis of ^{15}O-labelled water perfusion studies has been regarded as the most challenging due to the image noise and lack of immediate MP images. Despite this, even with ^{13}N-ammonia, quantitative analysis has seldom been included in the clinical evaluation. One of the reasons for this may have been limited availability of robust analysis software for routine clinical practice. These facts together may explain why absolute quantitation has been much underutilized in clinical cardiac PET imaging. Clinical evidence of the value of absolute quantitation is limited and without larger clinical experience it is difficult to justify buying commercial software for this task.

Conclusion

This study has demonstrated the excellent reproducibility of myocardial perfusion quantitation with ^{15}O-labelled water PET using the Carimas™ software. The results also support the claims of high clinical value of the software, yet do not undermine the value of experience of the practitioner.

Acknowledgements We thank Stephen Hitchens (University of Sheffield, Sheffield, UK) for his help with English.

The study was conducted within the “Centre of Excellence in Molecular Imaging in Cardiovascular and Metabolic Research" supported by the Academy of Finland, University of Turku, Turku University Hospital and Åbo Academy.

References

1. Hartiala J, Knuuti J. Imaging of the heart by MRI and PET. Ann Med 1995;27 1:35–45.
2. Merhige ME, Breen WJ, Shelton V, Houston T, D’Arcy BJ, Perna AF. Impact of myocardial perfusion imaging with PET and (82)Rb on downstream invasive procedure utilization, costs, and outcomes in coronary disease management. J Nucl Med 2007;48 7:1069–76.
3. Smith MF. Advances in rubidium PET and integrated imaging with CT angiography. Curr Cardiol Rep 2008;10 2:135–41.
4. Wijns W, Camici PG. The value of quantitative myocardial perfusion imaging with positron emission tomography in coronary artery disease. Herz 1997;22 2:87–95.
5. Pandit-Taskar N, Grewal RK, Strauss HW. Cardiovascular system. In: Christian PE, Waterstram-Rich KM, editors. Nuclear medicine and PET/CT technology and techniques. St. Louis: Mosby Elsevier; 2007. p. 479–512.
6. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105 4:539–42.
7. Kaufmann PA, Gnecchi-Ruscone T, Yap JT, Rimoldi O, Camici PG. Assessment of the reproducibility of baseline and hyperemic myocardial blood flow measurements with 15O-labeled water and PET. J Nucl Med 1999;40:1848–56.
8. Lodge MA, Bengel FM. Methodology for quantifying absolute myocardial perfusion with PET and SPECT. Curr Cardiol Rep 2007;9 2:121–8.
9. Pitkänen OP, Nuutila P, Raitakari OT, Porkka K, Iida H, Nuotio I, et al. Coronary flow reserve in young men with familial combined hyperlipidemia. Circulation 1999;99 13:1678–84.
10. Kaufmann PA, Camici PG. Myocardial blood flow measurement by PET: technical aspects and clinical applications. J Nucl Med 2005;46 1:75–88.
11. Iida H, Rhodes CG, de Silva R, Yamamoto Y, Araujo LI, Maseri A, et al. Myocardial tissue fraction–correction for partial volume effects and measure of tissue viability. J Nucl Med 1991;32 11:2169–75.
12. Iida H, Rhodes CG, de Silva R, Araujo LI, Bloomfield PM, Lammertsma AA, et al. Use of the left ventricular time-activity curve as a noninvasive input function in dynamic oxygen-15-water positron emission tomography. J Nucl Med 1992;33 9:1669–77.
13. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imaging: results from the Adenoscan Multicenter Trial Registry. J Am Coll Cardiol 1994;23:384–9.
14. Wackers FJT, Bruni W, Zaret BL. Acquisition, processing, display, and analysis of PET images, Chap. 11. Nuclear cardiology: the basics: how to set up and maintain a laboratory. Totowa: Humana; 2008. p. 173–210.
15. Davis CR. Statistical methods for the analysis of repeated measurements. New York: Springer; 2002. p. 125–55.
16. Fleiss JL. Reliability of measurements. In: Fleiss JL, editor. The design and analysis of clinical experiments. New York: John Wiley & Sons; 1986. p. 1–32.
17. Katoh C, Kubo N, Shiga T, Kubo N, Nakada K, Tamaki N. Improvement of algorithm for quantification of regional myocardial blood flow using 15O-water with PET. J Nucl Med 2004;45 11:1908–16.
18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1 8476:307–10.